Phase II study of nivolumab and the antagonistic CSF-1R monoclonal antibody cabiralizumab (BMS-986227) in patients with relapsed/refractory peripheral T cell lymphoma

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I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

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Signature of Site Investigator Date

_____

Site Investigator Name (printed)

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Site Investigator Title

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Name of Facility

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SYNOPSIS

TITLE	Phase II study of nivolumab and the antagonistic CSF-1R monoclonal antibody cabiralizumab (BMS-986227) in patients with relapsed/refractory peripheral T cell lymphoma
PHASE	II
OBJECTIVES	Primary Objectives: 1) To estimate objective response (OR) rate (ORR) to nivolumab and cabiralizumab in relapsed/refractory peripheral T cell lymphoma (PTCL) by LYRIC criteria at 4 months 2) To estimate complete response (CR) rate (CRR) to nivolumab and cabiralizumab in relapsed/refractory peripheral T cell lymphoma (PTCL) by LYRIC criteria at 4 months Secondary Objectives: 1) To estimate ORR and CRR of this combination by Lugano criteria at 4 months. 2) To estimate the best OR (including PR and CR) at any time on trial by LYRIC and Lugano criteria 3) To estimate progression free survival (PFS), disease control rate (DCR), duration of response (DOR), and time to next treatment (TNT). 4) To evaluate the safety and tolerability of the combination of cabiralizumab and nivolumab. Exploratory Objectives: 1) To determine lymphoma associated macrophage (LAM), regulatory T cell (Treg), and cytotoxic T lymphocyte (CTL) densities (before and during treatment) as pharmacodynamic and prognostic biomarkers. 2) To determine lymphoma cell and tumor microenvironment expression of PD-L1 and CSF-1R as pharmacodynamic and prognostic biomarkers. 3) To examine the abundance of "exhausted" T cells in the peripheral blood as a pharmacodynamic and prognostic biomarker. 4) To evaluate the feasibility and utility of minimal residual disease monitoring throughout treatment as a pharmacodynamic and prognostic biomarker. 5) To evaluate the role of myeloid derived suppressor cells as a pharmacodynamic and prognostic biomarker. 6) To biobank diagnostic biopsy specimens and PBMC for future correlative studies.
STUDY DESIGN	Open label, single arm, non-randomized trial
KEY ELIGIBILITY CRITERIA	**Inclusion criteria:** 1) Able to voluntarily provide written IRB-approved informed consent. 2) At least 18 years of age or older at the time of enrollment. 3) ECOG Performance Status of 0-2 4) Histologic confirmation of peripheral T-cell lymphoma (PTCL) with measurable disease on imaging. Adult T-cell leukemia/lymphoma (ATLL) are excluded.

	5) Documented disease progression after receiving at least two prior therapeutic regimens including brentuximab vedotin in patients with CD30 positive disease (defined as >10% CD30 positive cells). 6) Prior cancer treatment must be completed at least 28 days prior to treatment and the subject must have recovered from all treatment related toxicities (less than grade 3) or returned to baseline prior to treatment. Steroids at <10 mg prednisone equivalent daily allowed. 7) Adequate hematological function: a. ANC ≥1,000 cells/uL b. Platelets ≥75,000 cells/uL 8) Adequate renal function: a. Serum creatinine ≤1.5 x ULN, or calculated creatinine clearance >30 mL/min. 9) Adequate hepatic function: a. Bilirubin ≤1.5 times the specific institutional upper limit of normal (ULN) (except patients with Gilbert's syndrome, who must have total bilirubin <3 mg/dL) b. AST and ALT each ≤1.5 x ULN (or ≤2.0 x ULN in the presence of known or suspected hepatic involvement) 10) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity of 25 IU/L or equivalent units of human chorionic gonadotropin) performed at screening and within 24 hours prior to the start of study treatment. 11) Females of childbearing potential must be willing to abstain from heterosexual activity or use an effective method of contraception from the time of informed consent until 5 months after the last dose of investigational product 12) Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men receiving study drugs and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 7 months after the last dose of investigational product. 13) Able to understand and comply with study procedures. **Exclusion Criteria:** 1) PTCL histology consistent with ATLL 2) A history of, or a concurrent, clinically significant illness, medical condition or laboratory abnormality that, in the investigator's opinion, could affect the conduct of the study. 3) Active infection requiring systemic therapy. 4) Recent (<100 days) autologous stem cell transplant, or previous allogeneic stem cell transplant. 5) Known positive test for hepatitis B surface antigen, hepatitis C, or HIV 6) Pregnant or breastfeeding female. 7) Known additional malignancy that is active/progressive requiring treatment. Exceptions include: a. basal cell skin cancer

	b. squamous cell skin cancer c. in situ cervical cancer d. in situ bladder cancer 8) Prior treatment with cabiralizumab 9) Prior treatment with nivolumab or other medications within the checkpoint blockade family. Please see body of protocol for full exclusion criteria.
STATISTICAL CONSIDERATIONS	We propose a two-stage design with co-primary endpoints of complete response (CR) and overall response (OR), testing a "both-and" null hypothesis against an "either-or" alternative hypothesis. Specifically, we posit that a CRR of 30% or ORR of 60% is achievable. Initially, 17 eligible patients will be followed for response. At this point, if fewer than 3 patients demonstrate CR (<18%) and fewer than 7 patients demonstrate OR (<41%), the trial will be stopped for futility. Otherwise, we will enroll an additional 16 patients, and the trial will successfully conclude if at least 7 patients (out of 33 total) demonstrate CR (21%) or at least 17 patients demonstrate OR (52%). When the true CRR and ORR are simultaneously no greater than 10% and 30%, respectively, this design will successfully conclude with probability at most 0.05 (one-sided type I error) and stop at the interim analysis with probability at least 0.75. When the true CRR is at least 30% or the true ORR is at least 60%, this design will successfully conclude with probability at least 0.62 (power) and stop for futility at the interim analysis with probability at most 0.34. Multiple Grade 4+ adverse event (AE) stopping rules will be applied during enrollment of the first 17 patients. First, enrollment will stop for any grade 4 AE observed in ≥7 (7/17=41%) patients. Second, enrollment will stop for grade 4 AE requiring discontinuation of treatment, as specified in the protocol, observed in ≥3 (3/17=12%) of patients. Third, enrollment will stop if any Grade 5 AE is observed within the first 17 subjects. Peripheral T-cell lymphoma response and progression will be assessed using the provisional Lugano lymphoma response to immunomodulatory therapy criteria (LYRIC). Additional secondary endpoints include response by Lugano criteria, PFS, DCR, DOR, and TNT. Safety assessments will consist of the surveillance and recording of AEs and documentation of physical examination findings and laboratory data. Type, incidence, severity, seriousness, and relatedness of adverse events will be recorded.
TOTAL NUMBER OF SUBJECTS	33
ESTIMATED ENROLLMENT PERIOD	18 months
ESTIMATED STUDY DURATION	60 months

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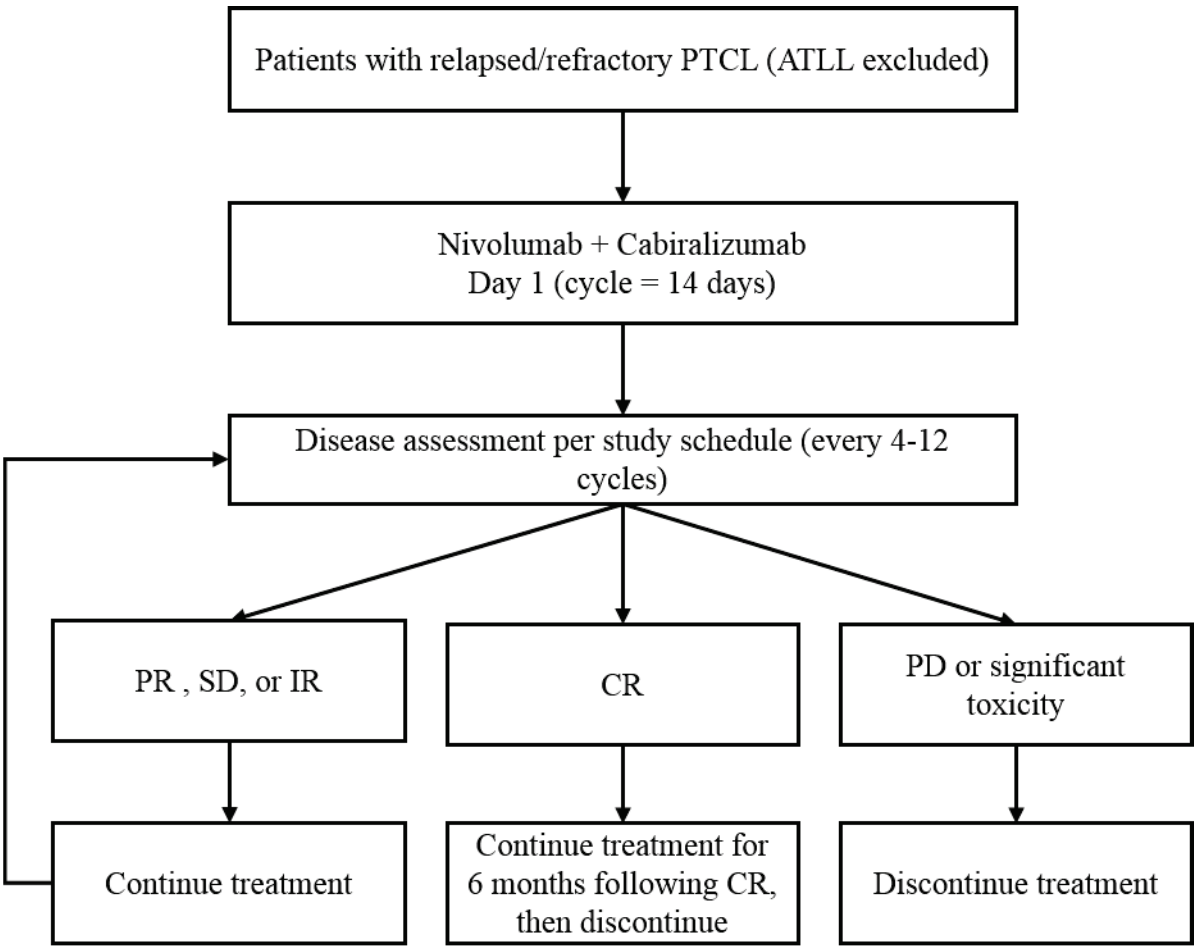
SCHEMA


Patients with relapsed/refractory PTCL (ATLL excluded)
Nivolumab + Cabiralizumab
Day 1 (cycle = 14 days)
Disease assessment per study schedule (every 4-12 cycles)
PR , SD, or IR
CR
PD or significant toxicity
Continue treatment
Continue treatment for 6 months following CR, then discontinue
Discontinue treatment

1. BACKGROUND AND RATIONALE

1.1 Background: Peripheral T Cell Lymphoma (PTCL)

Approximately 10-15% of non-Hodgkin lymphomas (NHL) are derived from mature (i.e. post-thymic) T lymphocytes [1]. The heterogeneity of these lymphomas and poor understanding of their pathogenesis continue to impede their classification and the development of novel therapeutic strategies. This is highlighted by the sobering observation that the most common subtype of peripheral T-cell lymphoma (PTCL) lacks any distinguishing characteristics and is designated by the World Health Organization as "PTCL, not otherwise specified (PTCL, NOS)" [1, 2]. While the development of combination immunochemotherapy (e.g. "R-CHOP") has led to significant survival benefits in B-cell NHL, the PTCLs are associated with inferior responses to therapy and overall survival [3]. In fact, the vast majority of PTCL patients will ultimately succumb to their disease, most within a few years of diagnosis [1, 2, 4]. Novel therapeutic strategies are needed if improved outcomes are to be achieved. The observation that PTCL incidence rates are increasing faster than almost any other subgroup of NHL further heightens this sense of urgency [5, 6].

Anthracycline-based therapies (e.g. CHOP) remain the mainstay of therapy for PTCL, even though the survival benefit associated with this approach remains suboptimal[2, 7]. More intensive induction regimens and consolidation with high-dose chemotherapy followed by autologous stem-cell transplantation are frequently employed strategies, but primary refractory disease and early relapses are common. Three novel agents, belinostat, pralatrexate and romidepsin, were granted FDA approval for relapsed/refractory PTCL and are associated with overall response rates of approximately 26% [8], 29%[9] and 25-38%[10, 11], respectively. A complete response rate of ~11% is observed in patients treated with belinostat or pralatrexate as single agents. Durable complete remissions are rarely achieved with these agents. Consequently, the outlook for PTCL patients with relapsed/refractory disease remains grim, and novel therapeutic strategies are needed[12, 13].

While preliminary results with checkpoint blockade (CPB) are encouraging, it is likely that novel combinatorial strategies will be required to improve outcomes in these patients following CPB [14].

Brentuximab vedotin also received FDA approved for the treatment of relapsed/refractory anaplastic large cell lymphoma (ALCL), a subtype of PTCL, based on phase II, open-label study of 58 patients. The overall response rate in this study was 86% with a complete response rate of 57% with a median duration of 13.2 months [15]. Grade 3/4 adverse events occurred in >10% of patients and included neutropenia, thrombocytopenia, and peripheral sensory neuropathy[15]. Another phase II, open-label, multicenter study evaluated the response rate of Brentuximab vedotin in relapsed CD30+ non-Hodgkin lymphomas which included PTCL and angioimmunoblastic T-cell lymphoma (AITL). The overall response rate in these cases was 41% with a complete response rate of 24% [16]. The duration of response is quite variable and short with the reported median duration of response of 7.6 months; however, the median duration of a complete response had not been reached at the time of the initial analysis[16]. Grade 3/4 events were similar to that of the ALCL study with neutropenia, peripheral sensory neuropathy and hyperkalemia being the most common events [16]. Brentuximab is a promising treatment agent but the most significant limitation is the need for continued treatment which is limited by cytopenias and peripheral neuropathy. Furthermore, the use of brentuximab within PTCL is limited to ALCL. Despite the use of these novel agents, the outlook for PTCL patients with relapsed/refractory disease remains grim, and novel therapeutic strategies are needed.

1.2 Background: Checkpoint blockade (CPB) in PTCL

While durable remissions with conventional chemotherapy are rarely achieved in relapsed/refractory T-cell NHL [12, 13, 17], durable remissions are achieved with immunomodulatory therapies, including extracorporeal photopheresis (ECP) and interferon-α [18]. While largely anecdotal, these observations suggest that host immunity, when properly harnessed, can lead to durable responses in selected patients. These observations, coupled with high-level PD-L1 expression in a substantial minority of patients, further provide a strong rationale for CPB in cutaneous T cell lymphoma (CTCL) and PTCL. While few of these patients have been included in early phase clinical trials and further experience with CPB in CTCL/PTCL is needed, few durable responses have been observed to date. Twenty-three CTCL/PTCL patients were enrolled in a phase Ib study with nivolumab in relapsed/refractory hematologic malignancies[19]. Among heavily pretreated (61% had received ≥4 prior therapies) CTCL/PTCL patients enrolled in this study, no complete remissions and 4 partial remissions were observed, for an overall response rate of 17% [19]. While the median progression-free survival was 10 weeks for all patients, two responding CTCL patients achieved responses that were ongoing at 24+ and 50+ weeks. A single PTCL patient achieved a response that was ongoing at 18+ months. Preliminary data from an ongoing phase II study with pembrolizumab in relapsed/refractory mycosis fungoides (MF) and Sezary syndrome (SS) has been reported[20]. Among 24 patients enrolled, no complete remissions and eight partial remissions were observed, for an overall response rate (ORR) of 33%. Among these responses, four were in MF (44% ORR in MF) and four in Sezary syndrome (27% ORR in SS). Responses were observed in advanced-stage MF, including patients with tumor-stage disease (2/2, ORR 100%) and large-cell transformation (1/3, ORR 33%). While these preliminary results are encouraging, improved understanding of the genomic and immunologic landscapes may be needed to further optimize CPB in the T-cell lymphoproliferative disorders.

1.3 Background: Lymphoma-associated macrophages (LAM) in PTCL

Gene expression by lymphoma-associated macrophages (LAM) and their density within the tumor microenvironment (TME) explain the variable natural history associated with many non-Hodgkin lymphomas. In most cancers, tumor-associated macrophages (TAM) promote tumorigenesis and are alternatively polarized. A growing body of evidence highlights the role of various subsets of myeloid-derived cells, including LAM, in tumorigenesis, and further supports the rationale for their therapeutic targeting in PTCL [21-26]. LAM are abundant constituents of the TME in PTCL, where they promote chemotherapy resistance[21, 24, 26]. Upon activation and differentiation, normal $CD4^+$ T cells produce cytokines that regulate LAM biology, including type 1 (IFN-γ) and type 2 (IL-4, IL-13) cytokines, which lead to “classical” and “alternative” pathways of LAM activation and functional polarization, respectively. Cytokines produced by malignant T cells similarly promote LAM recruitment/expansion within the TME [21], their functional (“alternative”) polarization [24], and PD-L1 expression [22]. For example, we have shown that IL-10 promotes alternative macrophage polarization in TCL and suppress anti-tumor immunity in a manner that is, at least partially, PD-L1 (B7-H1) dependent. Collectively, this data suggests that depletion of LAM in the T-cell lymphomas may impair the growth and survival of malignant T cells and reverse immune suppression within the TME, potentially augmenting the efficacy of novel immunotherapies, including checkpoint blockade, as demonstrated in other tumor models[27].

We have shown that PD-L1 is expressed by malignant T cells in 5-33% of PTCL, depending on the histologic subtype examined[22]. More commonly, PD-L1 is expressed by myeloid-derived cells, including LAM, within the TME in 22-73% of PTCL subtypes[22]. PD-L1 suppresses T-cell immunity both directly and indirectly, by inducing the generation of $FoxP3^+$ regulatory T cells (Treg)[22]. The extent to which immunomodulatory strategies, including LAM depletion, may improve responses to

checkpoint blockade in T-cell lymphomas is currently unknown, but warrants scrutiny in appropriately designed clinical trials.

While a number of tumor-derived factors have been implicated in the recruitment and survival of LAM, colony-stimulating factor-1 (CSF-1, or M-CSF) is required for normal macrophage homeostasis and viability. Mice lacking functional CSF-1 or nullizygous for CSF-1 receptor (CSF-1R, c-fms, CD115) have a marked decrease in tissue resident macrophages. Therefore, inhibition of CSF-1R has emerged as a rational therapeutic strategy in many solid tumors and hematologic malignancies[28-32]. We have demonstrated in pre-clinical in vitro studies that CSF-1R blockade prevents the generation of LAM in a variety of hematologic malignancies[33]. Neutralizing monoclonal antibodies have also been utilized to deplete lymphoma-associated macrophages and inhibit lymphoma progression in preclinical models[30, 34], and bolster response rates to checkpoint blockade[35].

