**NCI Protocol #:** N/A
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**TITLE:** A phase II trial of ipilimumab with and without nivolumab in patients with relapsed/refractory classic Hodgkin lymphoma


**Coordinating Center:** Dana-Farber Cancer Institute

**Principal Investigator (PI):** Reid Merryman, MD
Dana-Farber Cancer Institute
450 Brookline Avenue
Boston, MA 02215
Reid_Merryman@dfci.harvard.edu

**Senior Investigator:** Philippe Armand, MD, PhD
Dana-Farber Cancer Institute
Philippe_Armand@dfci.harvard.edu

Margaret Shipp, MD
Dana-Farber Cancer Institute
Margaret_Shipp@dfci.harvard.edu

**Statistician:** Robert Redd
Dana-Farber Cancer Institute
Robert_Redd@DFCI.HARVARD.EDU


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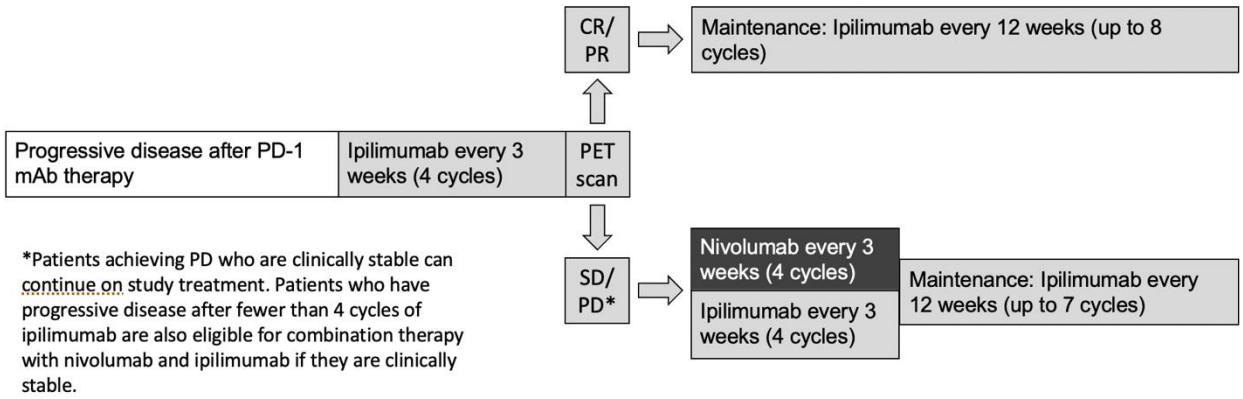
## SCHEMA




*Patients achieving PD who are clinically stable can continue on study treatment. Patients who have progressive disease after fewer than 4 cycles of ipilimumab are also eligible for combination therapy with nivolumab and ipilimumab if they are clinically stable.

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# 1. OBJECTIVES

## 1.1 Study Design

This is an open-label phase II study of ipilimumab with or without nivolumab for patients with relapsed or refractory (R/R) classic Hodgkin lymphoma (cHL).

Patients who have previously failed a PD-1 mAb will receive 4 cycles of ipilimumab monotherapy and then undergo a restaging PET scan. Patients achieving an objective response will continue ipilimumab maintenance therapy. Patients with SD or progressive disease (PD) (if clinically stable) will receive 4 cycles of combination therapy with ipilimumab and nivolumab followed by ipilimumab maintenance therapy. Patients who have progressive disease after fewer than 4 cycles of ipilimumab are also eligible to proceed to combination therapy with nivolumab and ipilimumab, if they are clinically stable. The primary endpoint will be objective response rate (ORR) to 4 cycles of ipilimumab monotherapy.

## 1.2 Primary Objectives

- To estimate the ORR of ipilimumab monotherapy in patients with R/R cHL who failed a PD-1 mAb

## 1.3 Secondary Objectives

- Best ORR, PRR, CRR assessed by PET/CT (using Lugano criteria and LYRIC criteria) after ipilimumab monotherapy
- Best ORR, PRR, CRR assessed by PET/CT (using Lugano criteria and LYRIC criteria) after ipilimumab and nivolumab combination therapy
- To evaluate the following outcomes among patients receiving ipilimumab maintenance:
    - DOR and PFS (Lugano criteria and LYRIC criteria)
    - OS
    - Above endpoints, stratified by best response to PD-1 mAb (non-responder versus responder)
- To evaluate the following outcomes among patients receiving re-induction with ipilimumab/nivolumab combination therapy:
    - DOR and PFS (Lugano criteria and LYRIC criteria)
    - OS
    - Above endpoints, stratified by best response to PD-1 mAb (non-responder versus responder)
- To evaluate the safety of study treatment (within the entire study popultion, among patients receiving ipilimumab maintenance, and among patients receiving ipilimumab/nivolumab combination treatment) as measured by:
    - Rate of grade 3 or higher toxicity regardless of attribution
    - Rate of grade 3 or higher toxicity at least possibly related to study treatment
    - Rate of grade 2 or higher toxicity at least probably related to study treatment

### 1.4 Exploratory Objectives

- To determine if features of the cHL TME are associated with response or resistance to study treatment
- To determine if early reduction in ctDNA is associated with improved PFS.
- To characterize the genetic bases of immune evasion and correlate these alterations with responses to therapy

## 2. BACKGROUND

### 2.1 Classic Hodgkin Lymphoma

Classic Hodgkin lymphoma (cHL) is diagnosed in approximately 8,500 people in the United States each year and is one of the most common cancers among young adults(1). The majority of patients are cured with first-line therapy, but approximately 10-15% of patients with early stage cHL and 15-30% of patients with advanced stage cHL will have primary refractory lymphoma or experience recurrence. Many of these patients may be cured with salvage chemotherapy and consolidative autologous stem cell transplantation (ASCT), but a significant cohort of patients are ineligible for these curative treatments due to chemoresistance, age, or comorbidities, or will relapse following ASCT.

Historically, patients who are ineligible for or relapse following ASCT have experienced poor outcomes with a median OS of approximately 2 years(2). With the development of new, highly active agents, however, the prognosis of chemotherapy-resistant disease has improved dramatically. Initial trials of brentuximab vedotin (BV) and PD-1 mAbs demonstrated high ORRs in patients with chemotherapy-resistant disease, however, CRRs are low (30-35% for BV and 15-25% for PD-1 mAbs) and a large majority of patients eventually relapse following these treatments(3–5). Currently, there are no therapies approved for progression after BV and PD-1 blockade. Depth of response appears to be a predictor of response duration for PD-1 mAbs. In the phase II trial of nivolumab, patients achieving a CR had more prolonged PFS compared to patients achieving a PR or stable disease(3). Novel treatment strategies are needed for patients who achieve an incomplete response or who experience progression on PD-1 blockade.

### 2.2 Ipilimumab

#### 2.2.1 Mechanism of Action

Ipilimumab has specificity and high affinity for human CTLA-4. Ipilimumab completely blocked binding of B7.1 and B7.2 to human CTLA-4 at concentrations higher than 6 ug/mL and 1 ug/mL, respectively. Data suggests that treatment with ipilimumab has a low ability to elicit effector functions able to deplete activated T cells in vivo.

#### 2.2.2 Non-clinical Pharmacology

The half-life of ipilimumab in cynomolgus monkeys was long (203 ± 62.8 to 339 ± 112 hours). Consistent with the long half-life, the total plasma clearance after a single dose of ipilimumab was low (0.196 ± 0.037 mL/h/kg). The steady state volume of distribution, 44.1 ± 6.05 mL/kg, was similar to the reported plasma volume of monkeys, suggesting that ipilimumab remained in the vascular system.

In accordance with regulatory guidelines for biotechnology-derived pharmaceuticals, no tissue distribution studies with ipilimumab have been conducted in animals. However, the low volume of distribution in cynomolgus monkeys (0.046 to 0.060 L/kg) for each study drug indicates that there is little extravascular distribution of the drug. The expected in vivo degradation of mAbs is to small peptides and amino acids via biochemical pathways that are independent of cytochrome P450 enzymes.

### 2.2.3 Clinical Pharmacology

Ipilimumab has a terminal half-life of approximately 15.4 days. A population PK analysis of ipilimumab (n=785) demonstrated that the PK of ipilimumab is linear and exposures are dose proportional across the tested dose range of 0.3 to 10 mg/kg. Upon repeated dosing of ipilimumab, administered every three weeks, minimal systemic accumulation was observed by an accumulation index of 1.5-fold or less and ipilimumab steady-state concentrations were achieved by the third dose.

The effects of various covariates on the PK of ipilimumab were assessed in population PK analyses. The clearance of ipilimumab increased with increasing body weight supporting the recommended body weight (mg/kg) based dosing. The following factors had no clinically important effect on the clearance of ipilimumab: age (range: 23 to 88 years), sex, performance status, renal impairment, mild hepatic impairment, previous cancer therapy, and baseline lactate dehydrogenase (LDH) levels. The effect of race was not examined due to limited data available in non-Caucasian ethnic groups.

*Renal Impairment*: The effect of renal impairment on the clearance of ipilimumab was evaluated in patients with mild, moderate, and severe renal impairment compared to patients with normal renal function in population PK analyses. No clinically important differences in the clearance of ipilimumab were found between patients with renal impairment and patients with normal renal function

*Hepatic Impairment*: The effect of hepatic impairment on the clearance of ipilimumab was evaluated in patients with mild hepatic impairment (n=76) compared to patients with normal hepatic function (n=708) in the population PK analyses, and no clinically important differences in the clearance of ipilimumab were found. Ipilimumab has not been studied in patients with moderate or severe hepatic impairment.

### 2.2.4 Safety and clinical activity

The overall safety experience with ipilimumab, as a monotherapy or in combination with other

therapeutics, is based on experience in dozens of clinical trials and post-approval safety monitoring. For monotherapy, the safety profile is similar across tumor types. In Phase 3 controlled studies, the safety profile of ipilimumab 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 manageable by delaying or stopping ipilimumab treatment and timely immunosuppressive therapy or other supportive care.

Several small studies have tested ipilimumab as a single agent in patients with cHL (see section 2.3). More extensive information regarding safety and clinical activity is available for other cancer histologies, in particular, melanoma. The safety and efficacy of adjuvant ipilimumab therapy was tested in randomized phase III trial among patients with resected stage III cutaneous melanoma (NCT00636168). Patients were randomized to receive ipilimumab 10 mg/kg or placebo as an intravenous infusion every 3 weeks for 4 doses, followed by ipilimumab 10 mg/kg or placebo every 12 weeks from Week 24 to Week 156 (3 years) or until documented disease recurrence or unacceptable toxicity. Ipilimumab treatment was associated with an improvement both recurrence-free survival (HR 0.75, $p<0.002$) and overall survival (0.72, $p<0.002$). Among the patients treated with ipilimumab, the most frequent adverse events included pruritus (41%), diarrhea (39%), fatigue (38%), rash (38%), headache (31%), weight loss (31%), nausea (24%), ALT elevation (16%), abdominal pain (14%), pyrexia (14%), cough (14%), decreased appetite (14%), AST elevation (12%), hypophysitis (13%), and vomiting (12%). Grade 3+ adverse events occurring in more than 1% of patients included: diarrhea (10%), colitis (7%), hypophysitis (5%), ALT elevation (5%), AST elevation (4%), pruritus (2%), fatigue (2%), rash (1%), nausea (1%), and pyrexia (1%)(6). Rates of irAEs and treatment discontinuation are lower when ipilimumab is dose at 3 mg/kg (7).

## 2.3 Nivolumab

### 2.3.1 Mechanism of Action

Nivolumab is an IgG4 antibody which binds to PD-1 (Programmed cell death protein 1; CD279) with nanomolar affinity and shows a high degree of specificity for PD-1 – blocking binding of PD-1 to PD-L1 and PD-L2. Nivolumab binds to human PD-1 and not to other members of the CD28 family, such as ICOS, CTLA-4 or BTLA. Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors.

### 2.3.2 Non-clinical Pharmacology

Cynomolgus monkeys received single IV doses of nivolumab at 1 mg/kg (3 males and 3 females) and 10 mg/kg (3 males). Nivolumab was immunogenic in this study: 5 of 6 animals administered doses of 1 mg/kg and 2 of 3 animals administered doses of 10 mg/kg tested positive for anti-nivolumab antibodies (determined to be neutralizing antibodies) 27 days after dosing. Nivolumab concentrations declined in a multi-phasic manner from the maximum concentration, which was observed at 0.25 to 0.5 hours. Concentrations were measurable through a median time of 384 hours for males and females at 1 mg/kg and through 648 hours for males at 10 mg/kg. The

apparent elimination half-life estimates for males and females at 1 mg/kg were similar, at 124 and 139 hours, respectively. The T-HALF estimate at 10 mg/kg for males was 261 hours, but the data were variable (SD = 200 hours). Consistent with the long half-life, total serum clearance was low. Systemic exposure to nivolumab increased in an approximately dose proportional manner.

### 2.3.3 Clinical Pharmacology

Nivolumab pharmacokinetics (PK) were assessed using a population PK approach for single-agent nivolumab. The PK of nivolumab was studied in patients over a dose range of 0.1 mg/kg to 20 mg/kg or as a flat dose of 240-480mg administered as a single dose or as multiple doses of nivolumab as a 60-minute intravenous infusion every 2 or 4 weeks. The exposure to nivolumab increases dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The predicted exposure of nivolumab after a 30-minute infusion is comparable to that observed with a 60-minute infusion. Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was 3.7-fold.

*Distribution:* The geometric mean volume of distribution at steady state and coefficient of variation is 6.8 L (27.3%).

*Elimination:* Nivolumab clearance decreases over time, with a mean maximal reduction from baseline values of 24.5% resulting in a geometric mean steady-state clearance of 8.2 mL/h in patients with metastatic tumors; the decrease in steady-state clearance is not considered clinically relevant. Nivolumab clearance does not decrease over time in patients with completely resected melanoma, as the geometric mean population clearance is 24% lower in this patient population compared with patients with metastatic melanoma at steady state. The geometric mean elimination half-life is 25 days.