In addition to its role in regulating LAM, CSF-1R may directly promote the growth and survival of malignant T cells due to is aberrant expression by malignant T cells and B cells in classical Hodgkin lymphoma (cHL)[36]. We have observed that CSF-1R, the expression of which is normally confined to myeloid-lineage cells, is aberrantly expressed in various T-cell lymphomas (and cHL). CSF-1R expression was examined by immunohistochemistry in a large cohort of PTCL specimens, and its expression (2-3+, >50% of PTCL cells) observed in 32% of PTCL, NOS, 69% of ALCL, and 40% of CTCL. Expression was rare in AITL. This lineage-inappropriate expression of CSF-1R is likely explained by activation of an epigenetically deregulated endogenous long-terminal repeat that drives transcription of an aberrant CSF-1R transcript[36]. CSF-1R signaling regulates cell growth, survival, and motility by activating many important pathways, including PI3K/AKT, ERK, and NF-κB. Therefore, CSF-1R may similarly promote the growth and survival of malignant T cells. To address that possibility, loss-of-function studies were performed in CSF-1R-expressing T-cell lymphoma cell lines that have been lentivirally transduced with an inducible non-targeting or CSF-1R-targeting shRNAs. We have shown that CSF-1R knockdown significantly inhibits cell growth and proliferation in these cells (data not shown). When CSF-1R$^+$ PTCL cell lines were grown as xenografts in immunodeficient (NSG) mice, administration of PLX3397 (a CSF-1R kinase inhibitor) significantly impaired tumor growth compared with sham treated controls. Further studies to elucidate the signaling mechanism(s) exploited by CSF-1R when expressed by malignant T cells are ongoing, using genetic and pharmacologic approaches.

The median overall survival of relapsed/refractory PTCL in patients that are not candidates for high-dose therapy and autologous stem-cell transplantation is <6 months[12, 13]. The dismal outcomes observed in relapsed/refractory PTCL are explained, at least in part, by the high-rate of chemotherapy resistance and high proliferation rates observed. The aggressive behavior of these lymphomas poses a challenge for immunotherapeutic strategies, as disease progression may outpace the host anti-tumor immune response elicited by therapeutic strategies, including checkpoint blockade, leading to cytokinetic failure. Therefore, therapeutic strategies, including CSF-1R inhibition, that may bolster anti-tumor immunity (upon LAM depletion) and slow the rate of disease progression (due to inhibition of CSF-1R's cell-autonomous effects on malignant lymphocytes) are extremely attractive.

1.4 Current Standard of Care

Anthracycline-based therapies (e.g. CHOP) remain the mainstay of therapy for PTCL, even though the survival benefit associated with this approach remains suboptimal[2, 7]. More intensive induction regimens and consolidation with high-dose chemotherapy followed by autologous stem-cell transplantation are frequently employed strategies, but primary refractory disease and early relapses are

common. Three novel agents, belinostat, pralatrexate and romidepsin, were granted FDA approval for relapsed/refractory PTCL and are associated with overall response rates of approximately 26% [8], 29%[9] and 25-38%[10, 11], respectively. A complete response rate of ~11% is observed in patients treated with belinostat or pralatrexate as single agents. Durable complete remissions are rarely achieved with these agents. Consequently, the outlook for PTCL patients with relapsed/refractory disease remains grim, and novel therapeutic strategies are needed[12, 13].

1.5 Investigational Treatment - Nivolumab

For the most current pre-clinical and clinical information on nivolumab, please refer to the Investigator's Brochure (IB). IB version 16 was used in the development of this protocol.

Mechanism of Action

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

Pharmacokinetics

The pharmacokinetics (PK) of nivolumab was studied in subjects over a dose range of 0.1 to 10 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. The geometric mean (CV%) clearance (CL) was 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state (Vss) was 8.0 L (30.4%), and geometric mean elimination half-life (t1/2) was 26.7 days (101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was approximately 3-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. Additionally, nivolumab has a low potential for drug-drug interactions. 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, solid 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. PPK analysis suggest that nivolumab CL in subjects with cHL was approximately 32% lower relative to subjects with NSCLC; however, the lower CL in cHL subjects was not considered to be clinically relevant as nivolumab exposure was not a significant predictor for safety risks for these patients. 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. A flat dose of nivolumab 240 mg Q2W was selected since it is identical to a dose of 3 mg/kg for subjects weighing 80 kg, the observed median body weight in nivolumab-treated cancer patients. Using a PPK model, the overall distributions of nivolumab exposures (Cavgss, Cminss, Cmaxss, and Cmin1) are comparable after treatment with either 3 mg/kg or 240 mg nivolumab. The predicted range of nivolumab exposures (median and 90% prediction intervals) resulting from a 240 mg flat

dose across the 35 to 160 kg weight range is maintained well below the corresponding exposures observed with the well tolerated 10 mg/kg nivolumab Q2W dosage.

Safety
The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 16,900 subjects treated to date. For monotherapy, the safety profile is similar across tumor types. There is no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. In Phase 3 controlled studies, the safety profile of nivolumab monotherapy is acceptable in the context of the observed clinical efficacy, and manageable using established safety guidelines. Clinically relevant AEs typical of stimulation of the immune system were infrequent and manageable by delaying or stopping nivolumab treatment and timely immunosuppressive therapy or other supportive care. In several ongoing clinical trials, the safety of nivolumab in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies is being explored. Most studies are ongoing and, as such, the safety profile of nivolumab combinations continues to evolve. The most advanced combination under development is nivolumab + ipilimumab, which is approved in subjects with unresectable or metastatic melanoma, and being studied in multiple tumor types. Results to date suggest that the safety profile of nivolumab+ipilimumab combination therapy is consistent with the mechanisms of action of nivolumab and ipilimumab. The nature of the AEs is similar to that observed with either agent used as monotherapy; however, both frequency and severity of most AEs are increased with the combination.

Across all studies conducted to date, drug-related AEs have included pulmonary toxicity, renal toxicity (including acute renal failure), endocrine abnormalities, GI toxicity, dermatologic toxicity (including rash), and hepatotoxicity. For nivolumab monotherapy and combination therapy, the majority of these AEs have been managed successfully with supportive care and, in more severe cases, a combination of dose delay, permanent discontinuation, and/or use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in the management guidelines provided in Appendix 17.1.

Summary of relevant clinical studies
The PK, clinical activity, and safety of nivolumab have been assessed in approximately 70 clinical studies sponsored by BMS, ONO, or other partners. Safety information is available in Section 5.6 of the IB. The description and status of studies with reference safety information are provided in Appendix 4 of the IB. Across those studies, approximately 16,900 subjects have received nivolumab monotherapy in single- or multiple-dose Phase 1/2/3 studies or studies with nivolumab in combination with other therapeutics (ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies).

Rationale for starting dose
The starting dose of nivolumab (240 mg every 2 weeks) has been chosen based on previous phase I and II data regarding safety and efficacy of nivolumab. This is the FDA approved dosing in numerous other tumor types including cHL.

Metabolism and route(s) of elimination
Nivolumab is an IgG4 monoclonal antibody, which is eliminated by mechanisms similar to that of

other antibodies, namely by non-specific catabolism (mainly by enzymes in the reticuloendothelial system)[37]. Steady-state concentrations of nivolumab were reached by approximately 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was approximately 3.7-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 clearance of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1, solid tumor type, baseline tumor size, and hepatic impairment. Although ECOG status, baseline glomerular filtration rate (GFR), albumin, and body weight had an effect on nivolumab CL, the effect was not clinically meaningful. PPK analysis suggested that nivolumab CL in subjects with cHL was approximately 32% lower relative to subjects with NSCLC; however, the lower CL in cHL subjects was not considered to be clinically relevant as nivolumab exposure was not a significant predictor for safety risks for these patients.

Drug interactions
Although monoclonal antibodies are not direct inhibitors/inducers of metabolizing enzymes, recent literature reports suggest that therapeutic proteins that are modulators of cytokines may indirectly affect expression of cytochrome (CYP) enzymes[38]. The indirect drug-drug interaction potential of nivolumab was assessed using systemic cytokine modulation data for cytokines known to modulate CYP enzymes, at single and multiple doses of 0.3 to 10 mg/kg Q3W from CA209009. There were no meaningful changes in cytokines known to have indirect effects on CYP enzymes across all dose levels of nivolumab (0.3, 2 and 10 mg/kg) during the course of treatment. This lack of cytokine modulation suggests that nivolumab has no or low potential for modulating CYP enzymes, thereby indicating a low risk of therapeutic protein-drug interaction. Nivolumab is an IgG4 monoclonal antibody, which is eliminated by mechanisms similar to that of other antibodies, namely by non-specific catabolism (mainly by enzymes in the reticuloendothelial system)[37]. These enzymes are not known to be inhibited or induced by drugs, and therefore it is unlikely that other drugs will have an impact on the PK of nivolumab.

1.6 Investigational Treatment - Cabiralizumab

For the most current pre-clinical and clinical information on cabiralizumab, please refer to the Investigator's Brochure (IB). IB version 6 was used in the development of this protocol.

Mechanism of Action
Cabiralizumab (BMS-986227) is a recombinant, humanized IgG4 monoclonal antibody that binds to human CSF1R. Binding of BMS-986227 to CSF1R antagonizes binding of CSF1 and IL34, the 2 ligands to CSF1R, thereby preventing activation of CSF1R. CSF1R signaling plays a fundamental role in the differentiation, maintenance, and function of monocytic lineage cells including monocytes, macrophages, and osteoclasts[39]. Two ligands have been identified for CSF1R, CSF1 and IL34. These 2 ligands share little amino acid homology, but both bind similar regions of the CSF1R with similar affinities (reviewed in [40]).

The tumor microenvironment, composed of non-cancer cells and stroma, is recognized as a major factor influencing the growth of tumor cells. Tumor-associated macrophages (TAMs) are particularly abundant in the tumor microenvironment and are thought to play a key role in promoting tumor growth. Substantial evidence suggests that TAMs are polarized towards an anti-inflammatory phenotype and

through the expression of cell surface T cell inhibitors and immunosuppressive soluble factors play a major role in inhibiting anti-tumor immune responses[41]. In the majority of tumors, TAMs are associated with a poor prognosis[42], making TAMs an attractive therapeutic target. Because CSF1 is a major survival factor for TAMs, targeting CSF1R through BMS-986227 should reduce tumor-associated macrophage-mediated immune suppression resulting in strengthening the anti-tumor response to immunotherapy.

1.6.1 Cabiralizumab Clinical Summary

The clinical summary of safety and efficacy is based on three clinical studies:

1. Study FPA008-001 evaluated the safety of cabiralizumab as single or double ascending doses in 48 healthy volunteers (36 received cabiralizumab and 12 received placebo). This study also evaluated the safety and efficacy of cabiralizumab administered as two or three doses, 14 days apart, in 18 rheumatoid arthritis (RA) subjects. This study has been completed.
2. Study FPA008-002 is evaluating the safety and efficacy of cabiralizumab monotherapy for 6 months in approximately 40 subjects with pigmented villonodular synovitis (PVNS).
3. Study FPA008-003 is evaluating the safety and efficacy of cabiralizumab as monotherapy and in combination with nivolumab in approximately 295 subjects with advanced cancers.

Clinical Pharmacology Summary (Pharmacokinetics, Immunogenicity, and Pharmacodynamics)
The available PK, ADA, and nonclassical CD16+ monocyte status following cabiralizumab treatment with either monotherapy or in combination with nivolumab were characterized in three trials: FPA008 001, FPA008-002, and FPA008-003. The PK, ADA, and nonclassical CD16+ monocyte data from Study FPA008-003 are summarized below; data from Studies FPA008 001 and FPA008-002 are presented in the cabiralizumab IB.

The PK profile of cabiralizumab is characterized by linear and nonlinear clearance pathways, with the latter likely mediated by binding to CSF1R on cells. As monocyte and macrophage cells are dependent on CSF1R for viability, these target-bearing cells are reduced in number following cabiralizumab treatment, resulting in a decrease of target-mediated clearance. Once target mediated clearance is saturated at high or repeat doses, cabiralizumab clearance is similar to other human IgG antibodies.

Study FPA008-003 – Advanced Cancer (Cabiralizumab Monotherapy)
In Phase 1a, subjects with cancer received cabiralizumab at doses of 2, 4, and 6 mg/kg Q2W as monotherapy and 1, 2, and 4 mg/kg Q2W in combination with 3 mg/kg nivolumab Q2W. There were a total of 25 subjects (n = 16 for monotherapy and n = 9 for combination treatment) with PK data as of 15 December 2016. Blood samples for determination of serum cabiralizumab concentration were collected before dosing and at various times through the study. Blood samples for determination for anti-FPA008 antibodies were collected before dosing and at various time points from Day 15 to end-of-treatment follow-up.

Following the first dose in cancer subjects at 2, 4, and 6 mg/kg as monotherapy or at 1, 2, and 4 mg/kg in combination with nivolumab, Cmax increased dose proportionally, while AUC and Cmin increased more than dose proportionally, suggesting target-mediated clearance. Accumulation was observed for Cmax and Cmin with ≥ 2 mg/kg Q2W dosing. Exposures were similar at 4 mg/kg for cabiralizumab as monotherapy and in combination with nivolumab (limited data).

Assessment of nonclassical CD16+ monocytes in Study FPA008-003 has been evaluated in cohorts receiving 2, 4, or 6 mg/kg cabiralizumab monotherapy. In addition, assessment of nonclassical CD16+ monocytes has been evaluated in cohorts receiving a combination of 1, 2, or 4 mg/kg cabiralizumab with 3 mg/kg nivolumab. In the 2 mg/kg monotherapy cohort, cabiralizumab reduced nonclassical CD16+ monocytes throughout the 2-week dosing interval in 2 of 3 subjects evaluated. In the 4 mg/kg monotherapy cohort, cabiralizumab reduced nonclassical CD16+ monocytes throughout the 2-week dosing interval in 9 of 10 subjects and monocyte levels begin to rise as cabiralizumab is cleared from the circulation in one subject who is evaluable. In the 6 mg/kg monotherapy cohort of cabiralizumab, all subjects showed reduction of nonclassical CD16+ monocytes through the 2-week dosing interval. End-of-treatment follow-up data are pending.

In the cohort receiving the combination of cabiralizumab at 1 mg/kg plus nivolumab, nonclassical CD16+ monocytes were reduced at 72 hours, but reduction was not maintained through the dosing interval. Nonclassical CD16+ monocytes returned to baseline levels in one subject and increased above baseline levels in two subjects. In the cohort receiving the combination of cabiralizumab at 2 mg/kg plus nivolumab, nonclassical CD16+ monocytes were reduced within 4 days of the first dose. However, in 2 of the 3 subjects dosed with 2 mg/kg, cabiralizumab in combination with nivolumab was insufficient to reduce nonclassical CD16+ monocytes throughout the 2-week dosing interval. In the cohort receiving 4 mg/kg cabiralizumab plus nivolumab, nonclassical CD16+ monocytes were reduced below the detection limits of the assay in all 3 subjects. Insufficient end-of-treatment follow-up data are available at this time.

Based on a review of PK and PD, the recommended dose for this study has been chosen as 4 mg/kg cabiralizumab in combination with 240 mg nivolumab every two weeks.

1.6.2 Clinical Safety Summary

Study FPA008-003 is evaluating the safety, PK, and efficacy of escalating doses of cabiralizumab monotherapy and in combination with nivolumab in subjects with selected advanced solid tumors The study includes a Phase 1a dose escalation, Phase 1a dose exploration cohorts, and a Phase 1b dose expansion.

As of the data cutoff date of 02-Jul-2018, a total of 312 subjects have been treated in Study FPA008-003; 24 subjects have been treated in the Phase 1a monotherapy cohorts, 16 subjects have been treated in the Phase 1a dose-escalation combination cohorts, and 272 subjects have been treated in the Phases 1a and 1b dose-expansion combination cohorts. A total of 265 subjects across the study were treated with the recommended dose of 4 mg/kg cabiralizumab + 3 mg/kg nivolumab Q2W, and the overall safety of these subjects is reported independently. This study is ongoing, but enrollment is completed. Preliminary safety data are described below.

1.6.2.1 Phase 1a Dose Escalation (Monotherapy)

Adverse Events

As of 02-Jul-2018, AEs were experienced by 22 of 24 (91.7%) subjects treated in Phase 1a monotherapy dose-escalation cohorts. There were no Grade 5 AEs experienced by any subject in Phase 1a monotherapy dose-escalation cohorts.

Treatment-related AEs

Treatment-related AEs were experienced by 17 of 24 (70.8%) subjects who received cabiralizumab monotherapy. The most commonly reported (≥ 25% of subjects) treatment-related AEs included AST increased (8 [33.3%] subjects), fatigue and periorbital oedema (7 [29.2%] subjects each), and blood creatine phosphokinase increased (6 [25.0%] subjects). The incidence of the treatment-related AEs that occurred in > 10% of the subjects is listed in Table 5.5.3.1-1 located in cabiralizumab IB v6. There were no Grade 5 treatment-related AEs experienced by any subject in Phase 1a monotherapy.

Serious Adverse Events
Of the 24 subjects receiving cabiralizumab monotherapy, 8 (33.3%) subjects experienced at least 1 SAE. Treatment-related SAEs occurred in 2 of 24 (8.3%) subjects and included Grade 3 blood creatine phosphokinase increase (1 [4.2%] subject) and Grade 3 rash (1 [4.2%] subject).

Dose-limiting Toxicities
Four DLTs were reported in the Phase 1a monotherapy arms of this study. One of the DLTs was a Grade 3 CK increase, and the other 3 DLTs were Grade 3 AST increases. The Grade 3 CK increase and 1 Grade 3 AST increase occurred at 6 mg/kg cabiralizumab monotherapy, and the other 2 Grade 3 AST increases occurred at 4 mg/kg cabiralizumab monotherapy. All DLTs resolved after discontinuation of study drug with no sequelae. These DLTs were all attributed to isolated increases in laboratory values (3 subjects due to elevation of AST and 1 subject due to elevation of CK), which were expected with administration of FPA008 due to diminished clearance of ALT, AST, CK, and LDH molecules from serum secondary to a reduced number of liver Kupffer cells. Based on this information, the management algorithms for hepatic AEs and liver enzyme alterations have been subsequently amended to allow higher cutoffs for these laboratory values as described in sections 17.1.2 and 17.1.3.

Discontinuations
A total of 3 of 24 (12.5%) subjects receiving cabiralizumab monotherapy discontinued study treatment due to a treatment-related AE, including Grade 3 AST increased (2 [8.3%] subjects) and Grade 3 blood creatine phosphokinase increased (1 [4.2%] subject).
Deaths
A total of 14 of 24 (58.3%) subjects receiving cabiralizumab monotherapy died during the course of Phase 1a monotherapy. No subjects died due to an AE.

Conclusion
Administration of cabiralizumab, as monotherapy, presents a tolerable safety profile. The most frequent AEs (AST and blood creatine phosphokinase increased) are aligned to the specific MOA of the molecule and can be managed by following the specific algorithms developed for cabiralizumab.

1.6.2.2 Phase 1a Combination Therapy Dose Escalation

Adverse Events
As of 02-Jul-2018, in the Phase 1a combination therapy dose-escalation cohorts, AEs were experienced by 15 of 16 (93.8%) subjects treated. In the Phase 1a combination therapy dose-escalation cohorts, 2 (12.5%) subjects had Grade 5 events, which included respiratory failure and treatment-related pneumonitis (1 subject each).

Treatment-related Adverse Events
In the Phase 1a combination therapy dose-escalation cohorts, treatment-related AEs were experienced by 13 of 16 (81.3%) subjects. The most commonly reported (≥ 3 subjects) treatment-related AEs included fatigue (8 [50%] subjects); periorbital oedema (7 [43.8%] subjects); and rash, blood creatine phosphokinase increased, AST increased, rash maculopapular, pruritus, and pneumonitis (3 [18.8%] subjects each). The incidence of the treatment-related AEs that occurred in > 10% of the subjects is listed in Table 5.5.3.2-1 in cabiralizumab IB v6. There was 1 (25%) subject in Cohort 1aC1 that experienced a Grade 5 treatment-related AE of pneumonitis. The subject, a 65-year-old female Caucasian, was diagnosed with pneumonitis and required intensive care, ventilation, and high doses of steroids. Despite the intensive care received, the subject experienced worsening of the pneumonitis and received 2 doses of infliximab. Over the course of the hospitalization, the pneumonitis became refractory to all medical therapies, and the subject developed Grade 4 pulmonary embolus, which was considered not related to study drug. Both the pneumonitis and pulmonary embolus led to respiratory failure, which led to death.

Serious Adverse Events
In the Phase 1a combination therapy dose-escalation cohorts, 6 of 16 (37.5%) subjects experienced at least 1 SAE. Treatment-related SAEs occurred in 2 of 16 (12.5%) subjects and included Grade 5 pneumonitis (1 [6.3%] subject) and Grade 3 colitis (1 [6.3%] subject).

Dose-limiting Toxicities
No DLTs were reported in the Phase 1a dose-escalation combination therapy arm of this study.

Discontinuations
In the Phase 1a combination therapy dose-escalation cohorts, 2 of 16 (12.5%) subjects discontinued study treatment due to a treatment-related AE and included Grade 4 pneumonitis (1 [6.3%] subject) and Grade 3 colitis (1 [6.3%] subject).

Deaths
In the Phase 1a combination therapy dose-escalation cohorts, 10 of 16 (62.5%) subjects died. One of 16 (6.3%) subjects died due to a treatment-related AE of pneumonitis.

Conclusion
The combination of cabiralizumab and nivolumab, as tested in Phase 1a combination therapy dose-escalation cohorts, presents a tolerable safety profile. The most frequent AEs (periorbital oedema, blood creatine phosphokinase, and AST increased) are aligned to the specific MOA of the molecule and, as described above, can be managed by following the specific algorithms developed for cabiralizumab.

1.6.2.3 Overall Safety of 4 mg/kg Cabiralizumab in Combination with 3 mg/kg Nivolumab Q2W (Cohort 1aC3 Dose Escalation, Cohorts 1b1-1b7 Dose Expansion, and Cohorts 1aE2-1aE4 Dose Exploration)

Adverse Events
As of 02-Jul-2018, AEs have been experienced by 264 of 265 (99.6%) subjects treated with 4 mg/kg cabiralizumab + 3 mg/kg nivolumab Q2W across multiple cohorts.

Treatment-related Adverse Events
Treatment-related AEs were experienced by 245 of 265 (92.5%) subjects. The most commonly reported (> 17% of subjects) treatment-related AEs included blood creatine phosphokinase increased (122 [46.0%] subjects), periorbital oedema (115 [43.4%] subjects), fatigue (102 [38.5%] subjects), AST increased (100 [37.7%] subjects), ALT increased and amylase increased (51 [19.2%] subjects each), rash (50 [18.9%] subjects), and pruritus (47 [17.7%] subjects). The incidence of the treatment-related AEs that occurred in > 10% of the subjects is listed in Table 5.5.3.3-1. Grade 5 treatment-related AEs were experienced by 3 (1.1%) subjects and included acute respiratory failure (2 [0.8%] subjects) and respiratory distress (1 [0.4%] subject). These are described below.

- A 65-year-old male Caucasian subject with NSCLC in Cohort 1b1 experienced a multifactorial acute respiratory failure, with potential contributing pneumonia, pneumonitis, and chemotherapy-related pneumonitis that, despite the administration of high doses of steroids, led to death.
- A 79-year-old male Caucasian subject with NSCLC in Cohort 1b1 experienced multiple episodes of pneumonitis that, in association with the underlying COPD and despite the administration of high doses of steroids, led to death.
- A 69-year-old male Caucasian subject with NSCLC in Cohort 1b1 with a positive history of cardiac disease experienced multiple episodes of dyspnea with progressive degeneration of cardiac function, which led to acute respiratory distress and death. The investigator confirmed that there was no evidence of non-ST elevation myocardial infarction (NSTEMI) on ECG results and no specific test determining myocarditis.
-

The incidence of the treatment-related AEs that occurred in > 10% of the subjects is listed in Table 5.5.3.3-1 in cabiralizumab IB v6.

Serious Adverse Events
A total of 134 of 265 (50.6%) subjects receiving 4 mg/kg cabiralizumab + 3 mg/kg nivolumab Q2W experienced at least 1 SAE. Treatment-related SAEs occurred in 47 of 265 (17.7%) subjects. The incidence of the treatment-related SAEs is listed in Table 5.5.3.3-2 in cabiralizumab IB v6.

Discontinuations
A total of 46 of 265 (17.4%) subjects receiving 4 mg/kg cabiralizumab + 3 mg/kg nivolumab Q2W discontinued study treatment due to an AE. A total of 43 of 265 (16.2%) subjects discontinued study treatment due to a treatment-related AE. The incidence of the treatment-related AEs is listed in Table 5.5.3.3-3 in cabiralizumab IB v6.

Deaths
A total of 128 of 265 (48.3%) subjects receiving 4 mg/kg cabiralizumab + 3 mg/kg nivolumab Q2W died during the course of the study. A total of 17 of 265 (6.4%) subjects died due to an AE, and treatment-related Grade 5 AEs were experienced by 3 of 265 (1.1%) subjects and included acute respiratory failure (2 [0.8%] subjects) and respiratory distress (1 [0.4%] subject).

Conclusion
The combination of 4 mg/kg cabiralizumab + 3 mg/kg nivolumab Q2W appears to be well tolerated. The most frequent treatment-related AEs (blood creatine phosphokinase increased, periorbital oedema, fatigue, AST increased, amylase increased, and ALT increased) are aligned to the MOA of

cabiralizumab or nivolumab and can be managed by following the specific algorithms developed for this specific combination. Of note, despite the high frequency of treatment-related AEs (92.5%), only a minority (16.2%) of the subjects treated with 4 mg/kg cabiralizumab + 3 mg/kg nivolumab Q2W discontinued the treatment due to a treatment-related AE.

1.6.3 Clinical Experience Involving Serum Enzyme Elevations

The safety and preliminary efficacy of cabiralizumab has been evaluated in multiple clinical trials as described in IB v6. A common feature observed across the clinical trials is an elevation of AST, CK, and LDH after the administration of cabiralizumab. These alterations are the consequence of the direct effect of anti-CSF1R antibodies on the Kupffer cell in the liver that results in a depletion of these cells. Depletion of Kupffer cells allows the enzymes, which are released following normally occurring liver cell turnover, to enter circulation (where they are measured by routine laboratory assessment) rather than being absorbed by the Kupffer cells. Elevated liver enzymes, thus, represent a PD marker rather than a safety signal. The observed elevations were asymptomatic not permanent and not associated with clinical sequelae. Similar effects have been observed across other CSF1R targeted agents (see cabiralizumab IB for additional details). The data with cabiralizumab and with other agents in the class suggest that the observed serum enzyme elevations do not compromise the safety profile of cabiralizumab and therefore support modification of the safety monitoring criteria.

Serum Enzyme Elevations in Cabiralizumab

See above sections for descriptions of serum enzyme elvations in various clinical trials. Based on phase 1a data from FPA008 003, the management algorithms for hepatic AEs and liver enzyme alterations have been subsequently amended to allow higher cutoffs for serum hepatic enzyme elevations as described in sections 17.1.2 and 17.1.3.

The new algorithms have been used to re-evaluate the safety of 4 mg/kg cabiralizumab monotherapy (7 subjects) and 4 mg/kg cabiralizumab in combination with 3 mg/kg nivolumab (3 subjects). No DLTs were reported in subjects treated at these doses under the revised algorithms.

Since then, approximately 274 subjects have been treated with 4 mg/kg cabiralizumab in combination with 3 mg/kg nivolumab using the new management algorithms for hepatic AE and liver enzyme, and no Grade 5 hepatic events have been reported, thus confirming the validity of the management algorithms.

Management of Isolated Laboratory Abnormalities

Given the physiologic rationale for asymptomatic serum enzyme elevations, the new proposed management algorithms allow serum enzyme elevations of AST, CK, and LDH up to 20X ULN. To rule out any potential hepatic injury in relation to elevated transaminases, additional monitoring following the DILI Guidance from FDA will be performed for bilirubin, INR, and ALT/AST. In the case of elevated CK, additional assessments will be performed for CK isoenzymes (CK-MM, CK-MB, and CK-BB) and troponins (I or T). The investigator should notify the Sponsor of increased serum levels above specific cutoffs, but below those that would trigger drug modification or discontinuation. Additional monitoring of clinical signs and symptoms known to be associated with hepatic damage, per the FDA DILI Guidance, is recommended. These additional measures should be followed as per the guidance in section 17.1.

Rationale for starting dose
The rationale for starting dose of combination therapy is based upon the dose escalation and expansion phases of FPA008-003 as in the Clinical Summary above. Since PPK and exposure response analyses support the use of 240 mg Q2W dosing in addition to the 3 mg/kg Q2W regimen for nivolumab (see Section 1.5), flat dosing of nivolumab at 240 mg Q2W has been chosen for this trial.

Drug interactions
As with nivolumab, cabiralizumab is not expected to have any drug-drug interactions via CYP enzymes. Its non-specific catabolism via enzymes of the reticuloendothelial enzymes make it unlikely that other drugs with have an impact on the PK of cabiralizumab.

1.7 Rationale

The tumor microenvironment, composed of non-cancer cells and stroma, is recognized as a major factor influencing the growth of tumor cells. Tumor-associated macrophages (TAMs) are particularly abundant in the tumor microenvironment and are thought to play a key role in promoting tumor growth. TAMs can promote angiogenesis (blood vessel formation in tumors), tumor survival, and metastasis, and may confer resistance to current therapies. TAMs are also immunosuppressive and through the release of soluble factors and cell surface T cell checkpoint inhibitors can suppress anti-tumor T cell responses [41]. In the majority of tumors increased numbers of TAMs correlate with poor clinical outcome[42], supporting TAMs as an attractive therapeutic target. Immunosuppressive TAMs are dependent on CSF1 for survival; a drug that inhibits CSF1R could limit the influence of TAMs on the tumor microenvironment and could be complementary and augment current cancer therapies, e.g., checkpoint-based immunotherapies such as antibodies that target the PD1 or CTLA4 pathways.

Targeting the CSF1R pathway with antibodies or small molecule inhibitors has been shown to be effective in mouse tumor models. In a MC38 colon adenocarcinoma model in syngeneic mice, an anti-CSF1R blocking antibody resulted in a significant reduction in TAMs, which was accompanied by a positive shift of the CD8 to CD4 ratio toward cytotoxic CD8 T cells[30]. This was associated with a decrease in FoxP3+ regulatory T cells. These data suggest that other immune effector cells were indirectly influenced by CSF1R blockade. In a mouse proneural glioblastoma multiform model, small molecule inhibition of CSF1R significantly increased survival, and established tumors regressed[29]. In this model, TAMs were not depleted, but in the presence of CSF1R inhibition, were pushed to a more proinflammatory phenotype.

In an orthotopic pancreatic ductal adenocarcinoma (PDAC) model, CSF1R pathway blockade with a small molecule or an anti-CSF1 antibody selectively decreased immunosuppressive TAMs, resulting in decreased immunosuppression, and enabled the remaining pro-inflammatory TAMs to support antigen presentation and bolster the anti-tumor T cell response[44]. This in turn led to an increased interferon response that upregulated T cell checkpoint inhibitors including PD-L1 on tumor cells. This counter regulation served to limit the anti-tumor T cell response through engagement of the T cell inhibitor PD1. Importantly, anti-PD1or anti-CTLA4 treatment was able to overcome the PDL1-mediated inhibition. Anti-PD1 or anti-CTLA4 as single agents showed limited efficacy in restraining PDAC tumor growth but combining these agents with CSF1R blockade potently elicited tumor regression even in large established tumors. These data suggest that reprogramming the TAM compartment in tumors by CSF1R blockade could improve the efficacy of checkpoint-based immunotherapies such as an anti-PD1 blocking antibody.

In a recent clinical study, RG7155 an anti-CSF1R blocking antibody was tested in patients with various types of solid tumors and was shown to substantially reduce CSF1R+ and CD163+ macrophages in tumors[30]. Similar to what was seen in the mouse model, reduction of TAMs was associated with an increase in the CD8 to CD4 T cell ratio, suggesting that TAM reduction leads to an increased CD8 cytotoxic T cell response in humans.

Together these data suggest that targeting CSF1R via BMS-986227 will reduce immunosuppressive TAMs in the tumor microenvironment and improve the efficacy of checkpoint-based immunotherapies such as PD1, PDL1, or CTLA4-blocking antibodies.

This rationale is particularly relevant for the treatment of PTCL. Malignant T cells in PTCL have aberrant expression of CSF1R which can lead to tumor growth (reviewed in section 1.3). Additionally, LAMs, which are dependent upon CSF1 for survival, have a well-established role in tumor progression in PTCL (reviewed in section 1.3). Previous clinical trials have shown significant responses to checkpoint blockade in patients with PTCL (reviewed in section 1.2). Therefore, we propose a multicenter, phase II study of nivolumab and the antagonistic CSF-1R monoclonal antibody cabiralizumab (BMS-986227) in patients with relapsed/refractory PTCL.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objectives

1) To estimate objective response (OR) rate (ORR) to nivolumab and cabiralizumab in relapsed/refractory peripheral T cell lymphoma (PTCL) by LYRIC criteria at 4 months
2) To estimate complete response (CR) rate (CRR) to nivolumab and cabiralizumab in relapsed/refractory peripheral T cell lymphoma (PTCL) by LYRIC criteria at 4 months

2.1.2 Secondary Objectives

1) To estimate ORR and CRR of this combination by Lugano 2014 criteria at 4 months.
2) To estimate the best OR (including PR and CR) at any time on trial by LYRIC and Lugano criteria
3) To estimate progression free survival (PFS)
4) To estimate disease control rate (DCR)
5) To estimate duration of response (DOR)
6) To estimate time to next treatment (TNT)
7) To evaluate the safety and tolerability of the combination of cabiralizumab and nivolumab.

2.1.3 Correlative/Exploratory Objectives

1) To examine the role of lymphoma associated macrophage (LAM), regulatory T cell (Treg), and cytotoxic T lymphocyte (CTL) densities (before and during treatment) as pharmacodynamic and prognostic biomarkers.
2) To examine the role of PD-L1 and CSF-1R expression as pharmacodynamic and prognostic biomarkers.
3) To examine the abundance of “exhausted” T cells in the peripheral blood as a pharmacodynamic and prognostic biomarker.

4) To evaluate the feasibility and utility of minimal residual disease (MRD) monitoring throughout treatment as a pharmacodynamic and prognostic biomarker.
5) To evaluate the role of myeloid derived suppressor cells (MDSC) as a pharmacodynamic and prognostic biomarker.
6) To biobank diagnostic biopsy specimens and other biologic specimens or blood for future correlative studies.

2.2 Endpoints

2.2.1 Primary Endpoints

1. Overall response, as determined by LYRIC criteria (Section17.5), within 4 months of initiation of first cycle
2. Complete response, as determined by LYRIC criteria (Section 17.5), within 4 months of initiation of first cycle

2.2.2 Secondary Endpoints

1. Overall response and complete response by Lugano criteria (Section 17.6) at 4 months.
2. Progression-Free Survival (PFS) as defined in section 9.3.4
3. Duration of Overall Response (DOR), as defined in section 9.3.6
4. Time to Next Treatment (TNT), as defined in section 9.3.7.
5. Adverse events (AEs) using NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.

3. ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

Subject must meet all of the following applicable inclusion criteria to participate in this study:

1. Written informed consent for clinical trial enrollment and mandatory consent for any biopsies as well as HIPAA authorization for release of personal health information. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately.
2. Age ≥ 18 years at the time of consent.
3. ECOG Performance Status of 0-2.
4. Histological confirmation of peripheral T-cell lymphoma (PTCL) with measurable disease on imaging. Adult T-cell leukemia/lymphoma (ATLL) are excluded.
5. Documented disease progression after receiving at least two prior therapeutic regimen including brentuximab vedotin in patients with CD30 positive disease (defined as >10% CD30 positive cells).
6. Prior cancer treatment must be completed at least 28 days prior to registration and the subject must have recovered from all reversible acute toxic effects of the regimen (other than alopecia) to ≤ grade 1 or baseline. Systemic steroids at a dose less than the equivalent of 10 mg/day of prednisone and inhaled, nasal, and topical steroids are permitted. Adrenal replacement steroid doses > 10 mg daily prednisone equivalent in the absence of active autoimmune disease are permitted. Treatment with a short course of steroids (< 5 days) up to 7 days prior to study registration is permitted. Intermittent dexamethasone for the treatment of nausea/emesis is also

permitted.

7. Demonstrate adequate organ function as defined in the table below; all screening labs to be obtained within 28 days prior to registration.