*Specific Populations:* The following factors had no clinically important effect on the clearance of nivolumab: age (29 to 87 years), weight (35 to 160 kg), sex, race, baseline LDH, PD-L1 expression, solid tumor type, tumor size, renal impairment (eGFR greater than or equal to 15 mL/min/1.73 $m^2$), and mild (total bilirubin [TB] less than or equal to the ULN and AST greater than ULN or TB greater than 1 to 1.5 times ULN and any AST) or moderate hepatic impairment (TB greater than 1.5 to 3 times ULN and any AST). Nivolumab has not been studied in patients with severe hepatic impairment (TB greater than 3 times ULN and any AST).

*Drug Interaction Studies:* When nivolumab 1 mg/kg was administered in combination with ipilimumab 3 mg/kg, the clearance of nivolumab was increased by 29% and the clearance of ipilimumab was unchanged compared to nivolumab administered alone. When nivolumab 3 mg/kg was administered in combination with ipilimumab 1 mg/kg, the clearance of nivolumab and ipilimumab were unchanged. When administered in combination, the clearance of nivolumab increased by 20% in the presence of anti-nivolumab antibodies.

### 2.3.4 Safety and clinical activity

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 20,200 subjects treated to date.
For monotherapy, the safety profile is similar across tumor types. 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.

Two studies evaluated the efficacy of nivolumab as a single agent in adult patients with cHL after failure of autologous stem cell transplantation (ASCT). CHECKMATE-205 (NCT02181738) was a single-arm, open-label, multicenter, multicohort trial in cHL. CHECKMATE-039 (NCT01592370) was an open-label, multicenter, dose escalation trial that included patients with cHL. Patients received nivolumab 3 mg/kg by intravenous infusion every 2 weeks until disease progression, maximal clinical benefit, or unacceptable toxicity. Efficacy was evaluated in 258 patients in CHECKMATE-205 and CHECKMATE-039 combined who had relapsed or progressive cHL after ASCT. Patients had a median of 4 prior systemic regimens (range: 2 to 15), with 85% having 3 or more prior systemic regimens and 76% having prior brentuximab vedotin. Patients received a median of 21 doses of nivolumab (range: 1 to 48) and achieved a best ORR of 69% and a CRR of 14%. The median PFS was 13.1 months. The median DOR has not yet been reached. In the larger phase II CHECKMATE-205 study, the most common drug-related adverse events were fatigue (23%), diarrhea (15%), infusion relation (14%), rash (12%), nausea (10%), and pruritus (10%). Grade 3 or higher drug-related adverse events occurring in at least 1% of patients included: lipase increase (5%), neutropenia (3%), ALT increase (3%), AST increase (2%), amylase increase (2%), pneumonia (1%)(3,8).

### 2.3.5 Safety of combination ipilimumab and nivolumab

The combination of nivolumab + ipilimumab is approved in subjects with unresectable or metastatic melanoma as well as metastatic renal cell carcinoma and is currently being studied in multiple tumors. 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.

The combination of nivolumab (3 mg/kg) plus ipilimumab (1 mg/kg) was tested in 550 patients with advanced stage renal cell carcinoma as part of a phase III trial. In this cohort, the most common treatment-related adverse events were fatigue (37%), pruritus (28%), diarrhea (27%), rash (22%), nausea (20%), increased lipase level (16%), decreased appetite (14%), asthenia (13%), and vomiting (11%). Grade 3 or higher drug-related adverse events occurring in at least 1% of patients included: increased lipase (10%), diarrhea (4%), fatigue (4%), rash (1%), nausea (1%), decreased appetite (1%), and asthenia (1%)(9). This combination was also tested in 31 patients with cHL as part of a phase 1b trial in 65 patients with relapsed hematologic malignancies. In this cohort, the most frequent adverse events were fatigue (26%), pyrexia (23%), and diarrhea (18%). In total, 19 pts (29%) had a drug-related AE of grade ≥3(10).

## 2.4 Rationale

Classic Hodgkin lymphoma (cHL) is characterized by an unusual tissue architecture composed of rare Reed-Sternberg (RS) cells surrounded by a complex network of immune cells that are unable to mount an effective anti-tumor immune response. In recent years, investigators have uncovered mechanisms by which RS cells evade immune detection, which has enabled significant therapeutic breakthroughs in cHL. Nearly all patients with cHL harbor genetic alterations in 9p24.1, an amplicon which contains the genes for both PD-1 ligands, PD-L1 and PD-L2(11). The amplicon also contains the JAK2 gene and augmented JAK/STAT signaling generates additional production of PD-L1 and PD-L2 proteins. Together, these alterations drive abundant expression of PD-1 ligands on RS cells which can bind to PD-1 on infiltrating effector immune cells leading to inactivation and immune evasion. Based on this genetic dependency, patients with cHL were included as independent cohort expansions in phase I trials of PD-1 inhibitors. These and subsequent phase II trials reported overall response rates (ORRs) of around 70% which led to the FDA approval of two PD-1 inhibitors, nivolumab and pembrolizumab, for relapsed/refractory (R/R) cHL(3,4,8,12).

However, even with the success of PD-1 directed mAb in cHL, significant challenges remain for patients with R/R disease. Approximately 10-15% of patients will progress rapidly with PD-1 blockade and many other patients will experience limited disease control with these agents(3,4). In particular, patients who achieve a best response of stable disease or partial response (~70% of all patients) achieve more limited progression-free survival (PFS) (11.2 months and 15.1 months, respectively) compared to patients who achieve a complete response (22.2 months)(3). Novel treatment strategies are needed for patients who achieve an incomplete response or who experience progression on PD-1 blockade.

While alterations in the PD-1 signaling axis are nearly universal and appear to be critical for cHL pathogenesis, numerous other immune checkpoint receptors and ligands are present in the cHL tumor microenvironment (TME) and may also play important roles in immune evasion. These immune checkpoints offer additional potential targets for therapeutic intervention. Patel et al. used multiplex immunofluorescence to analyze the expression and distribution of the inhibitory immune checkpoint receptor CTLA-4 and its ligand CD86 in cHL. They found frequent expression of CTLA-4 on intratumoral T cells and strong expression of CD86 on nearly all RS cells as well as on a subset of tumor-associated macrophages (TAMs). Intratumoral T cells were more likely to express CTLA-4 than PD-1 and both CTLA-4 and CD86 were enriched within PD-L1 positive clusters of RS cells and TAMS, suggesting that CTLA-4 may also be important for maintaining an immunosuppressive niche for RS cells. Importantly, frequent CTLA-4 and CD86 expression in the cHL TME was seen both before and after treatment with PD-1 blockade(13).

These results provide a strong scientific rationale for additional clinical investigation of CTLA-4 directed therapies in cHL. Already, there are several small studies that suggest that ipilimumab has clinical activity among patients with R/R cHL. Two trials have investigated single-agent ipilimumab among patients with relapsed disease after allogeneic transplantation. Two of fourteen patients achieved a complete response (CR) after a single dose of ipilimumab in an initial study(14), and 4 of 7 patients achieved a reduction in tumor burden (including 1 partial

response) in a subsequent study that employed repeated dosing of ipilimumab(15). Despite its use after allogeneic transplantation (where the risk of immune-related complications including graft-versus-host disease is high), the safety profile of single agent ipilimumab was manageable. The largest experience with CTLA-4 blockade in cHL comes from a trial combining ipilimumab (1 mg/kg) with nivolumab (3mg/kg) in patients with R/R hematologic malignancies. In this trial, 31 patients with HL received 4 cycles of combination therapy followed by nivolumab monotherapy every 2 weeks for up to 2 years. Response rates with the combination (ORR 74%, CRR 19%) were similar to PD-1 blockade monotherapy, but longer-term follow-up suggests that combination therapy may be associated with more durable remissions(10). The 18-month PFS with combination ipilimumab and nivolumab (~65%) which compares favorably to that observed with nivolumab monotherapy in the phase II CHECKMATE 205 trial (median PFS of 14.7 months). Higher rates of immune-related adverse events (irAEs) were observed with ipilimumab and nivolumab compared to nivolumab monotherapy, however, most irAEs were manageable. The rate of treatment discontinuation due to adverse events with combination therapy was similar to that observed in phase II trials of PD-1 mAb monotherapy (8% vs 4-6%)(3,4,10). Ipilimumab (1 mg/kg every 12 weeks) has also been tested in R/R cHL as part of a triplet therapy with nivolumab (3mg/kg every 3 weeks) and BV (1.8 mg/kg every 3 weeks). Among 22 patients, the ORR and CRR were 82% and 72%, respectively. Frequent adverse events were observed and while these were typically manageable, 3 patients (14%) discontinued therapy after one cycle(16).

The frequent expression of CTLA-4 and its ligand CD86 within the cHL TME provide a strong biologic rationale for CTLA-4 directed therapies in cHL. In addition, available clinical data suggests that ipilimumab has clinical activity and a tolerable risk profile when used as monotherapy or in combination with nivolumab. We have designed a phase II trial that targets the use of ipilimumab to those patients who derive less benefit from PD-1 blockade with the goal of limiting overall toxicity exposure. The trial will utilize a response-adapted design among patients who failed PD-1 mAb therapy. Patients will begin with ipilimumab monotherapy and then undergo a restaging PET/CT. Patients achieving an objective response will continue treatment with ipilimumab maintenance, while non-responders will receive ipilimumab and nivolumab re-induction therapy for 4 cycles followed by ipilimumab maintenance treatment. Given the key role of the PD-1 axis, we hypothesize that some patients may benefit from the addition of nivolumab to CTLA-4 blockade even after they have progressed following treatment with both treatments alone. Observation of objective responses to combination therapy with nivolumab and ipilimumab in this setting would provide strong evidence of synergy with combined PD-1 and CTLA-4 blockade.

## 2.5 Correlative Studies Background

### 2.5.1 Multiplex immunofluorescence (MIF):

This study will incorporate a laboratory technique known as MIF, which is used to examine the expression and distribution of up to 6 antigens of interest within formalin-fixed paraffin embedded (FFPE) tissue. The technique allows for examination of co-localization of proteins of interest and protein-protein interaction. MIF has been used successfully to interrogate the TME of multiple subtypes of lymphoma, including Hodgkin lymphoma, where it clarified the critical

roles of the PD-1 and CTLA-4 in maintaining an immunosuppressive microenvironment(13,17). We aim to use MIF to characterize the expression of immune checkpoint proteins (CTLA-4, CD86, PD-1, PD-L1, and others) and to describe the distribution of immune cells, including CD8+ T cells, CD4+ T cells, T regulatory cells, NK cells, and tumor-associated macrophages (TAMs). In addition, using on-treatment and post-progression tumor samples we will describe alterations following treatment with ipilimumab +/- nivolumab. We hypothesize that there may be baseline TME features that predicts response to ipilimumab +/- nivolumab therapy. In addition, post-progression biopsies may suggest mechanisms of resistance that could be explored further in subsequent studies.

2.5.2 Multiplex Ion Beam Imaging (MIBI):

Simultaneous detection of multiple targets is limited by spectral overlap of the fluorophores used to tag individual antibodies. Due to this technical limitation, MIF typically cannot assess more than 6 antigens at a time. Multiplex Ion Beam Imaging (MIBI) uses secondary ion mass spectrometry to image antibodies carrying metal isotopes. As a result, MIBI is capable of analyzing samples stained simultaneously with more than 40 metal-isotope labelled antibodies(18). This technique will be used in conjunction with MIF to analyze the TME of cHL, characterize the expression of immune checkpoint proteins, and describe the distribution of immune cells. In addition, using on-treatment and post-progression tumor samples we will describe alterations following treatment with ipilimumab +/- nivolumab.

2.5.3 Circulating tumor DNA (ctDNA):

Plasma is a source of circulating tumor DNA (ctDNA) which can be used for to identify tumor genotypes, copy number abnormalities, immunoglobulin gene rearrangements, and single gene mutations. In addition, serially collected plasma samples can be used to track the level of ctDNA over time in response to therapy. In multiple tumor lymphoma subtypes, including diffuse large B-cell lymphoma (DLBCL) and cHL, an early drop in level of ctDNA (i.e. 2 log reduction) after 2 cycles of induction chemotherapy has been associated with a significant improvement in PFS(19,20). Early data suggests that changes in levels of ctDNA may also hold predictive value for patients with lymphoma receiving immune-based therapies(21,22). We plan to collect serial plasma samples for analysis of ctDNA. Our group is currently developing an assay for ctDNA evaluation in cHL. We will quantify circulating tumor DNA at different timepoints and analyze changes in copy number abnormalities and relevant pathogenic gene. We hypothesize that an early reduction in ctDNA will be associated with clinical response and improved PFS. We will also use serial samples to characterize the genetic bases of immune evasion and correlate these alterations with responses to therapy

# 3. PARTICIPANT SELECTION

## 3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

3.1.1 Patients must have histologically determined classic Hodgkin lymphoma with pathologic review at the participating institution.

3.1.2 Participants must have measurable disease, defined as a lymph node or tumor mass ≥1.5 cm in at least one dimension by CT, PET/CT, or MR. Imaging must have been completed no greater than 6 weeks prior to study enrollment. Measurable disease that has previously been irradiated is permissible only if there has been evidence of progression since the radiation.

3.1.3 Patients must have progressed after two or more lines of systemic treatment, including autologous stem cell transplantation, if eligible.

3.1.4 Progression of disease or relapse following treatment with nivolumab or pembrolizumab. Intervening treatments with between PD-1 mAb therapy and the trial are permitted.

3.1.5 Patients may have had a prior autologous stem cell transplant and may have been treated with chimeric antigen receptor T-cells (CAR T-cells).

3.1.6 Age ≥18 years.

3.1.7 Eastern Cooperative Oncology Group (ECOG) performance status 0-2 (see Appendix A)

3.1.8 Adequate hematologic and organ function as defined below:

- Absolute neutrophil count > $1.0x10^9$/L unless due to marrow involvement by lymphoma in which case ANC must be >$0.75x10^9$/L. Growth factor support is allowed provided it is received at least 5 days prior to enrollment labs.
- Platelets > 75 $x10^9$/L, unless due to marrow involvement by lymphoma, in which case platelets must be >50 $x10^9$/L
- Estimated GFR (by Cockroft-Gault equation) > 40ml/min
- Total bilirubin < 1.5 X ULN
- AST/ALT < 2.5 X ULN

3.1.9 Ability to understand and the willingness to sign a written informed consent document.

3.1.10 Willingness to provide pre-treatment tumor sample by core needle or excisional surgical biopsy. An archival sample is acceptable in the following situations: the sample was acquired within 90 days of initiation of PD-1 therapy AND the following provisions are met: 1) availability of a tumor-containing formalin-fixed, paraffin-embedded (FFPE) tissue block, 2) if the tumor containing FFPE tissue block cannot be provided in total, sections from this block should be provided that are freshly cut and mounted on positively-charged glass slides (SuperFrost Plus are recommended). Preferably, 25 slides should be provided; if not possible, a minimum of 15 slides is required. Exceptions to this criterion may be made with approval of the Study Chair.

3.1.11 Willingness to use contraception during and after study treatment. Women of child-baring potential (WOCBP) will be instructed to adhere to contraception for a period of 5 months following last dose of nivolumab and 6 months following the last dose of ipilimumab. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 7 months after last dose of nivolumab and 6 months after the last dose of ipilimumab.

## 3.2 Exclusion Criteria

3.2.1 Patients currently receiving anticancer therapies or who have received anticancer therapies within 28 days of the start of study drug (including chemotherapy, radiation therapy, antibody-based therapy, etc.), or 56 days for radioimmunotherapy. Steroids for symptom palliation are allowed but must be either discontinued or on stable doses of < 10mg daily of prednisone (or the equivalent) at the time of initiation of protocol therapy.

3.2.2 Patients may not be receiving any other investigational agents or have received investigational agents within 4 weeks (or 3 half-lives, whichever is longer) of beginning treatment.

3.2.3 History of severe allergic or anaphylactic reactions to monoclonal antibody therapy unless in consultation with an allergy specialist they are deemed eligible for retreatment with desensitization.

3.2.4 Patients who have undergone prior allogeneic stem cell transplantation

3.2.5 Patients with a history of or active autoimmune disease (except controlled asthma, Hashimoto thyroiditis, atopic dermatitis, or vitiligo), or requiring systemic corticosteroids at a dose of 10mg prednisone equivalent daily. Patients with a history of autoimmune disease who never required corticosteroids and with no evidence of disease activity, and in whom the risk of reactivation is felt not to be serious, may be enrolled after discussion with the overall study chair. Exceptions to this are patients with a history of inflammatory bowel disease (ulcerative colitis and Crohn's disease). These patients are excluded regardless of whether their disease is active or inactive.

3.2.6 Patients who experienced grade 4 immune-related adverse events (irAEs) during treatment with a PD-1 mAb.

3.2.7 Patients with active pneumonitis or colitis, or patients with cirrhosis.

3.2.8 Patients, who have had a major surgery or significant traumatic injury within 4 weeks of start of study drug, patients who have not recovered from the side effects of any major surgery (defined as requiring general anesthesia).

3.2.9 Patients with known HIV infection or hepatitis B or C infection. Testing for HIV is optional. Testing for hepatitis B and C is mandatory. Patients with hepatitis B core Ab positivity but negative surface antigen and negative viral load may be enrolled if they can be treated with a prophylactic agent (eg, entecavir); patients with hepatitis C seropositivity who have a negative viral load can also be enrolled.

3.2.10 Patients with a systemic fungal, bacterial, viral, or other infection not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment).

3.2.11 Prior history of another malignancy (except for non-melanoma skin cancer or *in situ* cervical or breast cancer) unless disease free for at least 2 years. Patients with prostate cancer are allowed if PSA is less than 1.

3.2.12 Patients should not have received immunization with attenuated live vaccine within one week of study entry or during study period.

3.2.13 History of noncompliance to medical regimens.

3.2.14 Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study.

3.2.15 Patients with any one of the following currently on or in the previous 6 months will be excluded: myocardial infarction, congenital long QT syndrome, torsade de pointes, left anterior hemiblock, unstable angina, coronary/peripheral artery bypass graft, or cerebrovascular accident.

3.2.16 Other uncontrolled intercurrent illness that would limit adherence to study requirements.

### 3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

## 4. REGISTRATION PROCEDURES

### 4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Principal Investigator (PI) of the registering site. If the subject does not receive protocol therapy following registration, the subject must be taken off study in the CTMS (OnCore) with an appropriate date and reason entered.

### 4.2 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed.

### 4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at the Dana-Farber Cancer Institute by the Project Manager. All sites should call the Project Manager at 617-632-2328 to verify dose level availabilities.

Following registration, participants should begin protocol therapy within 5 days. Issues that would cause treatment delays should be discussed with the Sponsor-Investigator. If the subject does not receive protocol therapy following registration, the subject must be taken off study in the CTMS (OnCore) with an appropriate date and reason entered.

### 4.4 Registration Process for Other Investigative Sites

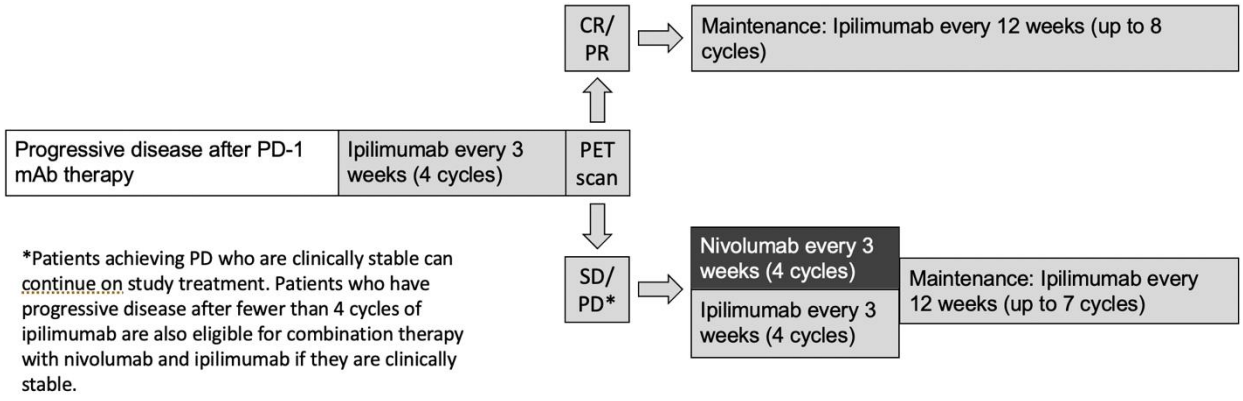
To register a participant, the following documents should be completed by participating site and e-mailed to the DFCI Project Manager.

- Copy of required assessments that support eligibility
- Signed informed consent document
- HIPAA authorization form (if applicable)
- Completed DFCI eligibility checklist

The participating site will e-mail the DFCI Project Manager to verify eligibility. The DFCI Project Manager will follow DF/HCC policy (REGIST-101) and register the participant on the protocol. The DFCI Project Manager will email the participant study number, and if applicable the dose treatment level, to the participating site. The DFCI Project Manager may also contact the participating site and verbally confirm registration.

## 5. TREATMENT PLAN

**Figure 1 Trial Schema**




Patients with R/R cHL who have previously failed a PD-1 mAb will be enrolled. For details regarding dosing, see section 5.1. Study therapy is expected to be administered on an outpatient basis. Patients will receive 4 doses of ipilimumab therapy dosed every 3 weeks (12 weeks), followed by a restaging PET/CT scan. Patients achieving an objective response to ipilimumab monotherapy will receive up to 8 doses of maintenance ipilimumab dosed every 12 weeks (96 weeks), for a total of 108 weeks of study therapy. Patients with SD or PD following ipilimumab monotherapy (who are clinically stable) will receive 4 cycles of combination ipilimumab and nivolumab therapy dosed every 3 weeks (12 weeks), followed by up to 7 doses of maintenance ipilimumab dosed every 12 weeks (84 weeks), for a total of up to 108 weeks of study therapy. Patients who have progressive disease after fewer than 4 cycles of ipilimumab are eligible to proceed to combination therapy with nivolumab and ipilimumab if they are clinically stable. Therapy will be stopped sooner for unacceptable toxicity, patient withdrawal, disease progression, physician decision, or death. Patients achieving a complete response for ≥ 6 months

can elect to stop study therapy.

Patients will be evaluated with PET/CT scans at baseline and again after 4 doses of ipilimumab monotherapy (week 12) (or earlier if there is clinical concern for progression). Among ipilimumab responders, restaging scans will occur prior to ipilimumab maintenance cycle 2 (week 24), cycle 3 (week 36), cycle 5 (week 60), and cycle 7 (week 84). Among ipilimumab non-responders, restaging scans will occur after 4 cycles of ipilimumab + nivolumab combination therapy (week 24) and prior to ipilimumab maintenance cycle 2 (week 36), cycle 4 (week 60), and cycle 6 (week 84). The end-of-treatment assessment will occur 4-12 weeks after the last doses of study therapy (i.e. weeks 112-120 for patients who complete all planned study therapy). Afterwards, patients will be re-imaged every 24 weeks. Patients in CR at any time point may have CT imaging only at subsequent time points.

Toxicity will be continuously monitored and recorded using CTCAE 5 criteria, up to 30 days following the last dose of the study treatment or until resolution of toxicity to grade 1 or baseline, whichever occurs last.

Tumor biopsies (pre-treatment, on-treatment, and post-progression) and serial peripheral blood samples will be used to identify possible genetic or immune biomarkers of response. When safely feasible, tumor biopsy (excisional or core needle) will be obtained at baseline (unless an archival sample within 90 days and without intervening treatment is available with at least 15 unstained slides). In addition, patients will undergo an optional core needle biopsy between day 14 and 21 of cycle 1 of therapy. When feasible, a core needle biopsy will also be obtained at the time of progression. Serial peripheral blood will be collected for research purposes (see Section 9).

## 5.1 Treatment Regimen

**Table 1 Treatment regimen**

| | | |
|---|---|---|
| **Induction treatment** | Ipilimumab 3 mg/kg every 3 weeks for 4 doses | Ipilimumab 3 mg/kg every 3 weeks for 4 doses |
| **Re-induction** | Ipilimumab responders: Not applicable | Ipilimumab non-responders: Nivolumab 3mg/kg + Ipilimumab 1 mg/kg every 3 weeks for 4 doses (i.e. on day 1 of each 3-week cycle) |
| **Maintenance treatment** | Ipilimumab 3 mg/kg every 12 weeks (for up to 8 doses) | Ipilimumab 3 mg/kg every 12 weeks (for up to 7 doses) |

Patients will receive ipilimumab 3 mg/kg every 3 weeks for 4 doses followed by a restaging PET/CT scan. Patients achieving an objective response to ipilimumab monotherapy will receive up to 8 doses of maintenance ipilimumab dosed at 3mg/kg every 12 weeks (96 weeks), for a total

of 108 weeks of study therapy. Patients with SD or PD after ipilimumab monotherapy, (who are clinically stable) will receive 4 cycles of combination ipilimumab 1 mg/kg and nivolumab 3 mg/kg dosed every 3 weeks (12 weeks), followed by up to 7 doses of maintenance ipilimumab dosed at 3 mg/kg every 12 weeks (96 weeks), for a total of up to 108 weeks of study therapy. Patients who have progressive disease after fewer than 4 cycles of ipilimumab are eligible to proceed to combination therapy with nivolumab and ipilimumab if they are clinically stable. Patients will continue study therapy until PD* or unacceptable toxicity. Patients achieving a complete response for ≥ 6 months can elect to stop ipilimumab therapy.

Patients can opt to continue trial therapy beyond progression if they meet the conditions described in Section 5.6.

## 5.2 Pre-Treatment Criteria

The following treatment parameters must be met at visits when each new cycle is being started:

- ANC must be ≥ 500/mm$^3$,
- Platelet count must be ≥ 50 x 10$^9$/L, All non-hematologic toxicities have improved sufficiently to restart treatment per Table 6.

## 5.3 Agent Administration

### 5.3.1 Ipilimumab

Ipilimumab will be administered intravenously as a 90-minute infusion (+/- 15 minutes) on day 1 of each cycle at a dose of 1 mg/kg when administered in combination with nivolumab and at a dose of 3 mg/kg when administered alone. Maintenance ipilimumab (3 mg/kg) will be administered once every 12 weeks. Dosing of ipilimumab will be based on actual body weight. When both study drugs are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be ipilimumab and will start no sooner than 30 minutes after completion of the nivolumab infusion. For management of infusion reactions, see section 6.6.

### 5.3.2 Nivolumab

Nivolumab will be administered intravenously as a 30-minute infusion (+/- 10 minutes) on day 1 of relevant treatment cycles at a dose of 3 mg/kg. When both study drugs are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be ipilimumab and will start no sooner than 30 minutes after completion of the nivolumab infusion. For management of infusion reactions, see section 6.6.

## 5.4 General Concomitant Medication and Supportive Care Guidelines

Medications or vaccinations specifically prohibited in the exclusion criteria are also not allowed during the active treatment period, except for administration of inactivated vaccines (for example, inactivated influenza vaccine). If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, permanent discontinuation from study therapy may be required. The Investigator should consult with the Principal investigator about individual cases. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the patient's primary physician. However, the decision to continue the patient on study therapy or medication/vaccination schedule requires the mutual agreement of the Investigator, the Principal investigator, and the patient. Prior/concomitant treatment considered necessary for the patient's well-being may be given at discretion of the treating physician.

Concomitant medications and treatments, including herbal supplements, will be recorded from 28 days prior to the start of study treatment and up to 90 days after the last dose of study treatment (at Days 30, 60, and 90 post-treatment +3 days). All concomitant medications and Non-Drug Supportive Interventions should be recorded in the CRF including supportive care drugs (eg, antiemetic treatment and prophylaxis), and the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions).