System	Laboratory Value
Hematological	
Absolute Neutrophil Count (ANC)	≥ 1000/mm^3
Platelets (Plt)	≥ 75,000/ mm^3
Renal	
Calculated creatinine clearance	≥ 30 cc/min using the Cockcroft-Gault formula
Serum creatinine	≤1.5 x ULN
Hepatic	
Bilirubin	≤ 1.5 × upper limit of normal (ULN) (except patients with Gilbert's syndrome, who must have total bilirubin <3 mg/dL)
Aspartate aminotransferase (AST)	≤ 1.5 × ULN or ≤ 2 × ULN in the presence of known or suspected hepatic involvement
Alanine aminotransferase (ALT)	≤ 1.5 × ULN or ≤ 2 × ULN in the presence of known or suspected hepatic involvement

8. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity of 25 IU/L or equivalent units of human chorionic gonadotropin) performed at screening and within 24 hours of first dose of investigational treatment. See Section 5.4.1 for definition of childbearing potential.
9. Females of childbearing potential must be willing to abstain from heterosexual activity or use an effective method of contraception from the time of informed consent until 5 months after the last dose of investigational product. See Section 5.4.1 for methods of contraception.
10. Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men receiving study drugs and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 7 months after the last dose of investigational product. See Section 5.4.1 for methods of contraception.
11. As determined by the enrolling physician or protocol designee, ability of the subject to understand and comply with study procedures for the entire length of the study

3.2 Exclusion Criteria

Subjects meeting any of the criteria below may not participate in the study:

1. PTCL histology consistent with ATLL.
2. A history of, or a concurrent, clinically significant illness, medical condition or laboratory abnormality that, in the investigator's opinion, could affect the conduct of the study.
3. Active infection requiring systemic therapy
4. Recent (<100 days) autologous stem cell transplant, or previous allogeneic stem cell transplant.
5. Known positive test for HIV. NOTE: HIV screening is not required.
6. History of any chronic hepatitis as evidenced by the following:
   a) Positive test for hepatitis B surface antigen

b) Positive test for qualitative hepatitis C viral load (by polymerase chain reaction [PCR]). NOTE: Participants with positive hepatitis C antibody and negative quantitative hepatitis C by PCR are eligible. History of resolved hepatitis A virus infection is not an exclusion criterion.

7. Pregnant or breastfeeding. NOTE: breast milk cannot be stored for future use while the mother is being treated on study.
8. Previous malignancies (except non-melanoma skin cancers and *in situ* bladder, gastric, colorectal, endometrial, cervical/dysplasia, melanoma, or breast cancers) unless complete remission was achieved at least 2 years prior to study entry and no additional therapy is required during the study period.
9. Prior treatment with cabiralizumab.
10. Prior treatment with nivolumab or other medications within the checkpoint blockade family.
11. Any unregulated nutritional or herbal supplement or recreational drug within 2 weeks prior to registration which, in the opinion of the study investigator, has the potential to cause hepatic injury.
12. Concomitant use of statins for treatment of hypercholesterolemia. Statins are allowed only if the patient is on a stable dose for over 3 months prior to study registration and is in a stable status without CK elevations.
13. Non-oncology vaccine therapies for prevention of infectious diseases (e.g., human papilloma virus vaccine) within 4 weeks of study registration. The inactivated seasonal influenza vaccine can be given to patients before treatment and while on therapy without restriction. Influenza vaccines containing live virus or other clinically indicated vaccinations for infectious diseases (i.e., pneumovax, varicella, etc.) may be permitted, but must be discussed with the sponsor investigator and may require a study drug washout period before and after administration of vaccine.
14. Known history of sensitivity to infusions containing Tween 20 (polysorbate 20) and Tween 80 (polysorbate 80)
15. History of allergy to any components of cabiralizumab or nivolumab
16. Active, known, or suspected autoimmune disease.
    NOTE: Participants with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, euthyroid participants with a history of Grave's disease (participants with suspected autoimmune thyroid disorders must be negative for thyroglobulin and thyroid peroxidase antibodies and thyroid stimulating immunoglobulin prior to first dose of study treatment), psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll after discussing with the sponsor investigator.
17. Interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected treatment-related pulmonary toxicity.
18. Current or history of clinically significant muscle disorders (e.g., myositis), recent unresolved muscle injury, or any condition known to elevate serum CK levels.
19. Uncontrolled or significant cardiovascular disease including, but not limited to, any of the following:
    a) Myocardial infarction or stroke/transient ischemic attack within the past 6 months
    b) Uncontrolled angina within the past 3 months
    c) Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes)

d) History of other clinically significant heart disease (e.g., cardiomyopathy (impaired LVEF), congestive heart failure with New York Heart Association functional classification III to IV, pericarditis, significant pericardial effusion, or myocarditis)
e) Cardiovascular disease-related requirement for daily supplemental oxygen therapy.

4. SUBJECT REGISTRATION

All subjects must be registered through Big Ten CRC Administrative Headquarters' electronic data capture (EDC) system. A subject is considered registered when an "On Study" date is entered into the EDC system.

Subjects must be registered prior to starting protocol therapy.

5. TREATMENT PLAN

This is a single arm phase II study. Please refer to study schema for overview. Therapy will consist of nivolumab 240 mg IV given over 30 minutes (-5/ +15 minutes) followed by 30 minutes (-5/ +15 minutes) of rest followed by cabiralizumab 4mg/kg IV over 30 minutes (-5/ +15 minutes). Treatment will be given on day 1 of every 14 day cycle. Participants may continue on treatment until withdrawal of consent, death, or initiation of another anti-cancer treatment.

If a trial participant achieves a complete response (CR) per criteria outlined in section 9, they will discontinue study therapy 6 months after confirmed and persistent CR (repeat evaluations required prior to therapy discontinuation as outlined in section 7). This will be followed by a period of observation. Patient will have a physical exam and labs (CBC, CMP, mineral panel, creatine kinase, LDH, amylase, lipase, TSH, free T4, and cortisol) every 3 months during observation. PET-CT will be obtained every 6 months; study labs including PBMC, whole blood, and serum will be collected with every imaging evaluation per the schedule of events in section 7. Observation will continue for a period of 2 years; if at any point during the 2 years of observation the patient relapses, they may resume therapy at the time of disease progression. Upon restarting therapy, the schedule of events will resume as if starting at C1D1 of therapy (ie PET every 4 cycles, every 2 week office visits with applicable labs, etc).

Study treatments				
Product Description / Class and Dosage Form	**Potency/ Route of Administration**	**Blinded or Open Label**	**Packaging**	**Storage Conditions**
Nivolumab (BMS-936558-01) Solution for Injection	100 mg (10 mg/mL)	Open label	Vial	Refer to the label on container
Cabiralizumab (BMS-986227) Solution for Injection	100 mg (20 mg/mL)	Open label	Vial	Refer to the label on container

5.1 Pre-medication and Hydration

In general, the use of pre-medications with nivolumab and cabiralizumab is not anticipated. Pre-medications including anti emetics are permitted if needed. Guidelines for premedication with subsequent cycles to prevent recurrence of infusion reaction are available in section 6.2.

5.2 Nivolumab plus Cabiralizumab Administration

Drug	Dose	Route	Schedule[1]	Cycle Length
Nivolumab	240 mg	Intravenously (IV) over 30 minutes (-5/ +15 min)	Day 1	14 days
Cabiralizumab	4 mg/kg[2]	IV over 30 minutes (-5/ +15 min) beginning 30 minutes (-5/ +15 min) **after** completion of nivolumab	Day 1	

[1] A window of ± 3 days may be applied to all study visits to accommodate observed holidays, inclement weather, scheduling conflicts etc. Date and time of each drug administration should be clearly documented in subject's chart and electronic case report forms (eCRFs).
[2] Cabiralizumab dose should be recalculated if Day 1 weight changes by >10%.

5.3 Concomitant Medications

5.3.1 Allowed Concomitant Medications

All treatments the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care including supportive care medications as outlined below in section 5.4.

5.3.2 Prohibited Concomitant Medications

Drug-drug interactions are not anticipated with the use of either nivolumab or cabiralizumab (see Drug Interactions in sections 1.5 and 1.6)

The following medications are prohibited during the study (unless utilized to treat a drug-related AE or specified in the eligibility section). Medications taken within 4 weeks prior to study drug administration must be recorded on the CRF. See exclusion criteria for full list of prohibited mediacations.

1) Immunosuppressive agents or immunosuppressive doses of systemic corticosteroids
2) Vaccines except as noted in Section 3.2.15.
3) Other anti-neoplastic therapies including biologic, immunotherapy, extensive non-palliative radiation therapy, standard treatments, or investigational agents or devices.
4) Systemic steroids at a dose greater than the equivalent of 10 mg/day of prednisone except as needed for immune related adverse events as outlined in section 17.1. Inhaled, nasal, and topical steroids are permitted. Intermittent dexamethasone for the treatment of nausea/emesis or infusion reactions is also permitted.
5) Concurrent use of hormones for noncancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.

5.4 Supportive Care

Supportive care will be provided in keeping with institutional standards of care. Management of immune related side effects due to nivolumab are included in Section 17.1 including recommended use of prophylactic antimicrobials while on steroids for treatment of suspected immune related adverse events.

If a patient experiences an infusion reaction prior to completion of the infusion, the infusion must be stopped, and the patient should be promptly managed according to signs and symptoms, and local

clinical protocol. The use of rescue medications such as diphenhydramine or steroids is permitted. Acetaminophen use is permitted but should be used with caution if the patient has any study related hepatic toxicity. The infusion may be restarted at a slower rate if all signs and symptoms have resolved. If the signs and symptoms do not resolve, the infusion should not be restarted. Further management guidelines can be found in section 6.2.

5.4.1 Contraception

Women of childbearing potential must be willing to abstain from heterosexual activity or use an effective method of contraception from the time of informed consent until 5 months after the last dose of investigational product. Women of childbearing potential are defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes. In addition, women under the age of 62 must have a documented serum follicle stimulating hormone (FSH) level higher than 40 mIU/mL.

Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men receiving study drug and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 7 months after the last dose of investigational product.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. To participate in the study, they must adhere to the contraception requirements described above for the duration of the study and during the follow-up period. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.4.1.1 Highly Effective Methods of Contraception

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner. Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- Nonhormonal IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy
- Complete Abstinence*
  *Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

5.4.1.2 Less Effective Methods of Contraception

- Diaphragm with spermicide
- Cervical cap with spermicide

- Vaginal sponge
- Male Condom without spermicide
- Progestin only pills by WOCBP subject or male subject's WOCBP partner
- Female Condom*.
  * A male and female condom must not be used together

6. TOXICITIES AND DOSE DELAYS/DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v5 will be used to grade adverse events.

Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar & Evaluations.

Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation as specified in Study Calendar & Evaluations.

Please see section 17.1 for management of toxicities that may arise during the course of treatment.

6.1 Dose Delays/Dose Modifications

Guidelines for delaying, restarting, or discontinuing therapy for various toxicities is included in sections 17.1 and 17.2. Dose modifications are not permitted for this protocol, except if Day 1 weight change by >10% necessitates a change in the dosing of cabiralizumab. If therapy is delayed, then next infusion date will be considered day 1 of the subsequent cycle.

In addition to sections 17.1 and 17.2, please see below for dose delays related to hematologic toxicity:

- For Grade 1-2 (neutrophils <LLN to 1,000/μL, hemoglobin <LLN to 8 g/dL, platelets <LLN to 50,000/μL)
  - Rule out alternative causes
  - Continue cabiralizumab and nivolumab therapy
  - Monitor CBC per schedule of events
  - If worsens, treat as grade 3-4 toxicity

- For Grade 3-4 (neutrophils < 1,000/μL, hemoglobin < 8 g/dL, platelets < 50,000/μL
  - Rule out alternative causes
  - Delay cabiralizumab and nivolumab therapy. If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient.
  - Treat autoimmune cytopenias per standard institutional guidelines (examples below):
    - Immune thrombocyoptenia may be treated with steroids, immune globulin, or rituximab
    - Immune mediated hemolytic anemia may be treated with steroids, immune globulin, or rituximab
    - Immune mediated neutropenia may be treated with steroids, colony stimulating factors, or immune globulin
  - If improves to < grade 3:

        - May resume cabiralizumab and nivolumab therapy per protocol
    - If does not improve or worsens:
        - Discontinue therapy. If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by patient.
        - Continue to treat immune mediated cytopenias per standard algorithms
        - Continue follow up until resolution
    - Grade 3 drug-related thrombocytopenia associated with grade ≥ 2 bleeding requires discontinuation regardless of duration of thrombocytopenia.

6.2 Cabiralizumab and Nivolumab-Related Infusion Reactions

Cabiralizumab and nivolumab may induce infusion or hypersensitivity reactions. If such reactions occur, they may manifest with fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension or hypertension, bronchospasm, or other symptoms.

Infusion reactions should be graded according to CTCAE v5 guidelines. Any Grade 3 or Grade 4 infusion reaction should be reported to Big Ten CRC AHQ within 24 hours and reported as an SAE if it meets the criteria.

The nivolumab 30-minute infusion will be administered first, with a 30-minute rest, followed by the cabiralizumab 30-minute infusion. It may be unclear if an infusion reaction is due to cabiralizumab, nivolumab, or to both study drugs. Therefore, one set of treatment recommendations (based on the most conservative treatments for infusion reactions due to either study drug) is provided below and may be modified based on clinical judgment, local treatment standards and guidelines, and/or specific symptoms, as appropriate.

For Grade 1 symptoms: Mild reaction (eg, localized cutaneous reactions including mild pruritus, flushing, and rash), requires infusion rate to be decreased; intervention may be indicated.

- Decrease the rate of the study drug infusion until recovery from symptoms.
- Remain at bedside and monitor the patient's vital signs until resolution of symptoms.
- Diphenhydramine 50 mg may be administered at the discretion of the treating physician.
- When symptoms resolve, restart the infusion at the original infusion rate.
- If a patient has an infusion reaction with nivolumab, cabiralizumab can be given (without prophylactic medications) if the infusion reaction resolves within 3 hours. For scheduling purposes, the cabiralizumab infusion may be given the next day. Prophylactic pre-infusion medications should be given prior to all subsequent nivolumab infusions.
- If a patient has an infusion reaction with cabiralizumab, prophylactic pre-infusion medications should be given prior to all subsequent cabiralizumab and nivolumab infusions.
- The following prophylactic pre-infusion medications are recommended prior to future infusions of cabiralizumab and nivolumab: diphenhydramine 50 mg (or equivalent) and/or paracetamol (acetaminophen) 325 mg to 1000 mg at least 30 minutes before additional study drug administrations.

For Grade 2 symptoms: Moderate reaction (ie, any symptom not listed above [mild symptoms] or below [severe symptoms] such as generalized pruritus, flushing, rash, dyspnea, and hypotension with systolic blood pressure >80 mmHg), requires infusion interruption but responds promptly to

symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, and IV fluids); prophylactic pre-infusion medications indicated for ≥24 hours.

- Interrupt the study drug infusion.
- Begin an IV infusion of normal saline and treat the patient with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol (acetaminophen) 325 mg to 1000 mg.
- Remain at bedside and monitor the patient's vital signs until resolution of symptoms.
- Corticosteroid therapy may be administered at the discretion of the treating physician.
- When symptoms resolve, restart the infusion at 50% of the original infusion rate; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate.
- Monitor the patient closely. If symptoms recur, immediately discontinue the infusion; no further study drug will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the patient until resolution of symptoms.
- If a patient has an infusion reaction with nivolumab infusion, cabiralizumab infusion can be given (without prophylactic medications) if the infusion reaction resolves within 3 hours. For scheduling purposes, the cabiralizumab infusion may be given the next day. Prophylactic pre-infusion medications should be given prior to all subsequent nivolumab infusions.
- If a patient has an infusion reaction with cabiralizumab, prophylactic pre-infusion medications should be given prior to all subsequent cabiralizumab and nivolumab infusions.
- The following prophylactic pre-infusion medications are recommended prior to future infusions of cabiralizumab and nivolumab: diphenhydramine 50 mg (or equivalent) and/or paracetamol (acetaminophen) 325 mg to 1000 mg should be administered at least 30 minutes before additional study drug administrations. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.
- The amount of study drug infused must be recorded.

For Grade 3 or Grade 4 symptoms: Severe reaction such as bronchospasm, generalized urticaria, systolic blood pressure <80 mmHg, or angioedema; Grade 3 symptoms including prolonged symptoms, which require 6 or more hours to respond to symptomatic medication and/or discontinuation of infusion; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae, such as renal impairment, pulmonary infiltrates; Grade 4: life-threatening; pressor or ventilation support indicated.

- Immediately discontinue the study drug infusion. No further study drug will be administered. The amount of study drug infused must be recorded on the CRF.
- Begin an IV infusion of normal saline and treat the patient as follows: Recommend bronchodilators, epinephrine 0.2 mg to 1.0 mg of a 1:1,000 solution for subcutaneous administration or 0.1 mg to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed.
- Remain at bedside and monitor the patient's vital signs until recovery from symptoms.
- The patient should be monitored until the investigator is comfortable that the symptoms will not recur.
- Investigators should follow their institutional guidelines for the treatment of anaphylaxis.

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

6.3 Protocol Therapy Discontinuation

The reason for discontinuation of protocol therapy will be documented on the electronic case report form (eCRF).

Instructions for management and discountinuation of therapy for common or expected AEs is included in sections 17.1 and 17.2. Please refer to these sections for instructions regarding therapy discontinuation for diarrhea/colitis, hepatic toxicity, renal toxicity, pulmonary toxicity, endocrinopathy toxicity, skin toxicity, neurologic toxicity, periorbital edema, uveitis, and CK or LDH elevation. In addition, criteria for discontinuation due to hematologic toxicity are outlined in section 6.1. In addition to these, a subject will also be discontinued from protocol therapy and followed up per protocol under the circumstances outlined below.

- Documented disease progression
- The treating physician thinks a change of therapy would be in the best interest of the subject
- The subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons
  - If a subject decides to prematurely discontinue protocol therapy ("refuses treatment"), the subject should be asked if he or she may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.
- A female subject becomes pregnant
- Any Grade 3 or higher infusion-related reactions and hypersensitivity requiring discontinuation. Any re-initiation of therapy in this circumstance would require consultation with the Sponsor's Medical Monitor or designee.
- Isolated Grade 3 electrolyte imbalances/abnormalities that are not associated with clinical sequelae
- Any Grade 4 drug-related AE or laboratory abnormality not addressed in sections 6.1, 17.1, or 17.2, except for the following events which do not require discontinuation:
  - Refractory hematologic toxicities as in section 6.1
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. The Sponsor's Medical Monitor or designee should be consulted for Grade 4 amylase or lipase abnormalities.
  - 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 drug-related endocrinopathy AEs, such as adrenal insufficiency, adrenocorticotropic hormone 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 Sponsor's Medical Monitor or designee.
- If CK is elevated, CK subsets, EKG and troponin will be obtained as outlined in section 17.2. If troponin is elevated above institutional upper limit of normal, evaluation of EF will be performed.