Medications intended solely for supportive care (ie, antiemetics, analgesics, megestrol acetate for anorexia) are allowed.

### 5.4.1 Pre-medications

No pre-medications are required with this regimen, unless the patient experiences an infusion-related reaction (see Section 6.4).

### 5.4.2 Antibiotics

Infectious prophylaxis is not required while on study.

### 5.4.3 Hydration

No pre-hydration or hydration is required with this regimen.

### 5.4.4 Other supportive treatments

Growth factors, blood product transfusions, and the use of bisphosphonates are permitted at the discretion of the treating physician.

### 5.4.5 Other Prohibited Concomitant Medications and Treatments

Patients are prohibited from receiving the following therapies during the treatment phase of this trial:

- Anti-cancer systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.

- Investigational agents other than ipilimumab +/- nivolumab.
- Immunosuppressive drugs, unless otherwise indicated for the treatment of irAEs (see Clarification About Steroid Use below), or for treatment of issues unrelated to study drug after consultation with study chair.
- Medications or vaccinations specifically prohibited in the exclusion criteria are also not allowed during the active treatment period; however, the administration of inactivated vaccines (eg, influenza vaccine) is allowed during the study.
- Herbal remedies with immunostimulating properties (eg, mistle toe extract) or known to potentially interfere with major organ function (eg, hypericin).
- Daily intake over 2 grams acetaminophen/paracetamol.
- Radiation therapy can be considered for treatment of isolated symptomatic site(s) after discussion with the study chair.

**Clarifications About Steroid Use with ipilimumab +/- nivolumab**: Data have indicated that corticosteroids have an adverse effect on T-cell function and that they inhibit and damage lymphocytes(24). Furthermore, as with all immunotherapies intended to augment cell mediated immunity, there is a risk that concomitant immunosuppressive therapies, such as steroids, will counteract the intended benefit of the proposed study treatment. However, studies with anti-CTLA-4 compounds have indicated that short-term use of steroids may be employed without compromising clinical outcomes(24). Therefore, the use of steroids during this trial is restricted as follows:

- Therapeutic use: for the treatment of infusion related reactions and treatment of irAEs, steroids are permitted according to the modalities indicated in Table 2: Management of Immune-Related Adverse Events.
- Physiologic use: steroid replacement for adrenal insufficiency at doses equivalent to ≤10 mg prednisone daily is acceptable.
- Other uses should be first discussed with the Study Chair

## 5.5 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), maintenance therapy may continue per Section 5.1 or until one of the following criteria applies:

- Disease progression. (*Note*: patients who have PD after ipilimumab may continue trial therapy with ipilimumab + nivolumab if they are clinically stable. Patients experience progressive disease at other time points may continue trial therapy beyond progression if they meet the criteria described in section 5.6).
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off of the study, the participant's status must be updated in OnCore in accordance with REGIST-OP-1.

## 5.6 Continuation of Treatment Beyond Progression

Accumulating evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses follows delayed kinetics of weeks or months and can be preceded by initial apparent radiological progression or appearance of new lesions or some enlarging lesions while certain target lesions are regressing ("mixed response"). It may thus reasonable to allow for these possibilities and continue to treat the subject until progression is confirmed at the next imaging assessment. These considerations should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment. Such deterioration will be assessed to have occurred after a clinical event that, in the Investigator's opinion, is attributable to disease progression, is unlikely to reverse with continued study treatment and therefore indicates that the subject is not benefiting from study treatment and cannot be managed by the addition of supportive care.

The following criteria must be met for a patient to receive study treatment beyond progression:

1. The treating physician feels that the patient is deriving clinical benefit from treatment
2. Restaging scan meets criteria for an indeterminate response based on the lymphoma response to immunomodulatory therapy criteria (LYRIC criteria) (23) (see Appendix C)
    a. Indeterminate response 1 (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
    b. 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
    a. Indeterminate response 3 (IR3) Increase in FDG uptake of 1 or more lesion(s) without a concomitant increase in lesion size or number.
3. Stable performance status
4. Tolerance of study therapy
5. Approval is granted by the study chair.

## 5.7 Duration of Follow Up

Participants will be followed for up to 10 years after removal from protocol therapy or until death, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

### 5.8 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Completion of all study activities
- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure the participant's status is updated in OnCore in accordance with REGIST-OP-1.

## 6. DOSING DELAYS/DOSE MODIFICATIONS

Every effort should be made to administer study drugs according to the planned dose and schedule.

Patients whose treatment is delayed due to adverse events should be evaluated at intervals of one week or less until adequate recovery has been documented or no further improvement is expected. Dose delays will be made as indicated in the following table(s). In the event of multiple toxicities, dose modifications should be based on the worst observed toxicity. Patients must be instructed to notify Investigators at the first occurrence of any adverse symptom/s.

Treatment modification recommendations should be followed unless previously discussed with and agreed by the study chair. All dose modifications/adjustments must be clearly documented in the patient's notes and in the CRF. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

### 6.1 Management of Adverse Events

Both ipilimumab and nivolumab stimulate the immune system and can result in immune-related adverse events (irAEs). Any event suspected to be immune-related should be managed according to the guidance for management of immune-related adverse events in this section and in Table 2. Adverse events that are felt to be non-immune-related should be managed based on Tables 3 or 4.

### 6.2 Immune Related Adverse Events (irAEs)

Immune-related adverse events described with these drugs include: pneumonitis, colitis, hepatitis, endocrinopathies (including thyroid disorders, adrenal insufficiency, hypophysitis, and diabetes mellitus or hyperglycemia), rash, nephritis and renal dysfunction, encephalitis, eye disorders (including uveitis, iritis), and other immune-mediated reactions including myositis and myocarditis.

Any adverse event which may have an underlying immune-mediated mechanism including those described above, and without other confirmed etiologies, should be considered immune-related. Treatment of irAEs should be based on the guidelines outlined in Table 2 but can be superseded by the judgment of the treating physician.

**Table 2 Management of Immune-Related Adverse Events**

| **Gastrointestinal irAEs** | | |
|---|---|---|
| **Severity of Diarrhea/Colitis (NCI-CTCAE v4)** | **Initial Management** | **Follow-up Management** |
| **Grade 1**<br>Diarrhea: < 4 stools/day over Baseline<br>Colitis: asymptomatic | Continue immunotherapy agent(s)<br><br>Symptomatic treatment (e.g. loperamide) | Close monitoring for worsening symptoms<br>Educate subject to report worsening immediately<br>If worsens:<br>Treat as Grade 2 or 3/4. |
| **Grade 2**<br>Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL<br>Colitis: abdominal pain; blood in stool | Withhold all immunotherapy agents<br>Symptomatic treatment | If improves to Grade ≤ 1:<br>Resume immunotherapy agents<br><br>If persists > 5-7 days or recurs:<br>Treat as Grade 3 or 4. |
| **Grade 3 to 4**<br>Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 h; interfering with ADL<br>Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs<br>Grade 4: life-threatening, perforation | Withhold all immunotherapy agents for Grade 3.<br>Permanently discontinue immunotherapy agents<br><br>1.0 to 2.0 mg/kg/day prednisone IV or equivalent<br>Add prophylactic antibiotics for opportunistic infections<br>Consider lower endoscopy | If improves:<br>Continue steroids until Grade ≤ 1, then taper over at least 1 month;<br><br>If worsens, persists > 3 to 5 days, or recurs after improvement:<br>Add infliximab 5mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis. |

| **Dermatological irAEs** | | |
|---|---|---|
| **Grade of Rash (NCI-CTCAE v4)** | **Initial Management** | **Follow-up Management** |
| **Grade 1 to 2**<br>Covering ≤ 30% body surface area or >30% of body surface area with mild symptoms only | Continue immunotherapy agent(s)<br>Symptomatic therapy (for example, antihistamines, topical steroids) | If persists > 1 to 2 weeks or recurs:<br>Withhold all immunotherapy agents<br>Consider skin biopsy<br>Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume immunotherapy agents following steroids taper.<br><br>If worsens:<br>Treat as Grade 3 to 4. |
| **Grade 3 to 4**<br>Grade 3: Covering > 30% body surface area with moderate to severe symptoms;<br>Grade 4: Life threatening consequences | Withhold all immunotherapy agents.<br>Permanently discontinue for Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or Grade 4 rashes.<br>Consider skin biopsy and dermatology consult<br>1.0 to 2.0 mg/kg/day prednisone or equivalent<br>Add prophylactic antibiotics for opportunistic infections | If improves to Grade ≤ 1:<br>Taper steroids over at least 1 month; resume immunotherapy agents following steroids taper (for Grade 3 only). |
| **Pulmonary irAEs** | | |
| **Grade of Pneumonitis (NCI-CTCAE v4)** | **Initial Management** | **Follow-up Management** |
| **Grade 1**<br>Radiographic changes only | Consider withholding all immunotherapy agent(s)<br>Monitor for symptoms every 2 to 3 days | Re-assess at least every 3 weeks<br><br>If worsens:<br>Treat as Grade 2 or Grade 3 to 4. |

| | | |
|---|---|---|
| **Grade 2**<br>Mild to moderate new symptoms | Withhold all immunotherapy agents<br>Consider Pulmonary and Infectious Disease consults<br>Monitor symptoms daily; consider hospitalization<br>1.0 to 2.0 mg/kg/day prednisone or equivalent<br>Consider adding prophylactic antibiotics for opportunistic infections | Re-assess every 1 to 3 days<br><br>If improves:<br>When symptoms return to Grade ≤ 1, taper steroids over at least 1 month, and then resume all immunotherapy agents following steroids taper<br><br>If not improving after 2 weeks or worsening:<br>Treat as Grade 3 to 4. |
| **Grade 3 to 4**<br>Grade 3: Severe new symptoms; New/worsening hypoxia;<br>Grade 4: Life-threatening | Permanently discontinue all immunotherapy agents.<br>Hospitalize.<br>Pulmonary and Infectious Disease consults.<br>1.0 to 2.0 mg/kg/day prednisone or equivalent<br>Add prophylactic antibiotics for opportunistic infections<br>Consider bronchoscopy, lung biopsy | If improves to Grade ≤ 1:<br>Taper steroids over at least 1 month.<br><br>If not improving after 48 hours or worsening:<br>Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil) |
| **Hepatic irAEs** | | |
| **Grade of Liver Test Elevation (NCI-CTCAE v4)** | **Initial Management** | **Follow-up Management** |
| **Grade 1**<br>Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin > ULN to 1.5 x ULN | Continue immunotherapy agent(s) | Continue liver function monitoring<br><br>If worsens:<br>Treat as Grade 2 or 3 to 4. |
| **Grade 2**<br>AST or ALT > 3.0 to ≤ 5 x ULN and/or total bilirubin > 1.5 to ≤ 3 x ULN | Withhold all immunotherapy agents<br>Increase frequency of monitoring to every 3 days. | If returns to Grade ≤ 1:<br>Resume routine monitoring; resume immunotherapy agents.<br><br>If elevation persists > 5 to 7 days or worsens:<br>Treat as Grade 3 to 4. |

| | | |
|---|---|---|
| **Grade 3 to 4**<br>AST or ALT > 5 x ULN and/or total bilirubin > 3 x ULN | Permanently discontinue all immunotherapy agents<br>Increase frequency of monitoring to every 1 to 2 days<br>1.0 to 2.0 mg/kg/day prednisone or equivalent (Use 2.0 mg/kg for grade 4 hepatic irAEs)<br>Add prophylactic antibiotics for opportunistic infections<br>Consult gastroenterologist/ hepatologist<br>Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted | If returns to Grade ≤ 1:<br>Taper steroids over at least 1 month.<br><br>If does not improve in > 3 to 5 days, worsens or rebounds:<br>Add mycophenolate mofetil 1 gram (g) twice daily<br>If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines. |
| **Renal irAEs** | | |
| **Grade of Creatinine Increased (NCI-CTCAE v4)** | **Initial Management** | **Follow-up Management** |
| **Grade 1**<br>Creatinine increased > ULN to 1.5 x ULN | Continue immunotherapy agent(s) | Continue renal function monitoring<br>If worsens:<br>Treat as Grade 2 to 3 or 4. |
| **Grade 2 to 3**<br>Creatinine increased > 1.5 and ≤ 6 x ULN | Withhold all immunotherapy agents<br>Increase frequency of monitoring to every 3 days<br>1.0 to 2.0 mg/kg/day prednisone or equivalent.<br>Add prophylactic antibiotics for opportunistic infections<br>Consider renal biopsy | If returns to Grade ≤1:<br>Taper steroids over at least 1 month, and resume immunotherapy agents following steroids taper.<br><br>If worsens:<br>Treat as Grade 4. |
| **Grade 4**<br>Creatinine increased > 6 x ULN | Permanently discontinue all immunotherapy agents<br>Monitor creatinine daily<br>1.0 to 2.0 mg/kg/day prednisone or equivalent. | If returns to Grade ≤1:<br>Taper steroids over at least 1 month. |

| | | |
|---|---|---|
| | Add prophylactic antibiotics for opportunistic infections<br>Consider renal biopsy<br>Nephrology consult | |
| **Cardiac irAEs** | | |
| **Myocarditis** | **Initial Management** | **Follow-up Management** |
| New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis. | Withhold all immunotherapy agents.<br><br>Consider hospitalization.<br><br>In the presence of life-threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management.<br><br>Cardiology consult to establish etiology and rule-out immune-mediated myocarditis.<br><br>Guideline based supportive treatment as per cardiology consult.*<br><br>Consider myocardial biopsy if recommended per cardiology consult. | If symptoms improve and immune-mediated etiology is ruled out, re-start immunotherapy agents.<br><br>If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis. |
| Immune-mediated myocarditis | Permanently discontinue all immunotherapy agents.<br>Guideline based supportive treatment as appropriate as per cardiology consult.*<br>1.0 to 2.0 mg/kg/day prednisone or equivalent<br>Add prophylactic antibiotics for opportunistic infections. | Once improving, taper steroids over at least 1 month.<br><br>If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A). |

*Local guidelines, or eg. ESC or AHA guidelines
ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines
AHA guidelines website:
http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001

**Endocrine irAEs**

| Endocrine Disorder | Initial Management | Follow-up Management |
|---|---|---|
| **Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)** | Continue immunotherapy agent(s)<br><br>Endocrinology consult if needed<br><br>Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate.<br><br>Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis) | Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.<br><br>For any symptomatic endocrine reactions lasting > 6 weeks, permanently discontinue both immunotherapy agents. |
| **Grade 3 or Grade 4 thyroid endocrinopathies (hypothyroidism, hyperthyroidism)**<br><br>**Grade 3 (diabetes mellitus/hyperglycemia)** | Withhold all immunotherapy agents<br>Consider hospitalization<br>Endocrinology consult<br><br>Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), or insulin (for type I diabetes mellitus) as appropriate.<br><br>Rule-out secondary endocrinopathies (i.e. hypopituitarism / | Resume all immunotherapy agents once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression).<br><br>Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.<br><br>For any symptomatic endocrine reactions lasting > 6 weeks, permanently discontinue both immunotherapy agents. |

| | | |
|---|---|---|
| | hypophysitis) | |
| **Grade 3 or Grade 4 adrenal insufficiency**<br><br>**Grade 4 diabetes mellitus/hyperglycemia** | Permanently discontinue all immunotherapy agents.<br><br>Consider hospitalization<br>Endocrinology consult<br><br>Start corticosteroid replacement (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate.<br><br>Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis) | Continue hormone replacement/suppression and monitoring of endocrine function as appropriate. |
| **Grade 1-3 Hypopituitarism/Hypophysitis (secondary endocrinopathies)** | If secondary thyroid and/or adrenal insufficiency is confirmed (i.e. subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH) :<br>• Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women)<br>• Hormone replacement/suppressive therapy as appropriate<br>• Perform pituitary MRI and visual field examination as indicated<br><br>**If hypophysitis confirmed:** | Resume all immunotherapy agents once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement).<br><br>In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented.<br><br>Continue hormone replacement/suppression therapy as appropriate.<br><br>For any symptomatic endocrine reactions lasting > 6 weeks, permanently discontinue both immunotherapy agents. |

| | | |
|---|---|---|
| | • Continue all immunotherapy agents if mild symptoms with normal MRI. Repeat the MRI in 1 month<br>• Withhold all immunotherapy agents if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month.<br>• Add prophylactic antibiotics for opportunistic infections. | |
| **Grade 4 Hypopituitarism/Hypophysitis (secondary endocrinopathies)** | Permanently discontinue all immunotherapy agents.<br><br>See additional recommendations for grade 1-3 hypophysitis above. | Continue hormone replacement/suppression and monitoring of endocrine function as appropriate. |
| **Ophthalmic irAEs** | | |
| **Grade (NCI-CTCAE v4)** | **Initial Management** | **Follow-up Management** |
| **Grade 1** | Continue immunotherapy agent(s) | Continue monitoring<br>If worsens:<br>Treat as Grade 2 to 3 or 4. |
| **Grade 2 to 4**<br>Creatinine increased > 1.5 and ≤ 6 x ULN | Withhold all immunotherapy agents<br>Increase frequency of monitoring to every 3 days<br><br>Initiate topical therapy and/or 1.0 to 2.0 mg/kg/day prednisone or equivalent.<br>Add prophylactic antibiotics for opportunistic infections | If returns to Grade ≤1 within two weeks:<br>Taper steroids over at least 1 month, and resume immunotherapy agents following steroids taper.<br><br>If does not return to Grade ≤1 within two weeks: permanently discontinue all immunotherapy |

| | | |
|---|---|---|
| | | agents |
| **Other irAEs (not described above)** | | |
| **Grade of other irAEs (NCI-CTCAE v5)** | **Initial Management** | **Follow-up Management** |
| **Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE** | Withhold all immunotherapy agents pending clinical investigation | If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting all immunotherapy agents<br>If irAE is confirmed, treat as Grade 2 or 3 irAE. |
| **Grade 2 irAE or first occurrence of Grade 3 irAE** | Withhold all immunotherapy agents<br>1.0 to 2.0 mg/kg/day prednisone or equivalent<br>Add prophylactic antibiotics for opportunistic infections<br>Specialty consult as appropriate | If improves to Grade ≤ 1:<br>Taper steroids over at least 1 month and resume all immunotherapy agents following steroid taper. |
| **Recurrence of same Grade 3 irAEs** | Permanently discontinue all immunotherapy agents. to 2.0 mg/kg/day<br>prednisone or equivalent<br>Add prophylactic antibiotics for opportunistic infections<br>Specialty consult as appropriate | If improves to Grade ≤ 1:<br>Taper steroids over at least 1 month.<br>Re-treatment can be considered (if deemed beneficial by the patient's treating physician) after discussion with the study chair. |
| **Grade 4** | Permanently discontinue all immunotherapy agents<br>1.0 to 2.0 mg/kg/day<br>prednisone or equivalent and/or other immunosuppressant as needed<br>Add prophylactic antibiotics for opportunistic infections<br>Specialty consult. | If improves to Grade ≤ 1:<br>Taper steroids over at least 1 month |
| **Requirement for 7.5 mg per day or greater prednisone or equivalent for more than 6 weeks for reasons other than hormonal replacement for adrenal insufficiency** | Permanently discontinue all immunotherapy agents<br>Specialty consult | If a steroid course of greater than 6 weeks is required, but a patient is later successfully weaned to a dose of less than 7.5 mg per day, study treatment may be resumed in select cases |

| | | |
|---|---|---|
| **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer** | | depending on the clinical benefit, the severity of the AE, in consultation with study chair. |

## 6.3 Non-Immune Related Adverse Events

Dose delays for drug-related non-immune related toxicities related to ipilimumab and nivolumab are detailed in Table 2 and Table 3. The treatment modifications detailed in these tables should be followed for both ipilimumab and nivolumab.

**Table 3 Treatment Modifications for Non-Immune Treatment-Related Hematologic Toxicities**

| | **Treatment modification** |
|---|---|
| **Grade 1** | Continue per schedule |
| **Grade 2** | Continue per schedule |
| **Grade 3 Thrombocytopenia** | Withhold study treatment and provide growth factor or transfusion support if indicated until return to grade 2 or baseline level; if returns to grade 2 or less within 7 days, resume study treatment (first occurrence only). If the AE does not return to grade 2 or baseline level in 7 days or recurs after re-initiation of study therapy, we recommend a diligent search for alternative causes and consideration of discontinuation in consultation with study chair. |
| **Other Grade 3 Cytopenias** | Continue per schedule |
| **Grade 4** | Withhold study treatment and provide growth factor or transfusion support if indicated until return to grade 2 or baseline level; if returns to grade 2 or less within 7 days, resume study treatment (first occurrence only). If the AE does not return to grade 2 or baseline level in 7 days or recurs after re-initiation of study therapy, we recommend a diligent search for alternative causes and consideration of discontinuation in consultation with study chair. |

**Table 4 Treatment Modifications for Treatment-Related Non-Hematologic Toxicities**

| Non-Hematologic Toxicity | Treatment modification |
|---|---|
| **Grade 1** | Continue per schedule |
| **Grade 2** | Continue per schedule |
| **Grade 3** | First occurrence: Withhold until return to grade 1 or baseline level; re-initiate therapy (after discussion with study chair). For recurrent grade 3 AEs, permanently discontinue both immunotherapy agents |
| **Other-Grade 4** | Permanently discontinue* |
| **irAEs** | See Table 2 |
| **Infusion-related reactions** | See Section 6.6 |

*For asymptomatic grade 4 laboratory abnormalities including lipase, amylase, CK elevations, the subject may be restarted on treatment if the abnormality resolves to grade 1 or baseline, in cases where the investigator judges that the benefit of resuming treatment outweighs the risk, and after discussion with the Study Chair.

## 6.4 Treatment Delays

Treatment should be delayed per Tables 2-4 or based on any adverse event, laboratory abnormality, or condition that, in the judgment of the investigator, warrants delaying the dose of study medication. If a dose delay is necessary, all study drugs must be delayed until treatment can resume.

Subjects should resume treatment per Tables 2-4. Subjects must be re-treated within 6 weeks from the previous dose. Treatment may be resumed after 6 weeks after discussion with the Study Chair if the benefit/risk justify continuing study therapy. At least 19 days must elapse between the replacement dose of study therapy and administration of the subsequent dose of study therapy. In the case of endocrine-related AEs, hormone replacement therapy may be utilized to restore physiologic function and to permit retreatment with study drug. If this is not possible the subject must be discontinued from study therapy.

## 6.5 Dose Reductions

No dose reductions are permitted for ipilimumab or nivolumab.

## 6.6 Management of Infusion-Related Reactions

Infusion reactions with ipilimumab and nivolumab are rare and no empiric premedication is recommended. If an infusion related reaction occurs following infusion, managed guidelines are outlined in Table 5. Symptoms may include one or more of the following: fever, chills, rigors, diaphoresis, and headache.

Once the infusion rate has been decreased by 50% due to an infusion-related reaction, the same decreased infusion rate must be used for all subsequent infusions.

**Table 5 Treatment Modifications for Symptoms of Infusion Related Reactions**

| NCI-CTCAE Grade | Treatment Modification for ipilimumab and/or nivolumab |
|---|---|
| **Grade 1 – mild**<br>• Mild transient reaction; infusion interruption not indicated; intervention not indicated | • Decrease the infusion rate by 50% and monitor closely for any worsening |
| **Grade 2 – moderate**<br>• Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24h | • Temporarily discontinue infusion<br>• Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening |
| **Grade 3 or Grade 4 – severe or life-threatening**<br>• Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae<br>• Grade 4: Life-threatening consequences; urgent intervention indicated | • Stop the infusion immediately and disconnect infusion tubing from the subject<br>• Subjects cannot receive any further treatment with the offending agent. |

IV: intravenous; NCI-CTCAE: National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs: nonsteroidal anti-inflammatory drugs.

### 6.6.1 Additional Treatment Modifications for Patients with Grade 2 Infusion-Related Reactions

In the event of a Grade 2 infusion-related reaction that does not improve or that worsens following implementation of the modifications indicated in Table 5 (including reducing the infusion rate by 50%), the Investigator may consider treatment with corticosteroids per local guidelines, and the infusion should be stopped for that day. At the time of the next cycle, the following prophylactic pre-medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional study drug administrations.

6.6.2 Management of Severe Hypersensitivity Reactions and Flu-Like Symptoms

Symptoms of hypersensitivity may include impaired airway, decreased oxygen saturation (<92%), confusion, lethargy, hypotension, pale or clammy skin, and cyanosis. These symptoms may, if necessary, be managed with epinephrine and dexamethasone. Oxygen therapy should be administered as appropriate. Patients should be monitored per institutional standards.

## 6.7 Discontinuation of One Study Drug

Patients receiving combination therapy with both ipilimumab and nivolumab may experience a severe adverse event that is felt to be primarily attributable to only one of the study drugs (i.e. an infusion-related reaction during nivolumab or an irAE more commonly observed with ipilimumab, etc). If a patient experiences an AE that would result in study treatment discontinuation per protocol that is felt to be primarily related to a single study drug, the patient may continue receiving the other agent on protocol, if approved by the principal investigator.

## 6.8 Study-wide early stopping rules

Observation of >1 treatment-related grade 5 event would pause accrual and initiate a study-wide review.

Excessive toxicity will be defined as grade 4 AEs or grade 3 AEs lasting > 72 hours (excluding asymptomatic laboratory AEs). Observation of excessive toxicity in >3 patients would pause accrual and initiate a study-wide review.

# 7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

## 7.1 Expected Toxicities

7.1.1 Adverse Events List(s)

7.1.1.1 Ipilimumab

**Common (>20% incidence)**

- Diarrhea, nausea
- Fatigue
- Immune-related adverse events including the following:
    - Dermatitis

**Occasional (4-20% incidence)**

- Abnormal heartbeat
- Hearing loss
- Swelling and redness of the eye
- Pain
- Difficulty swallowing, eating
- Constipation, vomiting
- Weight loss, loss of appetite
- Fever
- Dehydration
- Pain or swelling of the joints
- Infusion reaction during or following a drug infusion
- Immune-related adverse events including the following:
    - Pneumonitis
    - Colitis
    - Kidney problems, including nephritis and kidney failure requiring dialysis
    - Myositis
    - Neuritis
    - Endocrine gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas

**Rare (<3% incidence)**

- Bleeding
- Bowel obstruction
- Fluid around heart
- Severe illness with multiorgan failure
- Swelling of the brain which may cause headache, blurred vision, stiff neck, and/or confusion
- Immune-related adverse events including the following:
    - Hyperglycemia
    - Myocarditis, including swelling and heart failure.
- Complications associated with stem cell transplant using donor stem cells

7.1.1.2 Nivoluamb

**Frequent (>10% incidence)**

- Diarrhea
- Fatigue
- Itching
- Rash

**Occasional (1-10% incidence)**

- Allergic reaction (hypersensitivity).
- Abdominal pain
- Increased alkaline phosphatase, aspartate aminotransferase, bilirubin or alanine aminotransferase.
- Increased amylase or lipase

- Chills
- Constipation
- Cough
- Increased blood level of creatinine
- Decreased appetite
- Dizziness
- Dry mouth
- Dry skin
- Fever
- Headache
- Hyperglycemia
- Colitis
- Mucositis
- Infusion reaction
- Loss of color (pigment) from areas of skin
- Pneumonitis
- Muscle and/or bone pain
- Nausea
- Hyponatremia
- Swelling, including face, arms, and legs
- Hypothyroidism or hyperthyroidism
- Neuropathy
- Vomiting

**Rare (0.1%-1% incidence)**

- Hypophysitis
- Lung inflammation (bronchitis)
- Cranial nerve disorder, which may cause facial pain or twitching, dizziness, hearing loss, weakness, and/or paralysis.
- Dehydration
- Diabetes complications resulting in excessive blood acids
- Double Vision
- Dry eye
- Erythema Multiforme
- Hair loss
- Tachycardia or heart arrhythmias
- Hypertension
- Irregular heartbeat
- Hives
- Inflammation of the eye
- Nephritis
- Inflammation of the pancreas, causing pain in the upper abdomen.
- Inflammation of the pituitary gland, which may cause headaches, change in eyesight, few to no menstrual cycles (for women), increased thirst, and increased frequency passing urine.
- Gastritis

- Thyroiditis
- Hepatitis
- Joint pain or stiffness
- Low blood pressure
- Pemphigoid
- Pituitary gland function decreased
- Psoriasis
- Kidney failure
- Myositis (an infection of the muscle).
- Infection in the upper respiratory tract
- Vision blurred

**Very rare (< 0.1% incidence)**

- Life-threatening allergic reaction
- Damage to the protective covering of the nerves in the brain and spinal cord
- Disease caused by the body's immune system attacking healthy organs
- Drug induced liver injury
- A disorder called Guillain-Barré syndrome in which the body's immune system attacks part of the peripheral nervous system.
- Inflammation of blood vessels that can lead to damage of different organs
- Inflammation of the brain, potentially life-threatening or fatal Inflammation of the heart muscle.
- Inflammation of the lining of the brain and spinal cord
- Lung infiltrates, associated with infection or inflammation
- A neurologic syndrome characterized by muscle weakness called myasthenic syndrome, including myasthenia gravis
- Polymyalgia rheumatic
- Rupture of the intestine/hole in the intestine
- Sarcoidosis
- Stevens Johnson syndrome or Toxic Epidermal Necrolysis
- A disorder of the lymph nodes called histiocytic necrotizing lymphadenitis or Kikuchi lymphadenitis

## 7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity, or frequency from the expected toxicity information which is provided.

- Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

- **A serious adverse event (SAE)** is an AE that meets any of the following criteria:
  - Results in death (i.e., the AE actually causes or leads to death)
  - Is life-threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.)
  - Requires or prolongs inpatient hospitalization
  - Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
  - Results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to ipilimumab and/or nivolumab
  - Important medical events that may not result in death, are not immediately life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

## 7.3 Adverse Event Reporting

7.3.1 In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the PI.

7.3.2 Investigators **must** report to the PI any adverse event (AE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.3.3 Adverse Event Reporting Guidelines

All participating sites will report AEs to the Sponsor-Investigator per DF/HCC requirements, and the IRB of record for each site as applicable per IRB policies. The table below indicates which events must be reported to the DF/HCC Sponsor-Investigator.

| Attribution | Table 6 DF/HCC Reportable Adverse Events (AEs) | | | | |
|---|---|---|---|---|---|
| | **Gr. 2 & 3 AE Expected** | **Gr. 2 & 3 AE Unexpected** | **Gr. 4 AE Expected** | **Gr. 4 AE Unexpected** | **Gr. 5 AE Expected or Unexpected** |
| Unrelated Unlikely | Not required | Not required | 10 working days# | 10 working days | 24 hours* |
| Possible Probable Definite | Not required | 10 working days | 10 working days# | 10 working days | 24 hours* |
| # If listed in protocol or informed consent document as expected event does not need to be reported (except through routine reporting mechanisms) | | | | | |
| * For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 1 business day of learning of the event. | | | | | |

## 7.4 Reporting to Bristol-Myers Squibb

Bristol-Myers Squibb (BMS) will also be informed of any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment. Any SAE occurring after the reporting period must be promptly reported if a causal relationship in the investigational drug is suspected. Participant or partner pregnancy while on treatment or within 30 days of the last dose of treatment is also required to be reported to BMS via expedited reporting procedures.

Within 24 hours of first awareness of the event (immediately if the event is fatal or life-threatening), the study team will report to BMS by email (Worldwide.Safety@bms.com) any Serious Adverse Event ("SAE," as defined below) for which reporting is required under this provision (as described below). Such SAEs are to be reported for study subjects or individuals otherwise exposed to study drugs as described below. The study teams should report SAEs as soon as they are determined to meet the definition, even if complete information is not yet available.

SAEs to BMS will be reported on a SAE report form supplied by BMS and sent to the Sponsor-Investigator to review and report to Worldwide.Safety@bms.com on behalf of the reporting external site. Submissions should be made within 24 hours of the site's knowledge of the event.

### 7.4.1 SAE Definition for Reporting to BMS

An SAE is any adverse event, without regard to causality, that is life-threatening (i.e., causes an immediate risk of death) or that results in any of the following outcomes: death; in-patient hospitalization or prolongation of existing hospitalization; persistent or significant disability or incapacity (i.e. substantial disruption of the ability to conduct normal life functions); or a

congenital anomaly or birth defect. Any other medical event that, in the medical judgment of the Principal Investigator, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above is also considered an SAE. A planned medical or surgical procedure is not, in itself, an SAE.

#### 7.4.2 Exposure During Pregnancy, Exposure During Lactation, Occupational Exposure

Even though there may not be an associated SAE, occupational exposure to ipilimumab +/- nivolumab or exposure during pregnancy or lactation is reportable to BMS.

#### 7.4.3 Exclusions from SAE Reporting Requirements

Specifically excluded from the reporting requirements for SAEs under this provision is any SAE identified in the Protocol as anticipated to occur in the Study population at some frequency independent of drug exposure, unless the Principal Investigator assesses such an event as related to study medication. Also, specifically excluded from the reporting requirements is any SAE judged by the Overall Investigator to represent progression of the malignancy under study, unless it results in death within the SAE Reporting Period.

#### 7.4.4 SAE Reporting Period

The SAEs that are subject to this reporting provision are those that occur from after the first dose of study medication(s) through 30 calendar days after the last administration of the study medication(s). In addition, if a Sponsor-Investigator becomes aware of an SAE occurring within 30 days of last dose of study medication the Sponsor-Investigator should report that SAE to BMS if the Sponsor-Investigator suspects a causal relationship between the study drug and the SAE. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents.

### 7.5 Reporting to the Food and Drug Administration (FDA)

The Sponsor-Investigator will be responsible for all communications with the FDA. The Sponsor-Investigator will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

### 7.6 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports, sentinel events or unanticipated problems that require reporting per institutional policy.

### 7.7 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB,**

**FDA, etc.) must also be reported in routine study data submissions.**

## 8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or other agents administered in this study can be found in Section 7.1.

### 8.1 Ipilimumab

#### 8.1.1 Description

Ipilimumab is a fully human monoclonal immunoglobulin that binds to CTLA-4 and inhibits its interaction with ligands on antigen presenting cells. Ipilimumab has a terminal half-life of approximately 15.4 days. A population PK analysis of ipilimumab (n=785) demonstrated that the PK of ipilimumab is linear and exposures are dose proportional across the tested dose range of 0.3 to 10 mg/kg.

#### 8.1.2 Form

Injection: 50 mg/10 mL (5 mg/mL) as a clear to slightly opalescent, colorless to pale-yellow solution in a single-use vial.

#### 8.1.3 Storage and Stability

Ipilimumab should be stored under refrigeration at 2°C to 8°C (36°F to 46°F). Protect from light by storing in the original carton until time of use. Do not freeze or shake.

#### 8.1.4 Compatibility

When both ipilimumab and nivolumab are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be ipilimumab and will start no sooner than 30 minutes after completion of the nivolumab infusion.

#### 8.1.5 Handling

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

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the sponsor. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately.

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

Please refer to the current IB/pharmacy reference sheets for storage, handling and preparation instructions.

### 8.1.6 Availability

Ipilimumab will be provided by BMS from investigational supply.

### 8.1.7 Preparation

Please refer to the current IB/pharmacy reference sheets for preparation instructions. Study product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance. Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of biologic agents.

Dosing of ipilimumab will be based on the patient's weight in kilograms (kgs). All patients should be weighed within 3 days prior to dosing for every cycle to ensure they did not experience either a weight loss or gain >10% from the weight used for the last dose calculation. If the patient experienced either a weight loss or gain >10% compared to the weight used for the last dose calculation, the amount of study drug must be recalculated.

Vials are for single use only. Any unused portion of the solution must be discarded in a biohazard waste disposal container with final disposal according to accepted local and national standards of incineration.

### 8.1.8 Administration

Ipilimumab is to be administered as a 90-minute infusion. When both study drugs are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be ipilimumab and will start no sooner than 30 minutes after completion of the nivolumab infusion.

### 8.1.9 Ordering

Ipilimumab will be supplied by BMS. No patients or third-party payers will be charged. Use the Drug Supply Request Form provided to order ipilimumab. For all inquiries regarding ipilimumab supplies, please contact: Distribution.allentown@thermofisher.com.

8.1.10 Accountability

The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and disposition of ipilimumab using a drug accountability form that is compliant with local and federal guidelines.

Additionally, a designated study team member will complete drug accountability/reconciliation based on the participant actual drug return versus the anticipated drug return and document the findings according to local and federal regulations and guidance.

8.1.11 Destruction and Return

After full drug accountability and reconciliation, all unused ipilimumab will be destroyed according to site procedures. Destruction will be documented in the Drug Accountability Record Form. If any study drug is lost or damaged, the disposition of the study drug should be documented.

## 8.2 Nivolumab

8.2.1 Description

Nivolumab is a fully human, IgG4 (kappa) isotype, mAb that binds to PD-1. Following single dose, maximum concentration (Cmax), and area under the curve (AUCinf) of nivolumab were found to be dose proportional within the studied dose range of 0.3-10 mg/kg. The terminal half-life of nivolumab from single dose was 17-25 days in patients with multiple tumor types. Following multiple doses of 0.1 to 10 mg/kg administered every 2 weeks, Cmax and AUC of nivolumab were found dose proportional. The steady-state is expected to be achieved by the sixth dose.

8.2.2 Form

Injection: 100 mg/10 mL (5 mg/mL) as a clear, colorless to pale yellow liquid in a single-use vial.

8.2.3 Storage and Stability

Nivolumab should be stored under refrigeration at 2°C to 8°C (36°F to 46°F). Protect from light by storing in the original carton until time of use. Do not freeze or shake.

8.2.4 Compatibility

When both nivolumab and ipilimumab are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be ipilimumab and will

start no sooner than 30 minutes after completion of the nivolumab infusion.

### 8.2.5 Handling

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

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the sponsor. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately.

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

Please refer to the current IB/pharmacy reference sheets for storage, handling and preparation instructions.

### 8.2.6 Availability

Nivolumab will be provided by BMS from investigational supply.

### 8.2.7 Preparation

Please refer to the current IB/pharmacy reference sheets for preparation instructions. Study product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance. Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of biologic agents.

During the first 4 cycles, dosing of nivolumab will be based on the patient's weight in kilograms (kgs), whereas maintenance nivolumab will be administered at a flat dose of 480 mg. All patients should be weighed within 3 days prior to dosing for cycles 1-4 to ensure they did not experience either a weight loss or gain >10% from the weight used for the last dose calculation. If the patient experienced either a weight loss or gain >10% compared to the weight used for the last dose calculation, the amount of study drug must be recalculated.

Vials are for single use only. Any unused portion of the solution must be discarded in a biohazard waste disposal container with final disposal according to accepted local and national standards of incineration.

8.2.8 Administration

Nivolumab is to be administered as a 30-minute infusion. When both study drugs are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be ipilimumab and will start no sooner than 30 minutes after completion of the nivolumab infusion.

8.2.9 Ordering

Nivolumab will be supplied by BMS. No patients or third-party payers will be charged. Use the Drug Supply Request Form provided to order nivolumab. For all inquiries regarding nivolumab supplies, please contact: Distribution.allentown@thermofisher.com.

8.2.10 Accountability

The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and disposition of nivolumab using a drug accountability form that is compliant with local and federal guidelines.

Additionally, a designated study team member will complete drug accountability/reconciliation based on the participant actual drug return versus the anticipated drug return and document the findings according to local and federal regulations and guidance.

8.2.11 Destruction and Return

After full drug accountability and reconciliation, all unused nivolumab will be destroyed according to site procedures. Destruction will be documented in the Drug Accountability Record Form. If any study drug is lost or damaged, the disposition of the study drug should be documented.

## 9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

The biomarkers for the trial include measurements from tumor tissues and analyses of blood samples to explore molecular, cellular, and soluble markers that may be relevant to the mechanism of action of the drug(s) or response/resistance to the drug(s). The correlative studies are best described as ancillary. While the goal of the correlative studies is to provide supportive data for the clinical study, there may be circumstances when a decision is made to stop a collection, not perform, or discontinue an analysis due to practical reasons (e.g., inadequate sample number), issues related to the quality of the sample, or issues related to the assay that preclude analysis, etc). Therefore, depending on the results obtained during the study, sample collection/analysis may be omitted at the discretion of the PI.

A cheek swab/saliva sample will be collected prior to treatment. In addition, peripheral blood will be collected for research at baseline, and after 3, 6, 12, 24, and 48 weeks of therapy. In

addition, peripheral blood samples will be collected at the time of progression (when feasible). Analyses of these samples may include investigation of ctDNA, such as quantification of ctDNA at different timepoints and examination of changes in copy number abnormalities and relevant pathogenic genes.

When safely feasible, tumor biopsies (excisional or core needle) will be obtained at baseline, between day 14 and 21 of cycle 1 of therapy (optional), and at the time of progression (optional). An archival sample within 90 days and without intervening treatment is acceptable as the pre-treatment biopsy assuming that the following provisions are met: 1) Priority: tumor containing formalin-fixed, paraffin-embedded (FFPE) tissue block; 2) Priority: if the tumor containing FFPE tissue block cannot be provided in total, sections from this block should be provided that are freshly cut and mounted on positively-charged glass slides (SuperFrost Plus are recommended). Preferably, 25 slides should be provided; if not possible, a minimum of 15 slides is required.

These may be obtained by excisional or core needle biopsy. Biopsies may be analyzed for tumor and microenvironmental expression of checkpoint markers and for immune architecture by a combination of immunohistochemistry and multiparameter spectral imaging. Ideally, 5-6 core needle biopsies will be collected.