  - If Grade ≥2 myocarditis is confirmed per AHA diagnostic criteria (Bozkurt, Circulation. 2016 Dec 6;134(23):e579-e646.), patient will be taken off protocol.
- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Therapy discontinuation due to achievement of a CR as outlined in Section 5
  - Dosing delays to manage drug-related AEs are allowed. Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks from the previous dose, the Sponsor's Medical Monitor or designee must be consulted. Tumor assessments should continue as per-protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue per protocol, or more frequently if clinically indicated during such dosing delays or per the Investigator's discretion.
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Sponsor's Medical Monitor or designee. Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks, the Sponsor's Medical Monitor must be consulted. Tumor assessments should continue per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue per-protocol or more frequently if clinically indicated during such dosing delays or per the investigator's discretion.
- Any AE, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, presents a substantial clinical risk to the participant with continued cabiralizumab and/or nivolumab dosing
- If the causality of the AE requiring discontinuation is confirmed to be due to one of the study drugs in the combination therapy, the other drug(s) may be continued per-protocol schedule under the following scenarios:
  - Timely resolution of the AE based on the treatment modification table
  - Clinical benefit is shown by the participant based on investigator assessment.

6.4 Protocol Discontinuation

If a subject decides to withdraw from the study (and not just from protocol therapy) all efforts should be made to complete the final study assessments. The site study team should contact the subject by telephone or through a clinic visit to determine the reason for the study withdrawal. If the reason for withdrawal is an adverse event, it will be recorded on the eCRF and reported.

7. STUDY CALENDAR & EVALUATIONS

Cycle= **14 days**	Screen	Cycle Number[2]					6 months post CR[10]/ observation	Safety follow up	Long-term Follow up[4]
	-28 days	1	2	3	4	5+		30 days[2,3] post last dose	Every 3 months (±14 days)
		D1[1]	D1	D1	D1	D1			
REQUIRED ASSESSMENTS									
Review of eligibility criteria, Informed Consent	X								
Medical History[16], Diagnosis and Staging (Lugano[5])	X								
Physical Exam, Vital Signs[6], ECOG PS[7]	X	X	X	X	X	X[17]	Q3 mos	X	
EKG	X								
AEs & Concomitant Medications	X	X	X	X	X	X		D30, 100[3]	X[3]
LABORATORY ASSESSMENTS									
Complete blood cell count with differential (CBC)[15]	X	X	X	X	X	X	Q3 mos	X	
Comprehensive metabolic profile (CMP)[8, 15]	X	X	X	X	X	X	Q3 mos	X	
Mineral panel (phosphorus, magnesium, calcium) [15]	X	X	X	X	X	X	Q3 mos	X	
Creatine kinase, LDH[15]	X	X	X	X	X	X	Q3 mos	X	
Amylase, lipase[15]	X	X	X	X	X	X	Q3 mos	X	
TSH, free T4, cortisol[15]	X	X		X		C5, 7, etc	Q3 mos	X	
Pregnancy test (serum or urine) in WOCBP[9]	X	X		X		C5, 7, etc[9]			
DISEASE ASSESSMENT									
PET/CT Scan[10]	-30d					X[10]	Q6 mos		
Bone marrow aspirate and biopsy (unilateral)[11]	X					X	X[11]		
TREATMENT EXPOSURE									
Nivolumab 240 mg IV		X	X	X	X	X			
Cabiralizumab 4 mg/kg IV		X	X	X	X	X			
CORRELATIVE STUDIES (SPECIMEN COLLECTION)									
Fresh tumor tissue biopsy[12]	X					C5[13], @PR[13]			
Whole blood for somatic baseline		X							
PBMCs and plasma[14]		X		X		C5,@imaging	@imaging	X	
BANKING SAMPLES (SPECIMEN COLLECTION)									
Whole Blood[14]		X		X		C5, @imaging	@imaging	X	
Serum		X		X		C5, @imaging	@imaging	X	
Tumor Tissue[12]	X					C5[13], @PR[13]			
FOLLOW-UP									
Disease progression									X

Key to Footnotes

[1]If screening (baseline) labs were performed within 7 days of C1D1 of treatment, these do not need to be repeated.
[2]A window of 3 days will be applied to all treatment study visits; for safety follow-up visit, tumor imaging, bone marrow biopsy, and lymph node biopsy, a 7-day window will apply.
[3]A safety follow-up visit will occur 30 days (±7 days) after the last dose of treatment. Subjects who have an ongoing ≥ grade 2 or serious AE (SAE) at this visit will continue to be followed until the AE resolves to ≤ Grade 1 or baseline, is deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever is earlier. AEs will be collected for 100 days (±14 days) after the end of treatment. See Section 11.2.
[4]Subjects taken off treatment without documented disease progression will be followed for disease progression every 3 months for 1 year.
[5]See section 17.3 for Lugano staging system.
[6]Vital signs to include blood pressure, heart rate, respiratory rate, weight, and height (screening only).
[7]See section 17.4 for ECOG performance status scale.
[8]CMP: sodium, potassium, chloride, creatinine, blood urea nitrogen; liver function tests (LFTs): AST, ALT, total bilirubin, alkaline phosphatase.
[9]Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity of 25 IU/L or equivalent units of human chorionic gonadotropin) at screening and within 24 hours prior to the start of study treatment. Repeat testing every odd cycle while on treatment is required. If a urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
[10]Tumor response assessment by PET/CT will be performed within 30 days of C1D1; after cycles 4, 8, and 12; then every 8 cycles until 24 months after initiation of study treatment; then every 6 months (every 12 cycles) until study discontinuation. If IR determined on response evaluation, repeat PET is required in 8 weeks to evaluate for response or progression. Tumor response should also be evaluated at time of suspected clinical progression. If the patient achieves a CR, therapy will be continued for 6 months followed by repeat PET/CT to confirm ongoing CR prior to therapy discontinuation (see section 5). PET/CT performed as SOC prior to signing consent may be used for study as long as it is within the 30-day screening window.
[11]Bone marrow biopsy at screening to include biopsy for immunohistochemistry and aspirate for flow cytometry. If bone marrow is positive and PET is negative for bone marrow uptake, then bone marrow biopsy will be repeated at the time a radiographic CR is observed to confirm a CR. If bone marrow is positive and PET is positive for bone marrow uptake, then a bone marrow biopsy is not mandatory for response assessment. For patients achieving a CR who have completed an additional 6 months of therapy, a bone marrow biopsy will be performed prior to treatment discontinuation to confirm ongoing CR. If bone marrow and PET are negative, then a bone marrow biopsy will not be repeated unless deemed clinically necessary (e.g. to evaluate cytopenias). Biopsies will be performed within ±7 days from the time that PET/CT confirms CR.
[12]Fresh tumor biopsy is mandatory upon trial enrollment unless contraindicated. FFPE and flash frozen cores for IHC testing for CSF-1R, PD-L1, lymphoma associated macrophages (LAM), regulatory T cells (Treg), and cytotoxic T lymphocytes (CTL) must be available. Biopsy samples will include FFPE for future analysis. See CLM for collection, processing, labeling and shipping instructions.
[13]Repeat tissue biopsy required only at first imaging assessment (after cycle 4) if residual tumor exists on imaging and disease is amenable to biopsy. If CR achieved, then no biopsy required. If PR or better response achieved during trial followed by relapse, then repeat biopsy requested at the time of relapse. Window of ±7 days from time that scan results are available. See CLM for collection, processing, labeling and shipping info.
[14]Whole blood for PBMCs, serum and plasma will be collected pre-dose at C1D1, C3D1, C5D1, and at every timepoint thereafter with imaging response assessment. Pre-dose correlatives must be drawn within 24 hours prior to infusion. See CLM.
[15] See sections 17.1 and 17.2 for management of laboratory abnormalities.
[16]Medical history to include smoking history and trial awareness question.
[17] The physical exam, vital signs and ECOG PS may be switched to every 4 weeks at physician discretion after the first disease assessment (after C4) if a subject is not progressing and is tolerating the study drugs with minimal side effects.

7.1 Safety Follow-up Evaluations

A safety follow-up visit should occur when subjects permanently stop study treatment for whatever reason (toxicity, progression, or at discretion of site investigator) and should be performed 30 days (±7 days) after the last dose of treatment. Subjects who have any ongoing ≥ grade 2 or serious AE (SAE) at this visit will continue to be followed until the AE resolves to ≤ Grade 1 or baseline, is deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever is earlier. AEs, both serious and non-serious, will be collected for 100 days after the end of treatment. See Section 11.2.

7.2 Long Term Follow-up Evaluations

All subjects will be followed until documented disease progression. Subjects who discontinue treatment for any reason without documented disease progression will be followed for disease progression every 3 months (±14 days) for 1 year. Follow up may be accomplished via clinic visit, phone call, or other avenues as appropriate.

8. BIOSPECIMEN STUDIES AND PROCEDURES

Biospecimens will be collected according to the schedule of events for correlative/exploratory endpoints as outlined below.

1) To examine lymphoma associated macrophage (LAM), regulatory T cell (Treg), and cytotoxic T lymphocyte (CTL) densities (before and during treatment) as pharmacodynamic and prognostic biomarkers.

   Please see sections 1.2 and 1.3 for relevant background. Immunohistochemistry will be performed on pre-treatment biopsy material and serially compared with a paired "on treatment" biopsy performed after cycle 4 (in patients with disease that is amenable to biopsy). We anticipate that therapy will be associated with significant macrophage depletion and increased CTL infiltration (and/or increase the ratio of CTL:Treg), and that these changes within the tumor microenvironment may be predictive of response.

2) To examine the role of PD-L1 and CSF-1R expression as pharmacodynamic and prognostic biomarkers.

   Please see sections 1.2 and 1.3 for relevant background. Immunohistochemistry will be performed on pre-treatment biopsy material and serially compared with a paired "on treatment" biopsy performed after cycle 4 (in patients with disease that is amenable to biopsy). We anticipate that pre-treatment PD-L1 and CSF-1R expression may be associated with a response to therapy. Treatment is anticipated to deplete CSF-1R expressing cells, including LAM.

3) To examine the abundance of "exhausted" T cells in the peripheral blood as a pharmacodynamic and prognostic biomarker.

   T cells that are chronically stimulated by antigen may become functionally anergic or "exhausted" [45]. T-cell exhaustion is characterized by reduced proliferative potential, loss of

effector functions, sustained upregulation of inhibitory receptors (e.g. PD-1), and altered gene expression and metabolic reprogramming [45, 46].

Immunophenotyping of peripheral blood T cells will be performed by flow cytometry. The abundance of "exhausted" T cells will be determined by immunophenotyping for relevant antigens that may include (but are not limited to): PD-1, LAG-3, CTLA-4, TIM-3, TIGIT, and 2B4. We anticipate that therapy will decrease the frequency of exhausted T cells and that this may be associated with response.

4) To evaluate the feasibility and utility of minimal residual disease (MRD) monitoring as a pharmacodynamic and prognostic biomarker.

Despite the frequent loss of T-cell antigens, expression of the T-cell receptor (TCR) is retained in >90% of PTCL, NOS (reviewed in [47]). This observation suggests that the TCR may play a pathogenic role in PTCL. In fact, we have found that TCR engagement in primary malignant T cells leads to widespread changes in gene expression and the activation of important transcription factors, including NF-κB and GATA-3 (data not shown). Furthermore, TCR engagement promotes growth, survival, and resistance to chemotherapy (data not shown). These selective pressures apparently favor maintenance of TCR expression in PTCL and suggest that the TCR is an attractive candidate for MRD monitoring by high-throughput sequencing (HTS). HTS of the third complementarity determining region (CDR3) of the TCRβ or TCRγ genes is able to identify and quantify the relative frequency of clonal T cells in T-cell lymphomas[48-52].

High throughput screening of CDR3 of the T cell receptor β or γ genes will be used to identify and quantify the relative frequency of clonal T cells in patients who achieve a CR. We will also use stored samples from these patients collected at time points prior to frank relapse to determine whether MRD monitoring can be used as a predictor of relapse. We anticipate that detection of MRD in patients with CR will be predictive of future relapse.

5) To evaluate the role of myeloid derived suppressor cells (MDSC) as a pharmacodynamic and prognostic biomarker.

MDSC are not a discrete subset of myeloid-derived cells, but are a heterogenous population of immature myeloid cells functionally defined by their shared suppressive activity. In humans, MDSC express the common myeloid marker CD33, are CD11b+HLA-DR-/low and generally lineage negative (Lin-) (37-39). They may also variously express the granulocytic marker CD15[53] or the monocytic marker CD14 [54, 55], suggesting the presence of both granulocytic and monocytic MDSC [22, 56]. MDSC (or at least cells with an identical immunophenotype) comprise only a small percentage of (~0.5%) of peripheral blood mononuclear cells in normal humans [22, 57]. During a systemic inflammatory state, as may be observed in malignancy, MDSC greatly expand in response to both tumor- and stromal-derived factors and accumulate within the bone marrow, peripheral blood, spleen, lymph nodes, liver and tumors [22, 54, 58-67].

The mechanism of MDSC immunosuppression is mediated by a number of factors including expression of arginase (ARG1), inducible nitric oxide synthase (iNOS) [68-70], transforming

growth factor beta (TGF-β) [71, 72], IL-10[73], cyclooxygenase-2 (COX2) [74], sequestration of cysteine [75], and induction of Treg [76].

Recently, MDSCs were shown to correlate with clinical outcome of patients treated with ipilimumab [77, 78] or other immunomodulatory therapies like IL-2 [79] or antitumor vaccines [80]. These studies highlight the potential role of MDSCs as a valuable biomarker for response to immunotherapies and suggest that targeting MDSCs, as is possible with CSF1-R blockade, can lead to improved responses to such therapies [81].

To evaluate the role of MDSC in PTCL patients treated with immunotherapies, we will quantify the proportion of circulating MDSC and myeloid dendritic cells in patients pre and post treatment by flow cytometry. We anticipate that treatment will result in depletion of circulating MDSCs and will be predictive of response.

6) To biobank diagnostic biopsy specimens and other biologic specimens or blood for future correlative studies which may include somatic mutation testing and/or immune cell and cytokine analyses.

8.1 Source and Timing of Biospecimen Collections

Tissue collection:
Fresh tumor biopsy is mandatory prior to treatment unless contraindicated. Biopsy samples will include FFPE and flash frozen tissue for future analysis. Repeat biopsy (if tissue available) is also required after cycle 4 of treatment. Repeat biopsy is requested at the time of relapse if PR or greater achieved while on trial. See CLM for collection, processing, labeling and shipping instructions.

Blood Collections:
Whole blood will be collected and processed for PBMCs, serum, and plasma at C1D1, C3D1, C5D1, every timepoint for response assessment thereafter, and at 30 day safety follow up.

Whole blood for future somatic baseline will be collected at pre-treatment C1D1.

8.2 Storage of Biospecimens

Patient samples (tissue, blood, serum, plasma) collected for this study will be retained at the Hoosier Cancer Research Network, as Administrative Headquarters for the Big Ten CRC. Coded specimens will be stored indefinitely or until they are used up. If consent for future use of specimens is withdrawn by the subject, best efforts will be made to stop any additional studies and to destroy the specimens.

8.3 Banking of Leftover Biospecimens

Subject consent will be obtained to bank any leftover samples that were collected for study-specific correlative research. Hoosier Cancer Research Network (HCRN), as Administrative Headquarters for the Big Ten CRC, will manage the banked samples. Samples will be banked indefinitely in the Hoosier Cancer Research Network Biorepository and used for future unspecified cancer-related research.

8.4 Banking Samples for Future Unspecified Research

Subject consent will be obtained to collect additional samples collected for future unspecified Big Ten Cancer Research Consortium studies. HCRN will manage the banked samples. Samples will be banked indefinitely in the HCRN Biorepository.

This includes:

- Whole blood: Whole blood will be collected prior to treatment on C1D1, C3D1, C5D1, every timepoint for response assessment thereafter, and at 30 day safety follow up.
- Pre- and Post-treatment serum: Whole blood for serum will be collected prior to treatment on C1D1, C3D1, C5D1, every timepoint for response assessment thereafter, and at 30 day safety follow up.
- Unstained slides: Unstained slides will be obtained from the subject's formalin fixed paraffin embedded tumor sample.

Please refer to the Correlative Laboratory Manual (CLM) for all sample collection, processing, labeling, and shipping instructions.

8.5 Confidentiality of Biospecimens

Samples will be identified by a subject's study number assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject's study number.

9. CRITERIA FOR DISEASE EVALUATION

Response evaluations will be performed in accordance with the provisional Lugano lymphoma response to immunomodulatory therapy criteria (LYRIC) which incorporates a new response category, indeterminate response (IR)[82]. See Section 17.5.

Immune checkpoint inhibitors, have demonstrated impressive activity in a broad range of lymphoma histologies. However, these agents may be associated with clinical and imaging findings during treatment suggestive of progressive disease (PD) despite evidence of clinical benefit (eg, tumor flare or pseudoprogression). Considering this finding as PD could lead to patients being prematurely removed from a treatment from which they actually stand to benefit. This phenomenon has been well described with checkpoint blockade therapy in solid tumors and anecdotally seen in lymphoma as well. To address this issue in the context of lymphoma immunomodulatory therapy, a workshop was convened to provide provisional recommendations to modify current Lugano response criteria in patients receiving these and future agents in clinical trials. The criteria are largely in keeping with current Lugano response criteria[83] but the term "indeterminate response" (IR) was introduced within the LYRIC criteria to identify such lesions until confirmed as flare/pseudo-progression or true PD by subsequent imaging.

The term IR does not make direct reference to the underlying mechanism, recognizing that a delayed response and an immune mediated flare can both occur in the early treatment period and may be difficult to distinguish from progression by physical examination or imaging alone. Moreover, the term provides the flexibility to allow patients to continue treatment past IR in some circumstances with a mandatory subsequent response evaluation to confirm or refute true PD.

IR categories are defined as:

- IR1: Increase in overall tumor burden (as assessed by sum of the product of the diameters [SPD]) of ≥ 50% of up to 6 measurable lesions in the first 12 weeks of therapy, without clinical deterioration.

- IR2: Appearance of new lesions or growth of one or more existing lesion(s) ≥50% at any time during treatment; occurring in the context of lack of overall progression (<50% increase) of overall tumor burden, as measured by SPD of up to 6 lesions at any time during the treatment.
- IR3: Increase in FDG uptake of 1 or more lesion(s) without a concomitant increase in lesion size or number.

It is possible that, at a single time point, a patient could fulfill criteria for both IR1 or IR2 and IR3. For example, there could be a new FDG avid lesion in the absence of overall progression (IR2), and, at the same time, increase in FDG uptake of a separate lesion (IR3). In such cases, the designation IR1 or IR2 should take priority (i.e. IR2 in the above example).

As a secondary endpoint, patients will also be evaluated for response by Lugano 2014 criteria (Section 17.6).

9.1 Measurable and Non-Measurable Disease

Up to six of the largest target nodes, nodal masses, or extranodal lesions that are measurable in two diameters (longest diameter [LDi] and shortest diameter[SDi]) should be identified from different body regions representative of the patient's overall disease burden and include mediastinal and retroperitoneal disease, if involved. Measurable extranodal disease (eg, hepatic, splenic, renal, or pulmonary nodules) may be included in the six representative, measured lesions.

A measurable node must have an LDi greater than 1.5 cm. A measurable extranodal lesion should have an LDi greater than 1.0 cm. All other lesions (including nodal, extranodal, and assessable disease) should be followed as nonmeasured disease (eg, cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites).

9.2 Evaluation of Best Overall Response

Based on definitions provided in section 17.5

9.3 Definitions for Response Evaluation – LYRIC criteria

See section 17.5 for table outlining response criteria including indeterminate response (IR) criteria.

In patients categorized as having IR (described in section 9), it is mandatory to obtain a repeat imaging after an additional 8 weeks (or earlier if clinically indicated). At that time, response should be re-evaluated, and the patient should be considered to have true PD if the SPD of target lesion has increased further, with the considerations below:

- In the case of IR1, the comparison should be between the first IR1 and the current SPD, with an increase of ≥10% constituting PD. In addition, there should be an increase of ≥5 mm (in either dimension) of ≥1 lesion for lesions ≤2 cm and 10 mm for lesions >2 cm, to be consistent with the Lugano classification. The 10% threshold is empiric but designed to account for variability in measurement, especially when taken along with the minimum increase. If the target SPD increase is <10%, the response would still be categorized as IR1, and the patient could continue treatment until a subsequent scan shows either true PD (≥10% increase from first IR1 time point and an increase of >5 mm in either dimension of ≥1 lesion) or response (≥50% decrease from

baseline). In this situation, repeat imaging in 8 weeks of the original IR1 time point to ensure absence of significant further increase.

- In the case of IR2, the new or growing lesion(s) (unless biopsy proven to be benign) should be added to the target lesion(s), up to a total of no more than 6 total lesions. If the SPD of the newly defined set of target lesions has increased ≥50% from their nadir value (which may precede the IR time point), the patient should be considered to have PD.
- In the case of IR3, because inflammatory responses may result in an increase in the standardized uptake value of a lesion, the patient will not be considered to have PD unless there is evidence of PD by an increase in lesion size or the development of new lesions, as noted above.

If a patient is assessed as having IR and then "true" PD at a subsequent time point (without an intervening objective response between IR and PD), the IR assessment should subsequently be corrected to PD for reporting purposes to the date of the prior designation of IR.

9.3.1 First Documentation of Response

The time between initiation of therapy and first documentation of PR or CR.

9.3.2 Objective Response Rate

The objective response rate is the proportion of all subjects with confirmed PR or CR.

9.3.3 Complete Response Rate

The complete response rate is the proportion of all subjects with confirmed CR.

9.3.4 Progression Free Survival

A measurement from the date of enrollment until the criteria for disease progression (PD) is met or death occurs. Subjects who have not progressed will be right-censored at the date of the last disease evaluation.

9.3.5 Disease Control Rate

The disease control rate (DCR) is the proportion of all subjects with stable disease (SD) for 8 weeks, PR, or CR.

9.3.6 Duration of Response

Duration of response is the period measured from the time that measurement criteria are met for CR or PR (whichever status is recorded first) until the date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since treatment started).

9.3.7 Time to Next Treatment

The time to next treatment (TNT) is defined as the time from the date of enrollment to the institution of next treatment.

10. DRUG INFORMATION

For nivolumab, please refer to the latest version of the prescribing information that can be found at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/, and/or on the manufacturer's website.

For cabiralizumab, please refer to the current version of the Investigator's Brochure (IB) for additional information regarding this drug.

10.1 Cabiralizumab

Cabiralizumab (BMS-986227, FPA008) is a recombinant, humanized Immunoglobulin G4 (IgG4) monoclonal antibody that binds to human colony stimulating factor 1 receptor (CSF1R; c-fms). It is currently undergoing investigation in clinical trials, but has not yet been approved for commercial use.

10.1.1 Supplier/How Supplied

Bristol-Myers Squibb will supply cabiralizumab at no charge to subjects participating in this clinical trial. At the end of the study period, Bristol-Myers Squibb Company will not continue to supply study drug to subjects/investigators unless the Sponsor-Investigator chooses to extend their study. The investigator is responsible to ensure that the subject receives appropriate standard of care or other appropriate treatment in the independent medical judgement of the Investigator to treat the condition under study.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

10.1.2 Preparation

Solutions of cabiralizumab for IV infusion are prepared by dilution of the drug product in 0.9% sodium chloride or 5% dextrose injection. Since cabiralizumab solution contains no preservatives, diluted solutions for infusion should be administered or discarded within four hours after preparation. The IV administration set for cabiralizumab infusion must contain a 0.2 or 0.22 µm in-line filter or a 0.2 or 0.22 µm syringe filter.

10.1.3 Storage and Stability

Cabiralizumab drug product is shipped refrigerated at 2–8°C and stored refrigerated at 2–8°C until time of use. The contents of the vials supplied are sterile, pyrogen-free, and contain no preservatives. Vials are for single-use only. Drug product should be protected from light.

10.1.4 Handling and Disposal

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis.

After final drug reconciliation, unused cabiralizumab should be disposed at the site following procedures for the disposal of anticancer drugs.

10.1.5 Dispensing

Cabiralizumab must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Cabiralizumab should be stored in a secure area according to local

regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to subjects.

10.1.6 Adverse Events

Please refer to the most updated IB for a comprehensive list of adverse events. IB version 6 was used in preparation of this protocol.

The most common adverse events reported with cabiralizumab monotherapy include periorbital, facial, local and peripheral edema, pruritus, rash, and elevated lab values (CK, LDH, AST, ALT).

Hypersensitivity and/or infusion reaction is the most common toxicity with the use of monoclonal antibodies. There have been no infusion reactions or hypersensitivity reactions reported from any patients treated with cabiralizumab monotherapy to date while one patient in FPA008-003 that received cabiralizumab in combination with nivolumab experienced infusion reaction and another experienced a hypersensitivity reaction.

While no spontaneous infections in the nonclinical studies with cabiralizumab have been noted, macrophages play a role in innate immunity, and treatment with cabiralizumab may be associated with increased susceptibility to infections. Patients should be routinely monitored for signs and symptoms of infections during cabiralizumab treatment according to the clinical protocol.

In combination with nivolumab, the adverse event profile (other than infusion reactions as noted above) is similar to each agent individually.

10.2 Nivolumab

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes.1 Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens.

Nivolumab is approved in the United States for use in melanoma, non-small cell lung cancer, renal cell carcinoma, classical Hodgkin lymphoma, head and neck squamous cell carcinoma, and urothelial carcinoma.

10.2.1 Supplier/How Supplied

Bristol-Myers Squibb will supply nivolumab at no charge to subjects participating in this clinical trial. At the end of the study period, Bristol-Myers Squibb Company will not continue to supply study drug to subjects/investigators unless the Sponsor-Investigator chooses to extend their study. The investigator is responsible to ensure that the subject receives appropriate standard of care or other appropriate treatment in the independent medical judgement of the Investigator to treat the condition under study.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

10.2.2 Preparation

Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding (polyethersulfone membrane) in-line filter at the protocol-specified doses and infusion times. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL.

During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

10.2.3 Storage and Stability

Vials of nivolumab injection must be stored at 2ºC to 8ºC (36ºF to 46ºF) and protected from light and freezing.

The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°C to 8°C, 36°F to 46°F) for up to 24 hours, and a maximum of 8 hours of the total 24 hours can be at room temperature (20°C to 25°C, 68°F to 77°F) and room light. The maximum of 8 hours under room temperature and room light conditions includes the product administration period.

10.2.4 Handling and Disposal

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis.

After final drug reconciliation, unused nivolumab should be disposed at the site following procedures for the disposal of anticancer drugs.

10.2.5 Dispensing

Nivolumab must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Nivolumab should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to subjects.

10.2.6 Adverse Events

Please refer to the most updated IB for a comprehensive list of adverse events. IB version 16 was used in preparation of this protocol.

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 16,900 subjects treated to date. The most common adverse events include pneumonitis, colitis, diverticular perforation, hepatitis, endocrinopathies (hypophysitis, thyroiditis, adrenal insufficiency), pancreatitis, asymptomatic amylase/lipase elevations,

rash, pruritus, nephritis, encephalopathy, aseptic meningitis, peripheral sensory/motor neuropathies (Guillain-Barre, myasthenia gravis), infusion reactions (rare), uveitis, and myopathy including myocarditis.

In combination with cabiralizumab, the adverse event profile appears similar to each agent individually.

11. ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence whether or not considered related to the study drug that appears to change in intensity during the course of the study. The following are examples of AEs:

- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol
- An intercurrent illness or injury that impairs the well-being of the subject

Abnormal laboratory values or diagnostic test results constitute AEs only if they induce clinical signs or symptoms or require treatment or further diagnostic tests

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE.

11.1.2 Serious Adverse Event (SAE)

An SAE is an adverse event that:

- Results in death. NOTE: Death due to disease progression should not be reported as a SAE, unless it is attributable by the site investigator to the study drug(s)
- 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 for >24 hours or prolongation of existing hospitalization. **NOTE:** Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or 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 (e.g., 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 not resulting in hospitalization; or the development of drug dependency or drug abuse.
- Is an overdose (defined as the accidental or intentional administration of any dose of a product that is considered by the treating physician as both excessive and medically important.) All occurrences of overdose must be reported as an SAE.

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

11.1.3 Unexpected Adverse Event

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, package insert, or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

11.1.4 Relatedness

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms: Relatedness

Unrelated	The Adverse Event is ***not related*** to the drug(s)
Unlikely	The Adverse Event is ***doubtfully related*** to the drug(s)
Possible	The Adverse Event ***may be related*** to the drug(s)
Probable	The Adverse Event is ***likely related*** to the drug(s)
Definite	The Adverse Event is ***clearly related*** to the drug(s)

11.1.5 Pregnancy

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

The site investigator must immediately notify Big Ten CRC AHQ of this event via the SAE Submission Form in accordance with SAE reporting procedures. Big Ten CRC AHQ will then notify Worldwide Safety at BMS.

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

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the SAE Submission Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to Big Ten CRC AHQ via the SAE Submission Form in accordance with SAE reporting procedures. Big Ten CRC AHQ will then notify Worldwide Safety at BMS.

11.1.6 Drug Induced Liver Injury (DILI)

All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs. Potential drug induced liver injury is defined as:

1. An elevated AST or ALT lab value that is greater than 3 × the upper limit of normal, **and**
2. an elevated total bilirubin lab value that is greater than 2 × the upper limit of normal without initial findings of cholestasis (elevated serum alkaline phosphatase), **and**,
3. No other immediately apparent possible causes of aminotransferase (ALT or AST) 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.

DILIs that occur in any subject from the date of first dose through 100 days following discontinuation of dosing, whether or not related to the study drug, must be reported to Big Ten CRC AHQ within 24 hours/ 1 business day using the SAE Submission Form (see Documents/Info tab of the EDC). The form may be sent electronically to safety@hoosiercancer.org. Big Ten CRC AHQ will notify Worldwide Safety at BMS within 24 hours/ 1 business day.

11.2 Reporting

11.2.1 Adverse Events

- AEs will be recorded from time of signed informed consent until 100 days after discontinuation of study drug(s).
- AEs will be recorded regardless of whether or not they are considered related to the study drug(s).
- All AEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- All AEs considered related to study drug(s) will be followed until resolution to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever occurs first.
- Asymptomatic laboratory abnormalities that do not require treatment will not be collected as adverse events.

11.2.1.1 Big Ten CRC AHQ Requirements for Reporting AEs to Bristol-Myers Squibb

Adverse Events that are routinely collected according to Good Clinical Practice will be submitted to BMS every three (3) months by the last working day of the third month.

The Adverse Event information required to be sent to BMS as noted in the 'Bristol-Myers Squibb Early Asset Investigator Sponsored Research (ISR) Import Plan.' This document describes the method of collection and submission to BMS via the mailbox:

MG-RD-GPVE-PHARMACOVIGILANCE@bms.com

When the file is submitted to BMS, it will be noted that the file contains non-serious AEs not previously submitted to BMS within the previous 3 months.

11.2.2 Serious Adverse Events (SAEs)

11.2.2.1 Site Requirements for Reporting SAEs to Big Ten CRC Administrative Headquarters

- SAEs will be reported from time of signed informed consent until 100 days after discontinuation of study drug(s).

- SAEs will be reported on the SAE Submission Form and entered in the SAE tab in the EDC system **within 1 business day** of discovery of the event.
- SAEs include events related and unrelated to the study drug(s).
- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- All SAEs regardless of relation to study drug will be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant and/or until a new anti-cancer treatment starts, whichever occurs first.

The site will submit the completed SAE Submission Form (see Documents/Info tab of the EDC) to Big Ten CRC AHQ within **1 business day** of discovery of the event. The form may be sent electronically to safety@hoosiercancer.org. If only limited information is initially available, follow-up reports are required.

The site investigator is responsible for informing the IRB and/or other local regulatory bodies of the SAE as per local requirements.

The original copy of the SAE Submission Form and the email correspondence must be kept within the study file at the study site.

If an ongoing SAE changes in its intensity, relationship to study drug, or if new information becomes available, sites must submit a follow up SAE Submission Form within 1 business day to Big Ten CRC AHQ electronically at safety@hoosiercancer.org. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

11.2.2.2 Big Ten CRC AHQ Requirements for Reporting SAEs to Bristol-Myers Squibb

Big Ten CRC AHQ will report all SAEs, regardless of relationship to study drug, to Bristol-Myers Squibb within 24 hours/1 business day of receipt of the SAE Reporting Form. Follow-up information will be provided to Bristol-Myers Squibb as reasonably requested.

SAE Email Address: Worldwide.Safety@BMS.com
SAE Facsimile Number: +1 609-818-3804

Follow-up SAE reports will be sent by Big Ten CRC AHQ within 24 hours/1 business day to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

SAE Reconciliation:
On behalf of the Sponsor Investigator, Big Ten CRC AHQ will ensure that all SAEs in the clinical database are reported to BMS and any applicable health authority during the conduct of the study. This reconciliation will occur at least quarterly and be initiated by Big Ten CRC AHQ. Big Ten CRC AHQ will request a reconciliation report from: aepbusinessprocess@bms.com. During reconciliation, any events found to not be reported previously to BMS must be sent to Worldwide.Safety@BMS.com.

All SAEs should be faxed or emailed to BMS at:

Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
Email: Worldwide.safety@bms.com

11.2.2.3 Sponsor-Investigator Responsibilities

Big Ten CRC AHQ will send a SAE summary to the sponsor-investigator and the Michigan Institute for Clinical and Health Research (MICHR) IND/IDE Investigator Assistance Program (MIAP) **within 1 business day** of receipt of SAE Submission Form from a site. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

11.2.2.4 Michigan Institute for Clinical and Health Research (MICHR) IND/IDE Investigator Assistance Program (MIAP) Responsibilities for Reporting SAEs to FDA

MICHR-MIAP is responsible for managing the Investigational New Drug Application (IND) associated with this protocol on behalf of the sponsor-investigator. Big Ten CRC AHQ will obtain a copy of the cross-reference letter(s) from Bristol-Myers Squibb and provide to MICHR-MIAP for the IND application (MICHRMIAP@med.umich.edu). MICHR-MIAP will cross-reference this submission to Bristol-Myers Squibb's parent IND at the time of submission. MICHR-MIAP will provide Big Ten CRC AHQ with a copy of the application and Big Ten CRC AHQ will provide a copy of these documents to Bristol-Myers Squibb.

MICHR-MIAP will be responsible for all communication with the FDA in accordance with 21CFR312 which includes but is not limited to the 7 and 15 Day Reports, as well as an Annual Progress Report. MICHR-MIAP will provide Big Ten CRC AHQ with copies of any FDA communication. Big Ten CRC AHQ will provide a copy of these reports to Bristol-Myers Squibb as required per contract.

11.2.2.5 IND Safety Reports Unrelated to this Trial

Bristol-Myers Squibb will provide Big Ten CRC AHQ with IND safety reports from external studies that involve the study drug(s) per their guidelines. Big Ten CRC AHQ will forward the safety reports to the sponsor-investigator who will review these reports and determine if revisions are needed to the protocol or consent. Big Ten CRC AHQ will forward these reports to participating sites **within 1 business day** of receiving the sponsor-investigator's review. Based on the sponsor-investigator's review, applicable changes will be made to the protocol and informed consent document (if required). Any changes made to the protocol and/or informed consent document will be submitted to the FDA by MICHR-MIAP. All IND safety reports will also be made available to sites via the EDC system.

Upon receipt from Big Ten CRC AHQ, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

12. STATISTICAL METHODS

12.1 Study Design

This is a phase II single arm, non-randomized, open label trial with an interim futility/safety analysis.

12.2 Endpoints

12.2.1 Definition of Primary Endpoints

See Section 9.3.

12.2.2 Definition of Secondary Endpoints

See Section 9.3

12.3 Sample Size, Accrual, and Interim Futility Analysis

We propose a two-stage design with co-primary endpoints of complete response (CR) and overall response (OR), testing a "both-and" null hypothesis against an "either-or" alternative hypothesis. Specifically, we posit that a CRR of 30% or ORR of 60% is achievable (note that CRR refers to the *marginal* CRR, that is, the complete response rate without respect to overall response status, and not the *conditional* CRR, which would be the complete response rate among any responders). Initially, 17 eligible patients will be followed for response. At this point, if fewer than 3 patients demonstrate CR (<18%) and fewer than 7 patients demonstrate OR (<41%), the trial will be stopped for futility.

Otherwise, we will enroll an additional 16 patients, and the trial will successfully conclude if at least 7 patients (out of 33 total) demonstrate CR (21%) or at least 17 patients demonstrate OR (52%).

We will also formally incorporate three Grade 4+ adverse event (AE) thresholds that will activate at the interim analysis. First, if the number of patients with any Grade 4 AE is greater than or equal to 7 (7/17=41%) by the interim analysis, enrollment will stop. Second, if the number of patients with Grade 4 AEs that *require discontinuation of study treatment, as specified in section 6.3*, is greater than or equal to 3 (3/17=12%) by the interim analysis, enrollment will stop. Third, enrollment will stop at the interim analysis for any Grade 5 AE attributable to drug.
To demonstrate the operating characteristics of this design, we simulated repeated trials under a grid of different true values of CRR, ORR, and Grade 4+ AE rate. When the true CRR and ORR are simultaneously no greater than 10% and 30%, respectively, and the true Grade 4+ AE rate is 32%, this design will successfully conclude with probability less than 0.05 (one-sided type I error) and stop (for futility or safety collectively) at the interim analysis with probability about 0.75. When the true CRR is at least 30% or the true ORR is at least 60%, this design will successfully conclude with probability at least 0.62 (power) and stop at the interim analysis with probability at most 0.34. The schematic in Figure 1, immediately below, gives the full operating characteristics over all considered combinations of CRR and ORR when the true Grade 4+ AE rate is 32%. The blue-purple region denotes the true generating scenarios satisifying the 'either-or' hypothesis, wherein at least one of the efficacy thresholds is met or exceeded. The green region denotes satisifying neither the null nor the alternative hypothesis, wherein both efficacy rates exceed their null values but neither meets the alternative. The red region denotes the 'both-and' null hypothesis.

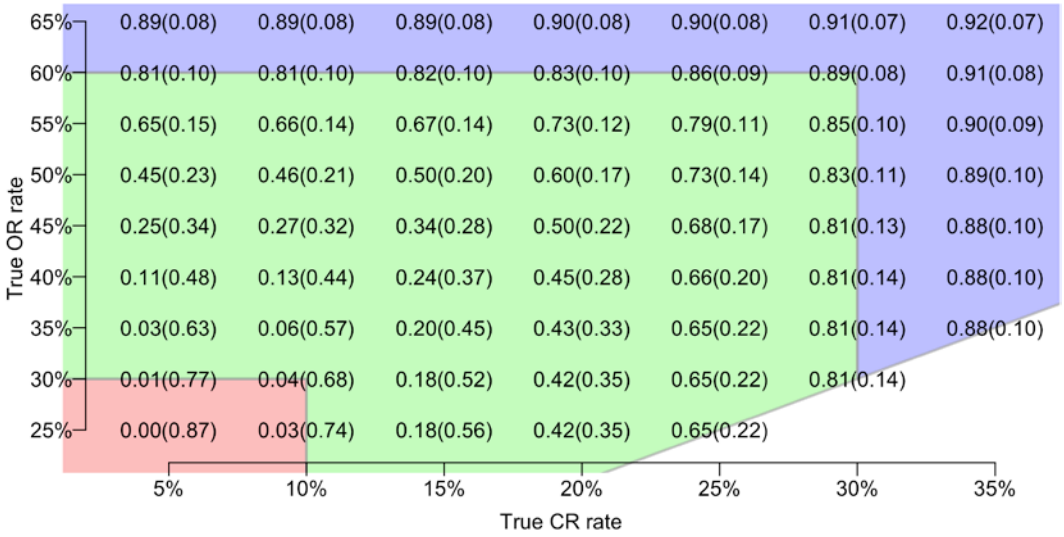


Figure 1: Probability of declaring success and, in parentheses, probability of stopping at the interim analysis for futility or toxicity, **when the true Grade 4+ AE rate is 32%.**

To demonstrate the effect of our toxicity stopping rule, Figure 2 below gives the operating characteristics of our design when the true Grade 4+ AE rate is 50%. The entire region is shaded red, because the treatment regimen is unacceptably toxic. The probability of declaring success, even when one of the efficacy thresholds is satisfied in truth, is always less than 0.16, and the trial stops at the interim analysis with probability at least 0.83.

Figure 2: Probability of declaring success and, in parentheses, probability of stopping at the interim analysis for futility or toxicity, **when the true Grade 4+ AE rate is 50%.**

Peripheral T-cell lymphoma response and progression will be assessed using the LYRIC criteria as outlined in section 9.

Safety assessments will consist of the surveillance and recording of AEs and documentation of physical examination findings and laboratory data. Type, incidence, severity, seriousness, and relatedness of adverse events will be recorded. Additional secondary analyses include PFS, DCR, DOR, and TNT.

12.4 Assessment of Safety

Any subject who receives at least one dose of treatment on protocol will be evaluated for safety using CTCAE v5.

12.5 Assessment of Efficacy

All subjects with measurable disease who have received at least one cycle of treatment and have their disease re-evaluated will be evaluable for assessment of objective response.

12.6 Data Analysis Plans

The primary analysis will compare the observed OR and CR rates to posited null values of 30% and 10%, respectively. We will calculate score-based confidence intervals for binomial proportions. At the critical values of 17/33 and 7/33, the confidence intervals for the ORR and CRR would be (35.2%, 67.5%) and (10.7%, 37.8%), respectively.The analyses of secondary safety objectives will be conducted using tabulations of adverse events, stratified by grade and attribution.

The analyses corresponding to secondary efficacy endpoints (PFS, DCR, DOR, TNT) will be summarized with typical 'time-to-event' analyses.

With regard to the exploratory objectives, we will evaluate pre-post changes in LAM, Treg,CTL, "exhausted" T cell, and MDSC densities, as well as lymphoma cell and tumor microenvironment expression of PD-L1 and CSF-1R. We posit that changes in some or all of these biomarkers will correlate with response, thus demonstrating potential as prognostic biomarkers. We will also evaluate MRD status in patients achieving CR and hypothesize that patients with CR but detectable MRD will predict relaps. We will quantify these associations using visual and statistical summarization.

12.6.1 Analysis Plans for Primary Objective

See section 12.3.

12.6.2 Analysis Plans for Secondary Objectives

See section 12.3.

12.6.3 Subgroup Analyses

There are no subgroup analyses planned

12.6.4 Other Planned Analyses

There are no other planned analyses.

13. TRIAL MANAGEMENT

13.1 Data and Safety Monitoring Plan (DSMP)

The Data and Safety Monitoring Committee (DSMC) of The University of Michigan Rogel Cancer Center is responsible for monitoring the safety and data integrity of the trial.

Big Ten CRC AHQ oversight activities include:

- Review and process all adverse events requiring expedited reporting as defined in the protocol

- Provide timely reports to MICHR-MIAP (MICHRMIAP@med.umich.edu) that require expedited reporting
- Notify participating sites of adverse events requiring expedited reporting
- Provide trial accrual progress, safety information, and data summary reports to the sponsor-investigator and MICHR-MIAP
- Coordinate quarterly meetings for this phase II study. These meetings will include each accruing site's principal investigator, clinical research specialist and/or research nurse (other members per principal investigator's discretion).
- The quarterly study team meetings will discuss matters related to:
  - Enrollment rate relative to expectations, characteristics of participants
  - Safety of study participants (Serious Adverse Event reporting)
  - Adherence to protocol (protocol deviations)
  - Completeness, validity and integrity of study data
  - Retention of study participants
- These meetings are to be documented by the site data manager or study coordinator using the Protocol Specific Data and Safety Monitoring Report (DSMR), signed by the site principal investigator or designated co-investigator. Big Ten CRC AHQ will assist in this process. The DSMR can be found in the Documents/Info tab of the EDC. Each site is required to submit the completed DSMR to Big Ten CRC AHQ on a quarterly basis together with other pertinent documents for submission to the DSMC.

13.2 University of Michigan Data Safety Monitoring Committee

The DSMC will review the information included on the DSMRs from the first subject enrolled until the last subject has completed the study drug interventions. Documentation of DSMC reviews will be provided to sponsor-investigator and Big Ten CRC AHQ. Issues of immediate concern by the DSMC will be brought to the attention of the sponsor-investigator and other regulatory bodies as appropriate. The sponsor-investigator will work with Big Ten CRC AHQ and MICHR-MIAP to address the DSMC's concerns.

The DSMC will provide the sponsor-investigator and Big Ten CRC AHQ evidence of its review. Big Ten CRC AHQ will distribute this information to the participating sites for submission to their respective IRB per the local IRB's policies and procedures.

13.3 Data Quality Oversight Activities

Remote validation of the EDC system data will be completed on a continual basis throughout the life cycle of the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRFs will be generated for each site and transmitted to the site and the site monitor. Corrections will be made by the study site personnel.

Monitoring visits to the trial sites will be made periodically during the trial to ensure key aspects of the protocol are followed. Additional for cause visits may occur as necessary. Source documents will be reviewed for verification of agreement with data entered into the EDC system. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by Big Ten CRC AHQ or its designee.

The trial site may also be subject to quality assurance audit by Bristol-Myers Squibb or its designee as well as inspection by appropriate regulatory agencies.

13.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. All results of primary and secondary objectives must be posted to CT.gov within a year of completion. The sponsor-investigator has delegated responsibility to Big Ten CRC AHQ for registering the trial and posting the results on clinicaltrials.gov. MICHR-MIAP will be responsible for submitting FDA Form 3674 to the FDA. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

14. DATA HANDLING AND RECORD KEEPING

14.1 Data Management

Big Ten CRC AHQ will serve as the Clinical Research Organization for this trial. Data will be collected through a web-based clinical research platform compliant with Good Clinical Practices and Federal Rules and Regulations. Big Ten CRC AHQ personnel will coordinate and manage data for quality control assurance and integrity. All data will be collected and entered into the EDC system by study site personnel from participating institutions.

14.2 Case Report Forms and Submission

Generally, clinical data will be electronically captured in the EDC system and correlative results will be captured in the EDC system or other secure database(s). If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in the EDC system, according to study-specific objectives. Please see the Data and Safety Oversight Process (DSOP) guidelines for further details.

The completed dataset is housed at Big Ten CRC AHQ and is the sole property of the sponsor-investigator's institution. It should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from the sponsor-investigator and Big Ten CRC AHQ. After the initial publication, the complete data set will be available to all Big Ten CRC institutions.

14.3 Record Retention

To enable evaluations and/or audits from Health Authorities/Big Ten CRC AHQ, the site investigator agrees to keep records, including the identity of all subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's file and retained by the site investigator in compliance with local and federal regulations. No records will be destroyed until Big Ten CRC AHQ confirms destruction is permitted.

14.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel.

Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, Big Ten CRC AHQ, Bristol-Myers Squibb IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subjects's identity will remain confidential.

15. ETHICS

15.1 Institutional Review Board (IRB) Approval

The final study protocol and the final version of the informed consent form must be approved in writing by an IRB. The site investigator must submit written approval by the IRB to Big Ten CRC AHQ before he or she can enroll subjects into the study.

The site investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB as local regulations require.

Progress reports and notifications of adverse events will be provided to the IRB according to local regulations and guidelines.

15.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki. Conduct of the study will be in compliance with ICH Good Clinical Practice, and with all applicable federal (including 21 CFR parts 56 & 50), state, or local laws.

15.3 Informed Consent Process

The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

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17. APPENDICES

17.1 Management of toxicities

These general guidelines constitute guidance to the Site Investigator and may be supplemented by discussions with the Sponsor Investigator. The guidance applies to all immuno-oncology (I-O) agents and regimens. A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated. Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids. Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended. The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

17.1.1 Gastrointestinal toxicity management

Gastrointestinal Adverse Event Management		
Rule out noninflammatory causes. If a noninflammatory cause is identified, treat accordingly and continue nivolumab therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.		
Grade of Diarrhea/Colitis	**Management**	**Treatment and Follow-Up**
Grade 1: Diarrhea:<4 stools/day over baseline; Colitis: asymptomatic	– Continue cabiralizumab and nivolumab therapy per protocol – Symptomatic treatment	– Close monitoring for worsening symptoms – Educate patient to report worsening immediately **If worsens:** – Treat as Grade 2 or 3/4
Grade 2: Diarrhea: 4–6 stools per day over baseline; IV fluids indicated <24 hours; not interfering with ADL; Colitis: abdominal pain; blood in stool	– Delay cabiralizumab and nivolumab per protocol[a] – Symptomatic treatment	**If improves to Grade 1 ≤4 days:** – Resume cabiralizumab and nivolumab therapy per protocol **If persists ≥5–7 days or recurs:** – 0.5–1 mg/kg/day methylprednisolone or oral equivalent – When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume cabiralizumab and nivolumab therapy per protocol **If worsens or persists >3-5 days with oral steroids:** – Treat as Grade 3 or 4
Grade 3–4: Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hours; interfering with ADL; Colitis (G3): Severe abdominal pain, medical intervention indicated, peritoneal signs **Grade 4:** Life-threatening, perforation	– Delay or Discontinue cabiralizumab and nivolumab therapy per protocol[b] – 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent[c] – Add prophylactic antibiotics for opportunistic infections – Consider lower endoscopy if clinically indicated	**If Grade 3 AE improves to Grade 1 or baseline within 28 days:** – Taper steroids over at least 1 month – Resume dosing of cabiralizumab and Nivolumab **If Grade 4:** – Permanently discontinue cabiralizumab and Nivolumab – Continue steroids until Grade 1, then taper steroids over at least 1 month **If persists >3-5 days, or recurs after improvement:** – Add infliximab 5 mg/kg (if no contraindications) – Follow up until resolution – Note: Infliximab should not be used in cases of perforation or sepsis

a. If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient
b. If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by patient
c. 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.

17.1.2 Hepatic toxicity management without liver metastasis

Hepatic Adverse Event Management without Liver Metastasis		
Rule out noninflammatory causes. If a noninflammatory cause is identified, treat accordingly and continue nivolumab therapy. Consider imaging for obstruction.		
Grade of Liver Test Elevation	**Management**	**Follow-Up**
AST or ALT >3.0x ULN ***and*** Total bilirubin >2x ULN **or** INR > 1.5	– Discontinue cabiralizumab and nivolumab per protocol – Start steroids	– Continue LFT monitoring per protocol until resolution. – Continue monitoring for and other associated clinical signs or symptoms – Contact the Sponsor Investigator – Evaluate for non drug related causes of the laboratory abnormalities (e.g. obstruction, viral infection, Gilbert's disease, etc) – Under selected circumstances (e.g alternative etiology is identified), patient may receive additional therapy only after consultation and agreement between the Sponsor/MM and the investigator if receiving additional treatment with cabiralizumab and nivolumab is in the best interest of the patient (e.g if the subject has demonstrated a response to therapy)
AST or ALT > 5 to ≤ 12 xULN ***and*** Total bilirubin ≤ 2 xULN	– Continue cabiralizumab and nivolumab therapy if there are no clinical signs of significant muscle or hepatic damage – Increase frequency of monitoring of AST, ALT, bilirubin, alkaline phosphatase and INR (every 48-72 hours or more frequently, as clinically indicated) – Monitor for other clinical symptoms (fatigue, nausea, vomiting, abdominal pain, fever, rash, and/or eosinophilia)	– Contact the Sponsor Investigator if there are clinical signs of muscle or hepatic injury or other clinical symptoms – Contact the Sponsor Investigator if there is a concurrent increase of bilirubin, AST, ALT, or alkaline phosphatase – Notify the Sponsor Investigator if there is an AST or ALT increase > 5 xULN – Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic – Consider gastroenterology or hepatology referral
AST or ALT > 12 to ≤ 20 xULN ***and*** Total bilirubin ≤ 2 xULN ***or*** Isolated total bilirubin > 2 to ≤ 3 xULN	– Delay cabiralizumab and nivolumab therapy per protocol[a] – Increase frequency of monitoring of (including but not limited to) AST, ALT, bilirubin, alkaline phosphatase and INR (every 48-72 hours or more frequently, as clinically indicated) – If there is a 2-fold ALT increase compared to the previous measurement, start steroids immediately – Consider steroid treatment on any total bilirubin increase of over 2.0x ULN – If there is a concurrent increase of alkaline phosphatase along with ALT, start steroids immediately – Monitor for other clinical symptoms (fatigue, nausea, vomiting, abdominal pain, fever, rash, and/or eosinophilia)	**If AST/ALT return to ≤ 12 xULN within ≤ 7 days:** – Resume routine monitoring – Resume cabiralizumab and nivolumab therapy at same dose level per protocol **If elevations persist and remain at the same level > 7 days but < 28 days:** – Start steroids immediately and discontinue further dosing – Continue monitoring and consider dosing the subject with nivolumab therapy at the same dose level Consider tapering steroids over at least 1 month **If elevations persist at the same level > 28 days or worsen:** – Discontinue cabiralizumab and nivolumab therapy per protocol – 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to Grade 1 or baseline, taper steroids over at least 1 month – Consider prophylactic antibiotics for opportunistic infections – Discuss with Sponsor Investigator

Hepatic Adverse Event Management without Liver Metastasis		
Rule out noninflammatory causes. If a noninflammatory cause is identified, treat accordingly a nd continue nivolumab therapy. Consider imaging for obstruction.		
Grade of Liver Test Elevation	**Management**	**Follow-Up**
AST or ALT > 20 xULN ***or*** Total bilirubin >3 xULN	– Discontinue cabiralizumab and nivolumab therapy[b] – Increase frequency of monitoring to every 1 to 2 days – Consider 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent[c] – Consider adding prophylactic antibiotics for opportunistic infections – Consult gastroenterologist and hepatologist, if clinically indicated	**If returns to Grade 2:** – Consider steroid taper over at least 1 month if they have been started **If does not improve in >3–5 days, worsens, or rebounds:** – Consider adding mycophenolate mofetil 1 g BID – If no response within an additional 3–5 days, consider other immunosuppressants per local guidelines – Follow up until resolution

a. If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient.
b. If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by patient.
c. 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.

17.1.3 Hepatic toxicity management with liver metastasis

Hepatic Adverse Event Management with Liver Metastasis		
Rule out noninflammatory causes. If a noninflammatory cause is identified, treat accordingly and continue nivolumab therapy. Consider imaging for obstruction.		
Grade of Liver Test Elevation	**Management**	**Follow-Up**
AST or ALT >3.0x ULN ***and*** Total bilirubin >2x ULN **or** INR > 1.5	– Discontinue cabiralizumab and nivolumab therapy per protocol – Start steroids	– Continue LFT monitoring per protocol until resolution. – Continue monitoring for and other associated clinical signs or symptoms – Contact the Sponsor Investigator – Evaluate for non drug related causes of the laboratory abnormalities (e.g. obstruction, viral infection, Gilbert's disease, etc) – Under selected circumstances (e.g alternative etiology is identified), patient may receive additional therapy only after consultation and agreement between the Sponsor/MM and the investigator if receiving additional treatment with cabiralizumab and nivolumab is in the best interest of the patient (e.g if the subject has demonstrated a response to therapy)
AST or ALT > 5 to ≤ 12 xULN ***and*** Total bilirubin ≤ 2 xULN	– Continue cabiralizumab and nivolumab therapy if there are no clinical signs of significant muscle or hepatic damage – Increase frequency of monitoring of AST, ALT, bilirubin, alkaline phosphatase and INR (every 48-72 hours or more frequently, as clinically indicated) – Monitor for other clinical symptoms (fatigue, nausea, vomiting, abdominal pain, fever, rash, and/or eosinophilia)	– Contact the Sponsor Investigator if there are clinical signs of muscle or hepatic injury or other clinical symptoms – Contact the Sponsor Investigator if there is a concurrent increase of bilirubin, AST, ALT, or alkaline phosphatase – Notify the Sponsor Investigator if there is an AST or ALT increase > 5 xULN – Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic – Consider gastroenterology or hepatology referral

Hepatic Adverse Event Management with Liver Metastasis		
Rule out noninflammatory causes. If a noninflammatory cause is identified, treat accordingly and continue nivolumab therapy. Consider imaging for obstruction.		
Grade of Liver Test Elevation	**Management**	**Follow-Up**
AST or ALT > 12 to ≤ 20 xULN ***and*** Total bilirubin ≤ 2 xULN ***or*** Isolated total bilirubin > 3.0 to ≤ 5 xULN	– Delay cabiralizumab and nivolumab therapy per protocol[a] – Increase frequency of monitoring of (including but not limited to) AST, ALT, bilirubin, alkaline phosphatase and INR (every 48-72 hours or more frequently, as clinically indicated) – If there is a 2-fold ALT increase compared to the previous measurement, start steroids immediately – Consider steroid treatment on any total bilirubin increase of over 2.0x ULN – If there is a concurrent increase of alkaline phosphatase along with ALT, start steroids immediately – Monitor for other clinical symptoms (fatigue, nausea, vomiting, abdominal pain, fever, rash, and/or eosinophilia)	**If AST/ALT return to ≤ 12 xULN within ≤ 7 days:** – Resume routine monitoring, resume cabiralizumab and nivolumab therapy at same dose level per protocol **If elevations persist and remain at the same level > 7 days but < 28 days:** – Start steroids immediately and discontinue further dosing – Continue monitoring and consider dosing the subject with nivolumab therapy at the same dose level – Consider tapering steroids over at least 1 month **If elevations persist at the same level >28 days or worsen:** – Discontinue cabiralizumab and nivolumab therapy per protocol – 0.5–1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to Grade 1 or baseline, taper steroids over at least 1 month – Consider prophylactic antibiotics for opportunistic infections – Discuss with Sponsor Investigator
AST or ALT > 20 xULN ***or*** Total Bilirubin > 5 xULN	– Discontinue cabiralizumab and nivolumab therapyb – Increase frequency of monitoring to every 1–2 days – Consider 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent[c] – Consider adding prophylactic antibiotics for opportunistic infections – Consult gastroenterologist and hepatologist, if clinically indicated	**If returns to Grade 2 or baseline:** – Consider steroid taper over at least 1 month if they have been started **If does not improve in >3–5 days, worsens, or rebounds:** – Consider adding mycophenolate mofetil 1 g BID – If no response within an additional 3–5 days, consider other immunosuppressants per local guidelines – Follow up until resolution

a. If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient.
b. If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by patient.
c. 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.

17.1.4 Renal toxicity management

Renal Adverse Event Management		
Rule out noninflammatory causes. If a noninflammatory cause is identified, treat accordingly and continue nivolumab therapy.		
Grade of Creatinine Elevation	**Management**	**Follow-Up**
Grade 1: Creatinine >1.0x to 1.5x baseline; >1 x ULN to 1.5x ULN	– Continue cabiralizumab and nivolumab therapy at the same dose level per protocol – Monitor creatinine weekly	**If returns to baseline:** – Resume routine creatinine monitoring per protocol **If worsens:** – Follow as stated below
Grade 2: Creatinine >1.5x to 3.0x baseline; >1.5 x ULN to 3.0x ULN	– Delay cabiralizumab and nivolumab therapy per protocol[a] – Monitor creatinine every 2 to 3 days – 0.5 to 1 mg/kg/day methylprednisolone IV or oral equivalent[c] – Consider renal biopsy if clinically indicated	**If returns to Grade 1 or baseline before the next dosing visit:** – Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume cabiralizumab and nivolumab therapy at the same dose level – Routine creatinine monitoring per protocol **If elevations persist >14 days or worsen:** – Treat as Grade 4
Grade 3: Creatinine >3.0 x baseline; >3.0x ULN to 6.0x ULN	– Delay cabiralizumab and nivolumab therapy per protocol[a] – Monitor creatinine every 2 to 3 days – 0.5 to 1 mg/kg/day methylprednisolone IV or oral equivalent[c] – Consider renal biopsy if clinically indicated	**If returns to Grade 1 or baseline before the next dosing visit:** – Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume cabiralizumab and nivolumab therapy at the same dose level – Routine creatinine monitoring per protocol **If elevations persist > 14 days or worsen:** – Treat as Grade 4
Grade 4: Creatinine >6.0x ULN	– Discontinue cabiralizumab and nivolumab therapy per protocol[b] – 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent[c] – Consult nephrologist – Consider renal biopsy if clinically indicated	**If returns to baseline or Grade 1:** – Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections **If worsens:** – Follow up until resolution – Clinical referrals as needed

a. If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient.
b. If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by patient.
c. 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.

17.1.5 Pulmonary toxicity management

Pulmonary Adverse Event Management		
Rule out noninflammatory causes. If a noninflammatory cause is identified, treat accordingly and continue nivolumab therapy. Evaluate with imaging and pulmonary consultation.		
Grade of Pneumonitis	**Management**	**Follow-Up**
Grade 1: Radiographic changes only	– Consider delay of cabiralizumab and nivolumab therapy – Monitor for symptoms every 2 to 3 days – Consider pulmonary and infectious disease consults	– Re-image at least every 3 weeks **If worsens:** – Treat as Grade 2 or 3–4
Grade 2: Mild to moderate new symptoms	– Delay cabiralizumab and nivolumab therapy per protocol[a] – Pulmonary and infectious disease consults – Monitor symptoms daily, consider hospitalization – 1 mg/kg/day methylprednisolone IV or oral equivalent – Consider bronchoscopy, lung biopsy, if clinically indicated	– Re-image every 1–3 days **If improves <14 days:** – When symptoms return to near baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume cabiralizumab and nivolumab therapy per protocol **If does not improve after 2 weeks or worsens:** – Treat as Grade 3–4
Grade 3–4: Severe new symptoms; New/worsening hypoxia; Life-threatening	– Discontinue cabiralizumab and nivolumab therapy per protocol[b] – Hospitalization – Pulmonary and infectious disease consults – 2 to 4 mg/kg/day methylprednisolone IV or IV equivalent[c] – Add prophylactic antibiotics for opportunistic infections – Consider bronchoscopy, lung biopsy if clinically indicated	**If improves to baseline:** – Taper steroids over at least 6 weeks **If does not improve after 48 hours or worsens:** – Add additional immunosuppression (e.g. cyclophosphamide, IVIG, or mycophenolate mofetil) – Follow up until resolution

a. If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient.

b. If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by patient.

c. 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.

17.1.6 Endocrinopathy toxicity management

Endocrinopathy Adverse Event Management		
Rule out noninflammatory causes. If a noninflammatory cause is identified, treat accordingly and continue nivolumab therapy. Consider visual field testing, endocrinology consultation, and imaging.		
Description	**Management**	**Follow-Up**
Asymptomatic TSH elevation	– Continue cabiralizumab and nivolumab therapy per protocol	**If TSH <0.5x LLN, or TSH >2x ULN, or consistently out of range in 2 subsequent measurements:** – Consider endocrinology consult
Symptomatic endocrinopathy	– Evaluate endocrine function – Consider pituitary scan **Symptomatic with abnormal lab/pituitary scan:** – Delay cabiralizumab and nivolumab therapy per protocol[a] – 1 to 2 mg/kg/day methylprednisolone IV or PO equivalent[c] – Initiate appropriate hormone therapy **No abnormal lab/pituitary MRI scan but symptoms persist:** – Repeat labs in 1–3 weeks and MRI in 1 month	**If improves within 28 days (with or without hormone replacement):** – Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections – Resume cabiralizumab and nivolumab therapy per protocol – Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component **If persists for over 28 days:** – Delay cabiralizumab and nivolumab therapy – Continue steroids as needed – Upon resolution, discuss with Sponsor Investigator if patients are clinically stable on further dose delay and discontinuation – Follow up until resolution or return to baseline
Suspicion of adrenal crisis (e.g. severe dehydration, hypotension, shock out of proportion to current illness)	– Delay or discontinue cabiralizumab and nivolumab therapy per protocol[a,b] – Rule out sepsis – Stress dose of IV steroids with mineralocorticoid activity – IV fluids – Consult endocrinologist – If adrenal crisis is ruled out, treat as above for symptomatic endocrinopathy	

a. If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient.
b. If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by patient.
c. 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.

17.1.7 Skin toxicity management

Skin Adverse Event Management		
Rule out noninflammatory causes. If a noninflammatory cause is identified, treat accordingly and continue nivolumab therapy.		
Grade of Rash	**Management**	**Follow-Up**
Grade 1–2: Covering ≤30% BSA[d]	– Symptomatic therapy (e.g. antihistamines, topical steroids) – Continue cabiralizumab and nivolumab therapy per protocol	**If persists >1-2 weeks or recurs:** – Consider skin biopsy – Delay cabiralizumab and nivolumab therapy per protocol – Consider 0.5–1 mg/kg/day methylprednisolone IV or oral equivalent. – Once improving ,taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume cabiralizumab and nivolumab therapy per protocol **If worsens:** – Treat as Grade 3–4
Grade 3–4: Covering >30% BSA; Life-threatening consequences[d]	– Delay or discontinue cabiralizumab and nivolumab therapy per protocol[a,b] – Consider skin biopsy and dermatology consult – 1 to 2 mg/kg/day IV methylprednisolone IV or IV equivalent[c]	**If improves to Grade 1 within 28 days:** – Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections – Resume cabiralizumab and nivolumab therapy per protocol **If Persists >28 days or worsens** – Consider to discontinue cabiralizumab and nivolumab therapy per protocol

a. If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient
b. If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by patient
c. 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.
d. Refer to NCI CTCAE v5 for term-specific grading criteria.

17.1.8 Neurologic toxicity management

Neurological Adverse Event Management		
Grade of Neurological Toxicity	**Management**	**Follow-Up**
Grade 1: Asymptomatic or mild symptoms; Intervention not indicated	– Continue cabiralizumab and nivolumab therapy per protocol	**If worsens:** – Treat as Grade 2, 3, or 4
Grade 2: Moderate symptoms; Limiting instrumental ADL	– Delay cabiralizumab and nivolumab therapy per protocol[a] – Treat symptoms per local guidelines – Consider 0.5 to 1 mg/kg/day methylprednisolone IV or PO[c]	**If improves to baseline within 28 days:** – Resume cabiralizumab and nivolumab therapy at same dose level per protocol when improved to baseline **If worsens or persists after 28 days:** – Treat as Grade 3-4
Grade 3–4: Severe symptoms; limiting self-care ADL; life-threatening	– Discontinue cabiralizumab and nivolumab therapy[b] – Obtain neurology consult – Treat symptoms per local guidelines 1 to 2 mg/kg/day IV methylprednisolone or PO[c] – Add prophylactic antibiotics for opportunistic infections	**If improves to Grade 2:** – Taper steroids over at least 1 month **If worsens or atypical presentation:** – Consider IVIG or other immunosuppressive therapies per local guidelines – Continue follow up until resolution

a. If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient.
b. If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by patient.
c. 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.

17.1.9 Periorbital edema management

Periorbital Edema Adverse Event Management		
Grade of Periorbital Edema	**Management**	**Follow-Up**
Periorbital Edema > baseline but **< Grade 2**	– Continue cabiralizumab and nivolumab therapy per protocol – Monitor edema weekly	**If worsens:** – Follow as stated below
Grade 2	– Delay cabiralizumab and nivolumab therapy per protocol[a] – Start systemic treatment including steroids, eye drops, or analgesics as needed[c]	**If returns to Grade 1 or baseline before the next dosing visit:** – Continue systemic treatment – Resume cabiralizumab and nivolumab therapy at same dose level without delay – Routine eye monitoring per protocol, if clinically stable **If swelling persists >14 days but returns back to baseline or normal within 28 days:** – Continue nivolumab and cabiralizumab dosing at same level – If recurs at Grade 2 or above, discontinue cabiralizumab and nivolumab therapy
Grade ≥3	– Discontinue cabiralizumab and nivolumab therapy per protocol[b] – Systemic treatment including steroids, eye drops, or analgesics as needed[c] – Consult Ophthalmologist if needed	**If returns to Grade 1 after discontinuation:** – Systemic treatment including tapering steroids as needed – Any follow up and ophthalmology consults, if clinically indicated – Monitor and follow up until resolution

a. If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient.
b. If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by patient.
c. 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.

17.1.10 Uveitis management

Uveitis Adverse Event Management		
Grade of Uveitis	**Management**	**Follow-Up**
Grade 1	– Observe symptoms – Continue cabiralizumab and nivolumab therapy	– Watch for worsening of symptoms including visual disturbances, light sensitivity, decrease vision – Monitor weekly **If worsens:** – Follow as stated below
Grade 2	– Delay or discontinue cabiralizumab and nivolumab therapy per protocol[a,b] – Start antibiotics and inflammatory medications including steroidsc – Ophthalmologic consult, if clinically indicated – Immunosuppressive agents (e.g, anti-TNF agents such as Infliximab)	**If symptoms resolve within 14 days:** – Continue cabiralizumab and nivolumab therapy at same dose level and start tapering of steroid doses **If symptoms resolve between 14 -28 days:** – Consider continuing dosing at same dose level for nivolumab and a dose level lower for cabiralizumab on resolution to baseline or Grade 1 and start tapering of steroid doses. – If it is Grade 2 drug related uveitis which does not resolve within 14 days, consider to discontinue study drug(s) **If symptoms persist or worsen in 28 days regardless of systemic treatment:** – Discontinue both cabiralizumab and nivolumab therapy – Continue monitoring of symptoms including visual disturbances, eye pain, and dimness of vision and follow up until resolution or return to baseline – Continue steroids, antibiotics, and other medications such as infliximab, as clinically indicated
Grade ≥3	– Discontinue cabiralizumab and nivolumab therapy per protocol[b] – Start antibiotics and inflammatory medications including steroids[c] – Ophthalmologic consult, if clinically indicated – Immunosuppressive agents (e.g, anti-TNF agents such as Infliximab)	– Discontinue both cabiralizumab and nivolumab therapy – Continue monitoring of symptoms including visual disturbances, eye pain, and dimness of vision and follow up until resolution or return to baseline – Continue steroids, antibiotics, and other medications such as infliximab, as clinically indicated – Follow up until resolution

a. If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient
b. If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by patient
c. 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.

17.2 Laboratory abnormalities management

Laboratory Abnormalities Management (CK and LDH)		
Grade of Liver Test Elevation	**Management**	**Follow-Up**
CK > 10 xULN	– Measure CK isoenzymes – Obtain EKG to evaluate arrhythmia/myocarditis	**If CK isoenzymes are abnormal** – Check troponin levels – Consider other assessments (including uromyoglobin and echocardiogram) as clinically indicated **If CK isoenzymes are normal** – Continue dosing, per protocol – Monitor CK level as clinically indicated
CK or LDH > 15 to ≤ 20 xULN	– Delay cabiralizumab therapy per protocol[a] – Measure CK isoenzyme panel to identify source of elevation, if abnormal check troponin and consider other assessments as clinically indicated – Increase frequency of monitoring (every 48-72 hours, or more, as clinically indicated) – Obtain EKG to evaluate arrhythmia/myocarditis – Notify the Sponsor Investigator	**If returns to ≤ 15 xULN within ≤ 28 days:** – Resume routine monitoring, resume cabiralizumab and nivolumab therapy at same dose level per protocol – If CK isoenzyme panel is normal continue monitoring the subject. – If CK isoenzyme panel is abnormal then consider measuring troponins. – If troponins are abnormal, contact Sponsor Investigator to determine if the subject can be retreated. **If elevations persist at the same level > 28 days or worsen:** – Discontinue further dosing – Discuss with Sponsor Investigator
CK or LDH > 20 xULN	– Discontinue cabiralizumab therapy per protocol – Obtain EKG to evaluate arrhythmia/myocarditis	– Follow up until resolution

a. If the AE requiring dose delay was due to one of the study drugs, the non-offending drug may be continued, taking into account the safety and clinical benefit to the patient.
b. If the AE requiring discontinuation was due to one of the study drugs, the non-offending drug may be continued, if there is timely resolution of AE and clinical benefit is shown by patient

17.3 Lugano staging criteria

Stage	Involvement	Extranodal (E) status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky*	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

*Defined as a mass with the largest diameter ≥10 cm, or, for the mediastinum only, a mass larger than one third of the measured chest diameter.

17.4 Eastern Cooperative Group (ECOG) Performance Status Scale

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 self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

17.5 LYRIC criteria for response

Response and Site	PET-CT-Based Response	CT-Based Response
Complete Response (CR)	**Complete metabolic response**	**Complete radiologic response (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

Response and Site	PET-CT-Based Response	CT-Based Response
Partial Response (PR)	**Partial metabolic response**	**Partial remission (all of the following)**
Lymph nodes and extralymphatic sites	Score 4 or 5* with reduced uptake compared with baseline and residual mass(es) of any size 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 lesion	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease (SD)	**No metabolic response**	**Stable disease**
Lymph nodes and extralymphatic sites	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 lesion	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

Response and Site	PET-CT-Based Response	CT-Based Response
Indeterminate Response 1 (IR1)		Increase in the overall tumor burden with SPD ≥50% of up to 6 measurable lesions in the first 12 weeks of therapy, without a clinical deterioration.
Indeterminate Response 2 (IR2)		Appearance of new lesions or growth of one or more existing lesion(s) ≥50% at any time during treatment; occurring in the context of lack of overall progression (<50% increase) of overall tumor burden, as measured by SPD of up to 6 lesions at any time during the treatment
Indeterminate Response 3 (IR3)	Increase in FDG uptake of 1 or more lesion(s) without a concomitant increase in lesion size or number	

Response and Site	PET-CT-Based Response	CT-Based Response
Progressive Disease (PD)	**Progressive metabolic disease**	**Progressive disease requires ≥1 of the following**
Lymph nodes	Score 4 or 5* with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesion	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Response and Site	PET-CT-Based Response	CT-Based Response

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.

Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

*PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly > liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

17.6 Lugano 2014 response criteria

Response and Site	PET-CT-Based Response	CT-Based Response
Complete Response (CR)	**Complete metabolic response**	**Complete radiologic response (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

Response and Site	PET-CT-Based Response	CT-Based Response
Partial Response (PR)	**Partial metabolic response**	**Partial remission (all of the following)**
Lymph nodes and extralymphatic sites	Score 4 or 5* with reduced uptake compared with baseline and residual mass(es) of any size 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 lesion	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease (SD)	**No metabolic response**	**Stable disease**
Lymph nodes and extralymphatic sites	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 lesion	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

Response and Site	PET-CT-Based Response	CT-Based Response
Progressive Disease (PD)	**Progressive metabolic disease**	**Progressive disease requires ≥1 of the following**
Lymph nodes	Score 4 or 5* with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesion	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Response and Site	PET-CT-Based Response	CT-Based Response

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.

Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

*PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly > liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.