Analysis of tumor samples may include interrogation of the TME using multiplex immunofluorescence (MIF) with a specific interest in the frequency and distribution of immune cells (CD4+ T cells, CD8+ T cells, Tregs, NK cells, tumor-associated macrophages) and relevant immune checkpoint pathways (CTLA-4/CD86, PD-1/PD-L1). Findings may be validated and explored further using multiplexed ion beam imaging (MIBI).

Banked biospecimens will be handled in a manner that protects each subject's privacy and confidentiality. Banked biospecimens will be assigned the subject's study identification code (ID) at the site. The data generated from these banked biospecimens will also be indexed by this ID. Biospecimens will be kept until destruction in facilities with access limited to authorized personnel, and biospecimen-derived data will be stored on password-protected computer systems. The key between the subject's ID and the subject's direct personally identifying information (eg, name, address) will be held at the study site. Biospecimens will be used only for the purposes described in the protocol and informed consent document; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored for many years (no time limit) to allow for research in the future, including research conducted during the lengthy drug-development process and also postmarketing research. Subjects may withdraw their consent for the use of their banked biospecimens at any time by making a request to the investigator; in this case, any remaining biospecimens will be destroyed, but data already generated from the biospecimens will continue to be available to protect the integrity of existing analyses. Unless prohibited by local regulations or ethics committee decision, a 4-mL blood genomic banked biospecimen Prep D1 (dipotassium edetic acid [ethylenediaminetetraacetic acid] [$K_2$EDTA] whole-blood collection optimized for DNA analysis) will be collected at the time specified in the Study Calendar section of the protocol to be retained for potential pharmacogenomic/genomic/biomarker analyses related to drug response and disease/condition under study. For example, putative safety biomarkers, drug-metabolizing enzyme genes, drug-transport protein genes, or genes thought to

be related to the mechanism of drug action may be examined. The primary purpose is to examine DNA; however, the biospecimen may also be used to study other molecules (eg, RNA, proteins, and metabolites).

Details of time points and sampling are provided in the Study Calendar. Reference the laboratory manual for specimen collection, processing, and shipment instructions.

In order to complete all the assessments on tumor materials and blood samples, the Principal Investigator will provide instructions and necessary supplies to the site, including shipping materials and prepaid mailers. The panel of biomarkers might be adjusted based on results from ongoing research and/or safety; therefore, each patient will also be asked whether any remaining tumor tissue and/or blood-derived samples can be stored at a central repository (until such time as these samples cannot support any further analysis) and can be used for future exploratory research on the drug(s) and / or disease-related aspects. Biomarker analyses may be conducted after the conclusion of this study and may be based on samples derived from multiple studies.

## 10. STUDY CALENDAR

A study calendar is below (Table 7).

### 10.1 Required Data for Study Screening

The following must be obtained within 28 days prior to the 1st day of treatment:

- Medical history, medication review, physical exam, vital signs, height and weight, ECOG performance status (see Appendix A)
- CBC with manual differential, blood chemistries including complete metabolic panel, phosphorus, magnesium, uric acid, LDH, TSH, creatinine kinase, lipase, triglycerides, PT/INR, PTT, hepatitis C antibody, hepatitis B surface antigen and hepatitis B core antibody. Urine studies to include a urine dipstick for blood and protein and if positive (2+ or greater for protein) a microscopic urinalysis and 24-hour urine collection (for protein).
- Serum or urine β-HCG for females of childbearing potential
- Tumor restaging (within 6 weeks). This will consist of PET/CT scans (including neck, chest, abdomen/pelvis).
- Peripheral blood sample for biomarker studies (Section 9).
- Tumor biopsy for biomarker studies (Section 9). An archival sample may be acceptable (see Section 3.1).
- 12-Lead Electrocardiogram (EKG).

### 10.2 Required Data During Study

The following must be obtained during the study:

- Medical history, medication review, physical exam, vital signs, and weight, ECOG performance status (see Appendix A)
- Toxicity assessment
- CBC with manual differential, blood chemistries including complete metabolic panel, phosphorus, magnesium. These are required at each planned study visit -- day 1 of cycles 1-4, day 1 all maintenance cycles, day 43 of maintenance cycles.
- TSH, creatinine kinase, lipase, and triglycerides, as well as urine studies to include a urinalysis (and if urine protein positive >=2+, a 24-hour urine collection to quantify proteinuria). These are required at each planned study visit -- day 1 of cycles 1-4, day 1 all maintenance cycles, day 43 of maintenance cycles. Patients do need to meet laboratory eligibility criteria on C1D1 (see section 5.2).
- Pregnancy test at screening and D1 of each cycle (for women of childbearing age only).
- Peripheral blood sample for biomarker studies will be collected for research (see Section 9)
- Tumor restaging: PET/CT scans will be performed at baseline and after 4 doses of ipilimumab monotherapy (week 12). Among ipilimumab responders, restaging scans will occur prior to ipilimumab maintenance cycle 2 (week 24), cycle 3 (week 36), cycle 5 (week 60), and cycle 7 (week 84). Among ipilimumab non-responders, restaging scans will occur after 4 cycles of ipilimumab + nivolumab combination therapy (week 24) and prior to ipilimumab maintenance cycle 2 (week 36), cycle 4 (week 60), and cycle 6 (week 84). The end-of-treatment assessment will occur 4-12 weeks after the last doses of study therapy (i.e. weeks 112-120 for patients who complete all planned study therapy). Afterwards patients will be re-imaged every 24 weeks.

### 10.3 Required at Progression or Treatment Discontinuation and Follow-Up

- Medication review, physical exam, vital signs, ECOG performance status (see Appendix A)
- Toxicity assessment
- CBC with manual differential, blood chemistries including complete metabolic panel, phosphorus, magnesium, uric acid, LDH, TSH, creatinine kinase, lipase, triglycerides. Urine studies to include a urine dipstick for blood and protein and if positive a microscopic urinalysis and 24-hour urine collection (for protein).
- Peripheral blood sample for biomarker studies at the time of progression (if feasible)
- Core-needle tumor biopsy at the time of progression (optional)
- Tumor restaging will be performed for patients in long-term follow-up who remain in remission. Patients who progress or receive other therapy for their lymphoma (for example, consolidation with transplantation or an alternative treatment) will only be followed for relapse and survival). Surveillance imaging will consist of PET/CT scans (including neck, chest, abdomen/pelvis) every 24 weeks for up to 2 years after initiation of study therapy.

- Patients in remission will be followed every 3 months for 2 years, then every 6 months for 3 years. Patients who progress or receive other therapy (for example consolidation with transplantation or an alternative treatment) will only be followed for relapse and survival.
- After 5 years of active follow up (for patients who remain in remission and do not receive additional treatment), patients will be followed only for relapse and survival with follow up by phone call with the patient or the local physician every 6 months for up to 5 years.

| Table 7 - Study Calendar | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Baseline** | **Cycle 1[a]** | | **Cycle 2** | **Cycle 3** | **Cycle 4** | **Re-induction cycles 1-4[b]** | **Maintenance Cycles[c]** | | **EOT** | **Follow-Up[d, j]** | **EDC Timepoints** |
| | Day-28 to Day 0 | Day 1 | Day 14-21 | Day 1 | Day 1 | Day 1 | Day 1 | Day 1 | Day 43 | 4-12 weeks from last study treatment | | |
| | | ±3 days | | | | | | | | ± 7 days | ±2 weeks | |
| Ipilimumab | | X | | X | X | X | (X) | X | | | | Day 1 of induction and re-induction cycles and each maintenance cycle |
| Nivolumab | | | | | | | (X) | | | | | Day 1 of re-induction cycles |
| Informed consent | X | | | | | | | | | | | N/A |
| Demographics | X | | | | | | | | | | | Baseline |
| Medical history | X | | | | | | | | | | | Baseline |
| B-HCG[e] | X | X | | X | X | X | | | | | | Baseline |
| Urinalysis | X | | | | | | | | | | | Baseline |
| Hepatitis B and C serologies[f] | X | | | | | | | | | | | Baseline |
| PT/PTT/INR | X | | | | | | | | | | | Baseline |
| EKG | X | | | | | | | | | | | Baseline |
| Concurrent Medications | X | X | | X---------- | | | | | | | X | N/A |
| Physical exam | X | X | | X | X | X | (X) | X | X | X | X | At each study visit |
| Vital signs | X | X | | X | X | X | (X) | X | X | X | X | At each study visit |
| Height | X | | | | | | | | | | | Baseline |
| Weight | X | X | | X | X | X | (X) | X | | | | Baseline, day |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | 1 induction and re-induction cycles and day 1 of each maintenance cycle |
| Performance status (Appendix A) | X | X | | X | X | X | (X) | X | X | X | X | A each study visit |
| CBC w/diff, serum chemistry[g] | X | X | | X | X | X | (X) | X | X | X | X | At each study visit[g] |
| TSH, creatinine kinase, lipase, triglycerides, urine dipstick for blood and protein[h] | X | X | | X | X | X | (X) | X | X | X | X | At each study visit[h] |
| Cheek swab/saliva sample | | X | | | | | | | | | | On Cycle 1 Day1 |
| Peripheral blood collection for biomarker studies[i] | | X | | X | X | | (X) | X[i] | X | X | | See footnote |
| Tumor biopsies[k] | X[k] | | (X)[k] | | | | | | | (X)[k] | | See footnote |
| Radiologic Evaluation[l] | X | | | | | | (X) | X[l] | | X | X | See footnote |
| Adverse Event Evaluation | | | X---------- | | | | | | | | ----------X | At each study visit |

a: Cycles 1-4 are 21 days
b: Patients who achieve an objective response after 4 cycles of ipilimumab therapy will proceed to maintenance ipilimumab treatment. Ipilimumab non-responders (who are clinically stable) will receive re-induction with ipilimumab and nivolumab.
c: Maintenance cycles are 12 weeks (84 days). (see section 5.1)
d: Follow-up evaluation. Patients will continue on treatment until disease progression, withdrawal of consent, adverse events preventing additional therapy, or completion of study therapy. After completing treatment, patients will have every 3-month visits for 2 years or until progressive disease, then every 6-month visits for 3 years. Survival follow-up will then continue to be captured every 6 months for 5 years or until participant withdrawal, death, or removal from study. Patient who receive subsequent anti-cancer therapy will be followed for relapse and survival (but will not require active follow-up and surveillance imaging on trial).
e: Pregnancy testing at screening and on D1 of each cycle (for women of childbearing age only)

f: Consisting at a minimum of hepatitis C antibody, hepatitis B surface antigen and hepatitis B core antibody.
g: See Sections 10.1 and 10.2. All tests will be required at screening.
h: See Sections 10.1 and 10.2.
i: Peripheral blood sample(s) will be collected for correlative studies per section 9
j: See Section 10.3.
k: All patients are required to provide a pre-treatment core needle or excisional biopsy or an archival sample provided it was obtained within 90 days of trial initiation (see section 3.1). In addition, optional core needle biopsies may be collected during cycle 1 (between day 14-21) and at the time of progression.
l: PET/CT scans will be performed at baseline and after 4 doses of ipilimumab monotherapy (week 12). Among ipilimumab responders, restaging scans will occur prior to ipilimumab maintenance cycle 2 (week 24), cycle 3 (week 36), cycle 5 (week 60), and cycle 7 (week 84) . Among ipilimumab non-responders, restaging scans will occur after 4 cycles of ipilimumab + nivolumab combination therapy (week 24) and prior to ipilimumab maintenance cycle 2 (week 36), cycle 4 (week 60), and cycle 6 (week 84).. The end-of-treatment assessment will occur 4-12 weeks after the last doses of study therapy (i.e. weeks 112-120 for patients who complete all planned study therapy). Afterwards patients will be re-imaged every 24 weeks.

# 11. MEASUREMENT OF EFFECT

## 11.1 Antitumor Effect

18F-fluorodeoxyglucose (18F-FDG) Positron Emission Tomography (PET) imaging will be used in conjunction with Computerized Tomography (CT) imaging to confirm a disease assessment of CR at the end of treatment. The screening 18F-FDG PET-CT imaging will be used to determine evaluable index lesions for each patient. For 18F-FDG PET-CT, tumor background ratios and development of new sites of abnormality will be recorded.

Results of the 18F-FDG PET studies will be scored according to methods developed by the American College of Radiology Imaging Network. All centers participating in the study will use the same 18F-FDG PET methodologies and measures, to the extent possible, and one center will be designated as the central lab to be used for final interpretation of 18F-FDG PET data.

Anti-cancer activity will be assessed as specified in the Study Calendar (Section 10) or whenever disease progression is suspected (eg, symptomatic deterioration), or at the time of withdrawal from treatment (if not performed in the previous 6 weeks).

If imaging is used in disease assessment, the same imaging technique (CT) used to characterize each identified and reported lesion at baseline will be employed in post-baseline disease assessments.

Assessment of response will be made using the Lugano 2014 criteria and LyRIC (Appendix D).

All patients' files and radiologic images and pathology samples must be available for source verification and for potential peer review.

### 11.1.1 Duration of Response

*Duration of overall response*: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

*Duration of overall complete response*: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

*Duration of stable disease*: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.2 Progression-Free and Overall Survival

*Overall Survival*: Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

*Progression-Free Survival*: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

*Time to Progression*: Time to Progression (TTP) is defined as the time from randomization (or registration) to progression, or censored at date of last disease evaluation for those without progression reported.

11.1.3 Response Review

For purposes of data analysis and reporting, responses on this trial will be centrally assessed through the Tumor Imaging Metrics Core at DF/HCC.

## 12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

### 12.1 Data Reporting

12.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) in accordance with DF/HCC policies.

### 12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Sponsor-Investigator and study team.

The DSMC generally reviews each protocol up to four times a year with the frequency determined by the outcome of previous reviews. Information to be provided to the committee

may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported across all sites; summary of all deaths occurring within 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

### 12.3 Multi-Center Guidelines

This protocol will adhere to DF/HCC Policy MULTI-100 and the requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Sponsor-Investigator, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix B.

## 13. STATISTICAL CONSIDERATIONS

This is an open label phase II clinical trial of ipilimumab with or without nivolumab in patients with relapsed/refractory classical Hodgkin lymphoma. The trial is designed to assess the efficacy of ipilimumab with or without nivolumab in patients with relapsed/refractory Hodgkin lymphoma.

### 13.1 Study Design/Endpoints

*Primary Endpoint*

- Best ORR (Lugano criteria)

*Secondary Endpoints*

- Best ORR, PRR, CRR assessed by PET/CT (using Lugano criteria and LYRIC criteria) after ipilimumab monotherapy
- Best ORR, PRR, CRR assessed by PET/CT (using Lugano criteria and LYRIC criteria) after ipilimumab and nivolumab combination therapy
- DOR (using Lugano criteria and LYRIC criteria) for patients receiving ipilimumab maintenance
- DOR (using Lugano criteria and LYRIC criteria) for patients receiving ipilimumab and nivolumab combination therapy
- PFS and OS (Lugano criteria and LYRIC criteria)
- Safety
- Above endpoints, stratified by best response to PD-1 mAb (non-responder versus responder)

<u>Correlative Endpoints</u>

- To determine if features of the cHL TME are associated with response or resistance to study treatment
- To determine if early reduction in ctDNA is associated with improved PFS.

- To characterize the genetic bases of immune evasion and correlate these alterations with responses to therapy

### 13.2 Sample Size, Accrual Rate and Study Duration

We anticipate that 13 patients will be enrolled in this phase II trial. We estimate that patients will be enrolled over a 30-month period. Up to 3 months of additional follow-up will be required to observe a participant's response. Therefore, we anticipate analysis of primary endpoints after a total of 33 months. The end of the trial will occur when all patients have stopped study treatment (due to progression, withdrawal of consent, adverse events, etc).

**Table 8 - Accrual Targets**

| **Ethnic Category** | **Sex/Gender** | | | | |
|---|---|---|---|---|---|
| | **Females** | | **Males** | | **Total** |
| Hispanic or Latino | 1 | + | 1 | = | 2 |
| Not Hispanic or Latino | 5 | + | 6 | = | 11 |
| **Ethnic Category: Total of all subjects** | 6 (A1) | + | 7 (B1) | = | 13 (C1) |
| **Racial Category** | | | | | |
| American Indian or Alaskan Native | 0 | + | 0 | = | 0 |
| Asian | 0 | + | 1 | = | 1 |
| Black or African American | 1 | + | 0 | = | 1 |
| Native Hawaiian or other Pacific Islander | 0 | + | 0 | = | 0 |
| White | 6 | + | 5 | = | 11 |
| **Racial Category: Total of all subjects** | 7 (A2) | + | 6 (B2) | = | 13 (C2) |
| | (A1 = A2) | | (B1 = B2) | | (C1 = C2) |

### 13.3 Analysis of Primary Endpoints

The desired sample size is 13 patients. We hope to demonstrate that ipilimumab monotherapy has significant clinical activity as a single agent, defined as an ORR of 40% or higher. The null hypothesis that the true ORR is 10% will be tested against a one-sided alternative (ORR 40%). The null hypothesis will be rejected if 4 or more patients of the 13 patients tested achieve an objective response. This design yields a type 1 error rate of 0.034 (one-sided) and a power of 0.83. Analysis of re-induction with ipilimumab + nivolumab among ipilimumab non-responders will be descriptive in nature.

### 13.4 Analysis of Secondary Endpoints

Secondary endpoints include, response assessments including ORR (defined as partial response and complete response), the duration of response (DOR) among patients who have achieved a PR or CR (defined as the time from first response to progression or last follow-up), progression free survival (PFS) (defined as the time from treatment start to progression, death or last follow-up, whichever comes first), and overall survival (OS) (defined as time from treatment start to death or last follow-up). The safety of study will be assessed as measured by: the rate of grade 3 or higher toxicity regardless of attribution, the rate of grade 3 or higher toxicity at least possibly related to study treatment, and the rate of grade 2 or higher toxicity at least probably related to study treatment.

For patients who respond to treatment (complete or partial response), duration of response will be calculated from the date of response to the date of progression of disease. Patients still responding at date of last follow-up will be censored. PFS will be calculated as the time from start of treatment to the date of progression, death or last follow-up. OS will be calculated as the time from the start of treatment to the date of death or last follow-up. OS, PFS and DOR will be calculated using Kaplan-Meier methodology. 95% confidence intervals will be calculated for all secondary endpoints.

Correlative studies analyzing tissue samples using MIF and/or MIBI and circulating tumor DNA using next-generation sequencing based platforms are exploratory in nature. This testing is not powered to detect associations, but rather is designed to generate hypothesis for future studies. Completion of correlative studies will depend upon sample collection and budget considerations.

## 13.5 Reporting and Exclusions

### 13.5.1 Evaluation of Toxicity

All participants who receive at least one dose of study therapy will be evaluable for toxicity from the time of their first treatment.

### 13.5.2 Evaluation of the Primary Efficacy Endpoint

The primary analysis will be performed on all evaluable patients.

# 14. PUBLICATION PLAN

The results of this study will be submitted for presentation at national meetings and for publication in appropriate journals within 24 months of the completion of the study. The first analysis and submission will be conducted when all patients have reached the End of Study visit (or been taken off study).

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## APPENDIX A PERFORMANCE STATUS CRITERIA

| ECOG Performance Status Scale | | Karnofsky Performance Scale | |
|---|---|---|---|
| Grade | Descriptions | Percent | Description |
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. | 100 | Normal, no complaints, no evidence of disease. |
| | | 90 | Able to carry on normal activity; minor signs or symptoms of disease. |
| 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work). | 80 | Normal activity with effort; some signs or symptoms of disease. |
| | | 70 | Cares for self, unable to carry on normal activity or to do active work. |
| 2 | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. | 60 | Requires occasional assistance, but is able to care for most of his/her needs. |
| | | 50 | Requires considerable assistance and frequent medical care. |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. | 40 | Disabled, requires special care and assistance. |
| | | 30 | Severely disabled, hospitalization indicated. Death not imminent. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. | 20 | Very sick, hospitalization indicated. Death not imminent. |
| | | 10 | Moribund, fatal processes progressing rapidly. |
| 5 | Dead. | 0 | Dead. |

# APPENDIX B DANA-FARBER/HARVARD CANCER CENTER MULTI-CENTER DATA SAFETY MONITORING PLAN

## INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP serves as a reference for any sites external to DF/HCC that are participating in a DF/HCC clinical trial.

### 1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

## 2 GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the following general responsibilities apply, in addition to those outlined in DF/HCC Policies for Sponsor-Investigators:

### 2.1 External Site

An External Site is an institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC investigator. The External Site acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Each External Site is expected to comply with all applicable DF/HCC requirements stated within this Data and Safety Monitoring Plan and/or the protocol document.

The general responsibilities for each External Site may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB. For studies under a single IRB, the Coordinating Center with regulatory documents or source documents as requested.
- Maintain regulatory files as per ICH GCP and federal requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required.
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities when required by the sponsor.

- Submit Serious Adverse Event (SAE) reports to the Sponsor, Coordinating Center, and IRB of Record as applicable.
- Submit protocol deviations and violations to sponsor, Coordinating Center, and IRB of record as applicable, in accordance with DF/HCC requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.
- Notify the sponsor immediately of any regulatory authority inspection of this protocol at the External Site.

# 3 DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

Certain DF/HCC Policy requirements apply to External Sites participating in DF/HCC research. The following section will clarify DF/HCC requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

## 3.1 Protocol Revisions and Closures

The External Sites will receive notification of protocol revisions and closures from the Coordinating Center. When under a separate IRB, it is the individual External Site's responsibility to notify its IRB of these revisions.

- **Protocol revisions:** External Sites will receive written notification of protocol revisions from the Coordinating Center. All protocol revisions must be IRB approved and implemented within a timely manner from receipt of the notification.

- **Protocol closures and temporary holds:** External Sites will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

## 3.2 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for External Sites. The External Site consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for Investigator-Sponsored Multi-Center Trials. This document will be provided separately to each External Site upon request.

External Sites are to send their version of the informed consent document to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent

form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each External Site will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. External Sites must follow the DF/HCC requirement that for all interventional drug, biologic, or device research, only attending physicians may obtain initial informed consent and any re-consent that requires a full revised consent form.

## 3.3 IRB Re-Approval

Verification of IRB re-approval from the External Sites is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

## 3.4 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned protocol case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

## 3.5 Participant Registration

### 3.5.1 Participant Registration

To register a participant, the following documents should be completed by the External Site and e-mailed to the Coordinating Center:

*Celeste Carey*
*Dana-Farber Cancer Institute*
*450 Brookline Ave*
*Boston, MA 02215*
*Celeste_Carey@dfci.harvard.edu*
*Phone: 857.215.1646*

- Copy of required assessments that support eligibility
- Signed informed consent document
- HIPAA authorization form (if applicable)
- Completed DFCI Eligibility Checklist

The Coordinating Center will review the submitted documents in order to verify eligibility and consent. To complete the registration process, the Coordinating Center will:

- Register the participant on the study with the DF/HCC Clinical Trial Management System (CTMS).
- Upon receiving confirmation of registration, the Coordinating Center will inform the External Site and provide the study specific participant case number, and if applicable, assigned treatment and/or dose level.

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. External Sites should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

### 3.5.2 Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before the initiation of treatment or other protocol-specific interventions. Treatment and other protocol-specific interventions may not be initiated until the External Site receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

### 3.5.3 Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without DFCI IRB approval will be permitted. All External Sites are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

## 3.6 Data Management

DF/HCC develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. DF/HCC provides a web based training for all eCRF users.

### 3.6.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality, Coordinating Center, or designee.

Responses to all queries should be completed and submitted within 14 calendar days.

If study forms are not submitted on schedule, the External Site will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

## 3.7 Protocol Reporting Requirements

### 3.7.1 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor and to the IRB of record.

### 3.7.2 Reporting Procedures

Requests to deviate from the protocol require approval from the IRB of record and the sponsor.

All protocol violations must be sent to the Coordinating Center in a timely manner. The Coordinating Center will provide training for the requirements for the reporting of violations.

### 3.7.3 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports per DF/HCC requirements, and ensure that all IND Safety Reports are distributed to the External Sites as required by DF/HCC Policy. External Sites will review/submit to the IRB according to their institutional policies and procedures.

# 4 MONITORING: QUALITY CONTROL

The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

## 4.1 Ongoing Monitoring of Protocol Compliance

The External Sites may be required to submit participant source documents to the Coordinating Center for monitoring. External Sites may also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that External Sites are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring practices may include but are not limited to; source data verification, and review and analysis of eligibility requirements, informed consent procedures, adverse events and all associated documentation, review of study drug administration/treatment, regulatory files, protocol departures reporting, pharmacy records, response assessments, and data management.

External Sites will be required to participate in regular Coordinating Center initiated teleconferences.

Remote Monitoring: External Sites will be required to forward de-identified copies of participants' medical record and source documents to the Coordinating Center to aid in source data verification.

and/or

On-Site Monitoring: Source documentation verification (SDV) will be conducted yearly by having access to participants' complete medical record and source documents.

### 4.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at External Sites that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.

### 4.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each External Site. Accrual will be monitored for each External Site by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

## 5 AUDITING: QUALITY ASSURANCE

### 5.1 DF/HCC Internal Audits

All External Sites are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2-day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

### 5.2 Audit Notifications

It is the External Site's responsibility to notify the Coordinating Center of all external audits or inspections (e.g., FDA, EMA, NCI) that involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

### 5.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The Coordinating Center, must forward any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

## 5.4 External Site Performance

The DF/HCC Sponsor and the IRB of record are charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

External Sites that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be put on hold or closed.

# APPENDIX C RESPONSE CRITERIA FOR LYMPHOMA: LUGANO 2014 AND LYRIC

| Criteria | Complete Response (CR) | Partial Response (PR) | Stable Disease (SD) | Progressive disease (PD) |
|---|---|---|---|---|
| Lugano | PET-CT, score 1, 2, or 3* with or without a residual mass on 5PS†<br><br>*Or*<br><br>on CT, target nodes/nodal masses must regress to ≤ 1.5 cm in LDi, and no extralymphatic sites of disease | PET-CT Score 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size.<br><br>*Or*<br><br>On CT ≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites; no increase in non-measured lesions; spleen if enlarged must have regressed by >50% in length beyond normal | Neither CR, PR, nor PD | PET-CT score 4 or 5 with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment.<br><br>*Or*<br><br>On CT, an individual node/lesion must be abnormal with:<br>LDi > 1.5 cm and<br>Increase by ≥ 50% from PPD nadir and<br>An increase in LDi or SDi from nadir<br>0.5 cm for lesions ≤ 2 cm<br>1.0 cm for lesions > 2 cm<br>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<br>New or recurrent splenomegaly.<br>New or clear progression of preexisiting nonmeasured lesions.<br>Regrowth of previously resolved lesions.<br>A new node > 1.5 cm in any axis or 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<br>Assessable disease of any size unequivocally attributable to lymphoma<br><br>*And/Or*<br><br>New or recurrent involvement of the bone marrow |

| Criteria | Complete Response (CR) | Partial Response (PR) | Stable Disease (SD) | Progressive Disease (PD) |
|---|---|---|---|---|
| LYRIC | Same as Lugano | Same as Lugano | Neither CR, PR, PD, nor IR | As with Lugano with the following exceptions:<br>Indeterminate response (IR)<br>IR1: ≥50% increase in SPD in first 12 wks<br>IR2: <50% increase in SPD with<br>a. New lesion(s), or<br>b. ≥50% increase in PPD of a lesion or set of lesions at any time during treatment<br>IR(3): Increase in FDG uptake without a concomitant increase in lesion size meeting criteria for PD |

SPD – sum of the product of the diameters; PPD – product of the perpendicular diameters; LDi – longest diameter; SDi – short diameter; 5PS – 5-point scale; IR – immune response

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate