**NCI Protocol #:** N/A

**DF/HCC Protocol #:** 17-566

**TITLE:** Biomarkers of response to ipilimumab and nivolumab as first-line therapy for metastatic non-small cell lung cancer (NSCLC): an open-label, single arm phase 2 study

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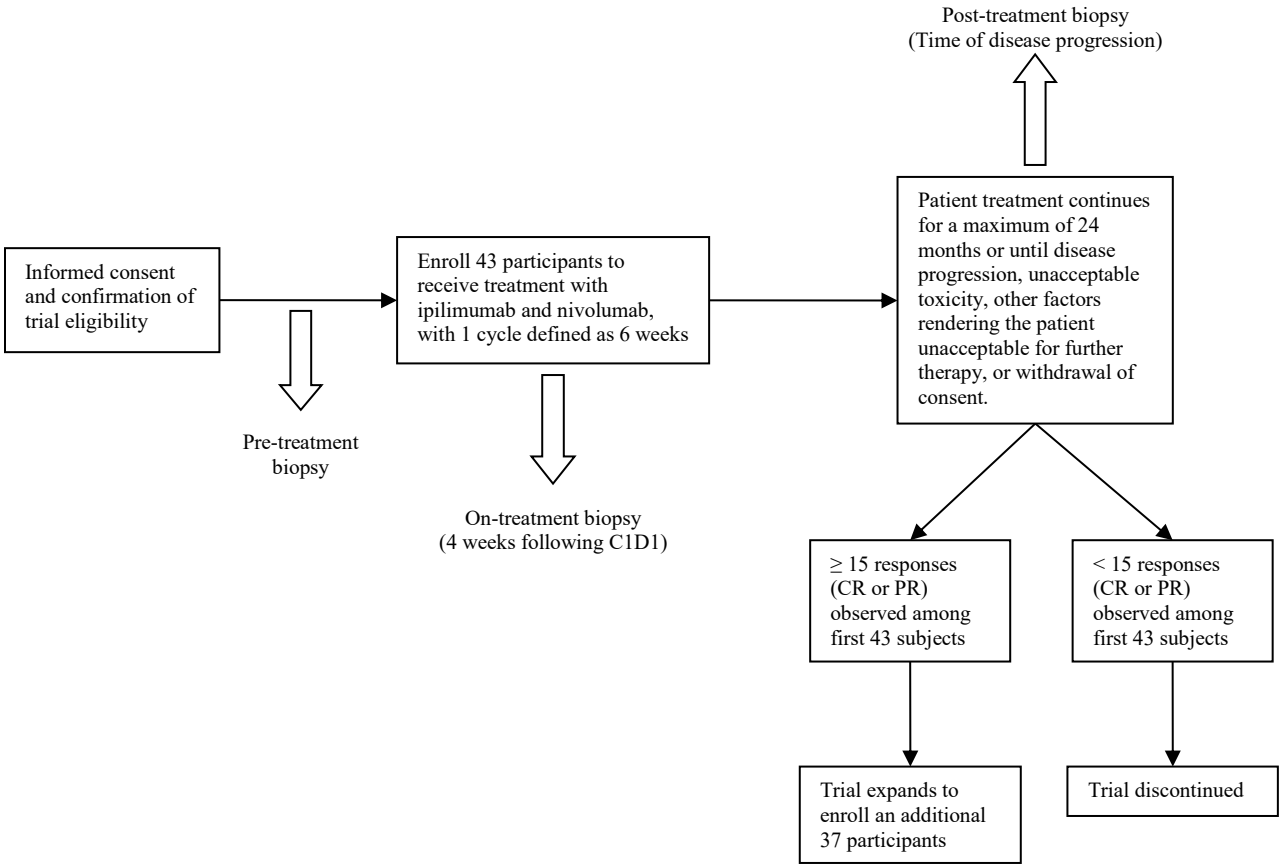
**SCHEMA**


Post-treatment biopsy
(Time of disease progression)
Informed consent and confirmation of trial eligibility
Enroll 43 participants to receive treatment with ipilimumab and nivolumab, with 1 cycle defined as 6 weeks
Patient treatment continues for a maximum of 24 months or until disease progression, unacceptable toxicity, other factors rendering the patient unacceptable for further therapy, or withdrawal of consent.
Pre-treatment biopsy
On-treatment biopsy
(4 weeks following C1D1)
≥ 15 responses (CR or PR) observed among first 43 subjects
< 15 responses (CR or PR) observed among first 43 subjects
Trial expands to enroll an additional 37 participants
Trial discontinued

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# 1. OBJECTIVES

## 1.1 Study Design

This is an open label phase II study evaluating potential immunologic biomarkers of response and resistance to first-line ipilimumab and nivolumab therapy in non-small cell lung cancer (NSCLC). The trial will employ a Simon 2-stage design, where 43 participants will be enrolled initially. If at least 15 radiological responses are observed among the first 43 participants, the trial will enroll an additional 37 subjects.

## 1.2 Primary Objective

- Assess the overall response rate (ORR) of ipilimumab and nivolumab in NSCLC using RECIST 1.1 criteria.

## 1.3 Secondary Objectives

- Evaluate immunologic correlates of response and primary resistance to ipilimumab and nivolumab therapy in NSCLC.
- Evaluate immunologic correlates of acquired resistance to ipilimumab and nivolumab in NSCLC, with acquired resistance defined as participants who experience an objective radiologic response or stable disease per RECIST 1.1 criteria followed by disease progression.
- Assess the progression-free survival (PFS) rate, duration of response (DoR), and overall survival (OS) of the combination utilizing RECIST 1.1 criteria.

# 2. BACKGROUND

## 2.1 Study Disease and Rationale

Lung cancer is the leading cause of cancer-related death worldwide in both men and women, and more people die from lung cancer than from colon, breast, and prostate cancer combined. In the United States, there will be 222,500 new cases of lung cancer in 2017 (116,990 in men and 105,510 in women), and an estimated 155,870 deaths from lung cancer (84,590 in men and 71,280 in women)[1]. NSCLC accounts for 85-90% of lung cancer and is comprised of three main histologic subtypes: adenocarcinoma (accounts for approximately 40% of lung cancers), squamous cell carcinoma (25-30%), and large cell (undifferentiated) carcinoma (10%).

The current standard of care for first-line treatment of metastatic NSCLC lacking *EGFR* mutations or *ALK* rearrangements is the programmed death protein 1 (PD-1) inhibitor pembrolizumab for tumors with high programmed death-ligand 1 (PD-L1) expression, or cytotoxic chemotherapy with a platinum doublet for tumors with low or absent PD-L1 expression, with an overall response rate (ORR) of 30-40%. Treatment with CTLA-4 inhibitor ipilimumab and the PD-1 inhibitor nivolumab also appears to be a promising combination for the first-line treatment of NSCLC, with reported ORR of 30-40% and an acceptable toxicity profile[2].

There is a critical need to identify additional biomarkers of response, primary resistance, and acquired resistance to the combination of ipilimumab and nivolumab in NSCLC. Among participants with NSCLCs with ≥ 50% PD-L1 expression, the response rate to pembrolizumab is only 45%, suggesting that there may be additional biomarkers that can distinguish responders from non-responders[3]. In addition, while Rizvi and colleagues showed that a higher non-synonymous mutation burden has been associated with increased objective responses, durable benefit, and progression-free survival (PFS) with PD-1 inhibition, some patients with high mutational load did not benefit from immunotherapy while other patients with low mutational load did benefit from immunotherapy[4]. This again suggests that there are other factors that contribute to response or resistance other than mutational load.

We have developed a comprehensive flow cytometry platform to dissect the immune profile of tumor cells and immune cells in thoracic malignancies[5,6]. Using this novel technique, we can identify immunologically "hot" and "cold" clusters of tumors and study expression of numerous immunologic markers (e.g. TIM3, LAG3, etc.) on individual immune cells.

Furthermore, the laboratories of Dr. Roger Kamm (Massachusetts Institute of Technology) and Dr. David Barbie (DFCI) have developed a technique using a microfluidic system to support primary human tumor culture. These tumor "spheroids" retain critical immune effector cells and allows for the *ex vivo* study of PD-1 and/or CTLA-4 inhibitor-induced immune responses[7,8].

## 2.2 Ipilimumab (YERVOY)

Ipilimumab (BMS-734016, MDX010, MDX-CTLA4) is a fully human monoclonal immunoglobulin (Ig) G1κ specific for human cytotoxic T-lymphocyte antigen 4 (CTLA-4, cluster of differentiation [CD] 152), which is expressed on a subset of activated T cells. CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a monoclonal antibody (mAb) that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell ($T_{reg}$) function, which may contribute to a general increase in T-cell responsiveness, including the anti-tumor response.

Ipilimumab has been approved for use in over 47 countries including the United States (US, Mar-2011), the European Union (EU, Jul-2011), and Australia (Jul-2011).

### 2.2.1 Non-Clinical Summary

Ipilimumab has specificity and a high affinity for human CTLA-4. The calculated dissociation constant value from an average of several studies was 5.25 nM. Binding of ipilimumab to purified, recombinant human CTLA-4 antigen was also demonstrated by enzyme-linked immunosorbent assay with half-maximal binding at 15 ng/mL, whereas saturation was observed at approximately 0.1 μg/mL. No cross-reactivity was observed against human CD28. Ipilimumab completely blocked binding of B7.1 and B7.2 to human CTLA-4 at concentrations higher than 6 and 1 μg/mL, respectively.

Please refer to the ipilimumab investigator's brochure (IB) for further information on pre-clinical development.

### 2.2.2 Clinical Studies

Bristol-Myers Squibb (BMS) and Medarex, Inc. (MDX, acquired by BMS in Sep-2009) have co-sponsored an extensive clinical development program for ipilimumab, encompassing more than 19,500 subjects (total number of subjects enrolled in ipilimumab studies) in several cancer types in completed and ongoing studies, as well as a compassionate use program. The focus of the clinical program is in melanoma, prostate cancer, and lung cancer, with advanced melanoma being the most comprehensively studied indication. Ipilimumab is being investigated both as monotherapy and in combination with other modalities such as chemotherapy, radiation therapy, and other immunotherapies.

Phase 3 programs are ongoing in melanoma, prostate cancer, and lung cancer. In melanoma, 2 completed phase 3 studies have demonstrated a clinically meaningful and statistically significant survival benefit in pretreated advanced melanoma and previously untreated advanced melanoma, respectively.

The safety profile of ipilimumab is generally consistent across these trials with a) the majority adverse events (AEs) being inflammatory in nature, which is consistent with the proposed mechanism of action of ipilimumab; b) the same types of such immune-mediated events in the gastrointestinal (GI) tract, skin, liver, and endocrine system being reported; and c) most of these events being manageable with immune suppressive therapies.

In melanoma, 2 BMS-sponsored phase 3 studies are ongoing in subjects with high-risk stage III melanoma and pretreated and treatment-naïve advanced melanoma (3 mg/kg versus 10 mg/kg ipilimumab).

The completed phase 3 study evaluated ipilimumab in subjects with metastatic castration-resistant prostate cancer (mCRPC) who had progressed during or following treatment with docetaxel. Eligible subjects were randomized to a single dose of bone-directed radiotherapy (RT), followed by either ipilimumab 10 mg/kg or placebo (799 randomized: 399 ipilimumab, 400 placebo). This study did not meet its primary endpoint of overall survival (OS). The hazard ratio (HR) of 0.85 (95% confidence interval [CI]: 0.72, 1.00) for survival favored ipilimumab but did not reach statistical significance with a P value of 0.053. Planned sensitivity analyses favored ipilimumab, where the greatest benefit appeared to be in subgroups defined by good prognostic features and low burden of disease. Additional evidence of ipilimumab activity observed in the study included a reduced risk of disease progression relative to placebo (HR = 0.70), superior clinical outcomes compared to placebo in tumor regression, and declines in prostate specific antigen (PSA). The safety profile in this study was consistent with the previously defined AE profile at the same dose.

A second phase 3 study evaluated ipilimumab 10 mg/kg versus placebo in men with asymptomatic or minimally symptomatic, chemotherapy-naïve mCRPC with no visceral metastases. A total of 602 subjects were randomized in a 2:1 ratio (400 subjects to 10 mg/kg

ipilimumab and 202 subjects to placebo). Preliminary data indicate the study did not meet its primary endpoint based on intent-to-treat analysis. The HR of 1.11 (95.87% CI: 0.88, 1.39; P value = 0.3667) for OS did not favor ipilimumab. A longer median progression-free survival (PFS) interval was observed for the ipilimumab group than for the placebo group, which may be indicative of activity of ipilimumab in delaying disease progression. The safety profile in this study was generally consistent with the previously defined AE profile at the same dose.

In addition, a completed, large phase 2 study has investigated the addition of ipilimumab to carboplatin and paclitaxel using 2 different schedules (concurrent and phased) in subjects with NSCLC or small cell lung cancer (SCLC, a secondary endpoint). Ipilimumab, given in combination with paclitaxel/carboplatin in a phased schedule improved immune-related progression-free survival (irPFS) compared to the control treatment, but no improvement was seen when ipilimumab was given in a concurrent schedule. Phased ipilimumab also improved PFS according to modified World Health Organization (mWHO) criteria and showed a trend for improved OS.

The efficacy and safety of ipilimumab in a phased schedule with carboplatin/paclitaxel is also being investigated in a phase 3 study in subjects with advanced squamous NSCLC (CA184104). The efficacy and safety of ipilimumab in a phased schedule with etoposide/platinum in subjects with extensive stage disease SCLC is being investigated in a phase 3 study (CA184156). In Study CA184104, the last patient, last visit was achieved in June 2015, and database lock occurred on 01-Sep-2015. No final data are currently available, but preliminary data indicate that no new safety concerns were identified in the course of standard clinical safety monitoring of the study. In Study CA184156, preliminary data indicate the primary endpoint of prolonging survival was not achieved, but no new safety signals were identified.

The unique immune-based mechanism of action is reflected in the clinical patterns of anti-cancer activity in some patients. Ipilimumab induces an immunologic response, and measurable clinical effects emerge after the immunological effects. Tumor infiltration with lymphocytes and the associated inflammation (documented by biopsy in some subjects) is likely the cornerstone of the effect of ipilimumab and can manifest in various patterns of clinical activity leading to tumor control. In some cases, inflammation may not be noted by radiological examination, and objective response is observed with the first tumor assessment in a manner seen in patients receiving other types of anti-cancer treatments. In other cases, response may be preceded by an apparent increase in initial tumor volume and/or the appearance of new lesions, which may be mistaken for tumor progression on radiological evaluations. Therefore, in patients who are not experiencing rapid clinical deterioration, confirmation of progression is recommended (at the investigator's discretion) to better understand the prognosis, as well as to avoid unnecessarily initiating potentially toxic alternative therapies in subjects who might be benefiting from treatment. Immune-related response criteria were developed based on these observations to systematically categorize novel patterns of clinical activity and are currently being prospectively evaluated in clinical studies.

In metastatic diseases, stabilization is more common than response, and in some instances is associated with a slow, steady decline in tumor burden over many months, sometimes improving to partial and/or complete responses (CRs). Thus, the immune-based mechanism of action of

ipilimumab results in durable disease control, sometimes with novel patterns of response, which contribute to its unique improvement in OS.

The unique immune-based mechanism of action is also reflected in the safety profile. The most common treatment-related AEs are inflammatory in nature, consistent with the mechanism of action of the drug and generally medically manageable with topical and/or systemic immunosuppressants. Such immunological safety events are described as immune-related adverse events (irAEs) or immune-mediated adverse reactions (imARs). The irAEs are described as AEs of unknown etiology, which were consistent with an immune phenomenon and considered causally related to drug exposure by investigators. The irAEs primarily involve the GI tract and skin. Immune-related AEs in the liver were also observed, particularly in subjects receiving 10 mg/kg. Endocrinopathy and neuropathy were important irAEs that were observed less frequently. The imARs were adjudicated in a blinded fashion based on Sponsor-physician data review to exclude noninflammatory etiologies, such as infection or tumor progression, and to consider available evidence of inflammation, such as tumor biopsies or responsiveness to steroids, in an effort to determine whether specific AEs or abnormal hepatic laboratory values were likely to be immune mediated and associated with ipilimumab treatment.

The early diagnosis of inflammatory events is important to initiate therapy and minimize complications. Inflammatory events are generally manageable using symptomatic or immuno-suppressive therapy as recommended through detailed diagnosis and management guidelines.

A program-wide independent Data Monitoring Committee (DMC) reviews data from the ipilimumab studies, allowing for an ongoing safety and benefit/risk assessment in subjects receiving ipilimumab. The DMC charter includes explicit stopping rules for some studies, allowing the DMC to recommend discontinuing further treatment across the ipilimumab program, if necessary.

In summary, ipilimumab offers clinically meaningful and statistically significant survival benefit to patients with pretreated advanced melanoma (as 3 mg/kg monotherapy compared to the melanoma peptide vaccine gp100) and previously untreated advanced melanoma (at 10 mg/kg in combination with dacarbazine [DTIC] compared to DTIC alone) and evidence of clinical activity in randomized studies in other tumor types. These findings, together with evidence of a safety profile that is manageable with careful monitoring and appropriate intervention for treatment of immune-related toxicities, suggest an acceptable benefit to risk ratio.

Please also refer to the IB for the most comprehensive clinical background information for ipilimumab.

### 2.2.3 Clinical Pharmacokinetics

The pharmacokinetics (PK) of ipilimumab has been extensively studied in subjects with melanoma, at the 3 and 10 mg/kg doses administered as a 1.5-hour IV infusion. The PK of ipilimumab was characterized by population PK (PPK) analysis and determined to be linear and time invariant in the dose range of 0.3 to 10 mg/kg. The mean CL (±SD) value after IV administration of 10 mg/kg was 18.3 ± 5.88 mL/h, and the mean steady-state volume of

distribution ($V_{ss}$) [±SD] value was 5.75 ± 1.69 L.

### 2.2.4 Pharmacodynamics

CTLA-4 is a key regulator of T-cell activity. Ipilimumab is a CTLA-4 immune checkpoint inhibitor that blocks T-cell inhibitory signals induced by the CTLA-4 pathway, increasing the number of tumor reactive T-effector cells that mobilize to mount a direct T-cell immune attack against tumor cells. Preclinical data indicate that CTLA-4 blockade can also reduce $T_{reg}$ function, which may lead to an increase in anti-tumor immune response. Ipilimumab may selectively deplete $T_{regs}$ at the tumor site, leading to an increase in the intratumoral T-effector/$T_{reg}$ cell ratio which drives tumor response leading to cell death[9].

#### 2.2.4.1 Ipilimumab Effect on Circulating T Cells

CTLA-4 is a negative regulator of T-cell activation. By blocking CTLA-4, ipilimumab increases the percentage of peripheral activated T cells and central memory T cells. These changes are evidenced by Week 4 and generally remain sustained through Week 1. The sum of these changes in immune cell subsets may result in anti-tumor activity, as well as irAEs.

**Table 1: Key T-cell Subsets following Ipilimumab Treatment**

| T-cell population | Ipilimumab Dose (mg/kg) | Fitted Mean Relative Frequency (%) Mean (95% CI) | | |
|---|---|---|---|---|
| | | Baseline[a] | Week 4[b] | Week 12[c] |
| Activated CD4+ / Total CD4+ | 3 | 17.0 (13.4, 20.6) | 25.2 (21.3, 29.2) | 24.7 (21.0, 28.3) |
| | 10 | 14.9 (11.2, 18.6) | 24.8 (20.8, 28.8) | 24.7 (20.5, 29.0) |
| Activated CD8+ / Total CD8+ | 3 | 24.7 (18.9, 30.5) | 31.1 (25.2, 37.1) | 33.4 (27.5, 39.4) |
| | 10 | 22.5 (16.5, 28.6) | 25.7 (19.6, 31.9) | 27.6 (21.0, 34.2) |
| Central Memory CD4+ / Total CD4+ | 10 | 54.5 (52.4, 56.7) | 59.6 (57.5, 61.7) | 62.0 (59.9, 64.1) |
| Central Memory CD8+ / Total CD8+ | 10 | 37.4 (33.8, 41.0) | 41.0 (37.5, 44.6) | 45.3 (41.7, 48.9) |

a. Baseline is defined as the pre-dose measurement closest in time to first dose.
b. Nominal Week 4 is defined as visits between study Days 8 and 42, inclusive.
c. Nominal Week 12 is defined as visits between study Days 64 and 98, inclusive.
Note: Means and 95% CI are estimates from extended linear models.

#### 2.2.4.2 Ipilimumab Effect on Absolute Lymphocyte Count

In clinical studies, ipilimumab increased absolute lymphocyte count (ALC) in peripheral blood.

In 214 subjects with advanced melanoma, ipilimumab increased ALC in a dose-dependent manner, with the largest increase observed at 10-mg/kg dose.

In phase 3 studies in advanced melanoma, high baseline ALC was found to be significantly associated with longer OS regardless of treatment. However, subjects with low baseline ALC treated with ipilimumab demonstrated longer OS relative to subjects not treated with ipilimumab.

#### 2.2.5 Clinical Efficacy

Ipilimumab prolongs survival in subjects with pretreated and previously untreated advanced melanoma and has demonstrated anti-tumor activity in other malignancies, including lung, prostate cancer, and renal cell carcinoma. Please refer to the IB for detailed efficacy information regarding ipilimumab monotherapy.

#### 2.2.6 Clinical Safety

Blockade of CTLA-4 by ipilimumab leads to T-cell activation, with the potential for clinical inflammatory adverse events (AEs) primarily involving the skin (dermatitis/pruritus), GI tract (diarrhea/colitis), liver (hepatitis), endocrine glands (e.g., hypophysitis and adrenal or thyroid abnormalities), and other less frequent organs (e.g., uveitis/episcleritis). The majority of these inflammatory AEs initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab. The majority of the inflammatory AEs are reversible with the guidance issued in **Section 6**. In rare cases, these inflammatory AEs may be fatal.

Patients should be assessed for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy, and clinical chemistries (including liver function, adrenocorticotropic hormone [ACTH] level, and thyroid function tests) should be evaluated.

During evaluation of a suspected inflammatory AE, all efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes. Serological, immunological, imaging, and biopsy with histology (e.g., biopsy-proven lymphocytic) data should be used to support the diagnosis of an immune-mediated toxicity or support an alternative cause of the AE. In general, for severe inflammatory AEs, ipilimumab should be permanently discontinued, and systematic high-dose corticosteroid therapy should be initiated. For moderate immune-mediated AEs, ipilimumab should be held or delayed, and moderate-dose corticosteroids should be considered.

Based on limited current clinical experience, corticosteroids do not appear to adversely affect the anti-tumor response. For example, disease control was maintained in subjects with objective responses who received corticosteroid administration for concomitant serious inflammatory AEs.

### 2.3 Nivolumab (OPDIVO)

Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the PD-1 cluster of differentiation 279 (CD279) cell surface membrane receptor[10]. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, PD-L1 and PD-L2, results in the

down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

Nivolumab is approved for use in multiple countries including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014).

### 2.3.1 Non-Clinical Summary

Nivolumab has been shown to bind specifically to the human PD-1 receptor and not to related members of the CD28 family. Nivolumab inhibits the interaction of PD-1 with its ligands, PD-L1 and PD-L2, resulting in enhanced T-cell proliferation and interferon-gamma (IFN-γ) release *in vitro*[11]. Nivolumab binds with high affinity to activated human T-cells expressing cell surface PD-1 and to cynomolgus monkey PD-1. In a mixed lymphocyte reaction (MLR), nivolumab promoted a reproducible concentration-dependent enhancement of IFN-γ release[12].

In intravenous (IV) repeat-dose toxicology studies in cynomolgus monkeys, nivolumab was well tolerated at doses up to 50 mg/kg, administered weekly for 5 weeks, and at doses up to 50 mg/kg, administered twice weekly for 27 doses. While nivolumab alone was well tolerated in cynomolgus monkeys, combination studies have highlighted the potential for enhanced toxicity when combined with other immunostimulatory agents.

In addition, an enhanced pre- and postnatal development (ePPND) study in pregnant cynomolgus monkeys with nivolumab was conducted. Administration of nivolumab at up to 50 mg/kg 2QW was well tolerated by pregnant monkeys; however, nivolumab was determined to be a selective developmental toxicant when administered from the period of organogenesis to parturition at ≥ 10 mg/kg ($AUC_{(0\text{-}168\ h)}$ 117,000 μg•h/mL). Specifically, increased developmental mortality (including late gestational fetal losses and extreme prematurity with associated neonatal mortality) was noted in the absence of overt maternal toxicity. There were no nivolumab-related changes in surviving infants tested throughout the 6-month postnatal period. Although the cause of these pregnancy failures was undetermined, nivolumab-related effects on pregnancy maintenance are consistent with the established role of PD-L1 in maintaining fetomaternal tolerance in mice[13].

Please refer to the nivolumab IB for further information on pre-clinical development.

### 2.3.2 Clinical Studies

The PK, clinical activity, and safety of nivolumab have been assessed in subjects with NSCLC, melanoma, clear-cell renal cell carcinoma (RCC), and classical Hodgkin Lymphoma (cHL) in addition to other tumor types.

Nivolumab monotherapy is approved in multiple countries, including the US and EU, for unresectable or metastatic melanoma, previously treated metastatic NSCLC, and previously treated advanced RCC; it is also approved for the treatment of cHL in the US. In addition,

nivolumab has been approved for use in combination with ipilimumab for unresectable melanoma in multiple countries, including the US and EU. Nivolumab is being investigated both as monotherapy and in combination with chemotherapy, targeted therapies, and other immunotherapies.

Please also refer to the IB for the most comprehensive clinical background information for nivolumab.

### 2.3.3 Clinical Pharmacokinetics

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

Although ECOG status, baseline glomerular filtration rate (GFR), albumin, body weight, and mild hepatic impairment had an effect on nivolumab CL, the effect was not clinically meaningful. PPK analysis suggest that nivolumab CL in subjects with cHL was approximately 32% lower relative to subjects with NSCLC; however, the lower CL in cHL subjects was not considered to be clinically relevant as nivolumab exposure was not a significant predictor for safety risks for these patients. When nivolumab is administered in combination with ipilimumab, the CL of nivolumab was increased by 24%, whereas there was no effect on the clearance of ipilimumab. Additionally, PPK and exposure response analyses have been performed to support use of 240 mg every 2 week (Q2W) dosing in addition to the 3 mg/kg Q2W regimen. A flat dose of nivolumab 240 mg Q2W was selected since it is identical to a dose of 3 mg/kg for subjects weighing 80 kg, the observed median body weight in nivolumab-treated cancer patients. Using a PPK model, the overall distributions of nivolumab exposures ($C_{avgss}$, $C_{minss}$, $C_{maxss}$, and $C_{min1}$) are comparable after treatment with either 3 mg/kg or 240 mg nivolumab. The predicted range of nivolumab exposures (median and 90% prediction intervals) resulting from a 240 mg flat dose across the 35 to 160 kg weight range is maintained well below the corresponding exposures observed with the well tolerated 10 mg/kg nivolumab Q2W dosage.

### 2.3.4 Pharmacodynamics

The clinical PDs were assessed for nivolumab monotherapy and for nivolumab in combination with ipilimumab.

The PD effects of nivolumab were studied by assessing receptor occupancy (RO), peripheral immune cell population modulation, systemic cytokine modulation, and change in absolute

lymphocyte count (ALC) in two studies. Results were as follows:

- Peripheral RO of PD-1 is saturated at doses ≥ 0.3 mg/kg dose levels as measured on CD3+ cells from frozen and fresh peripheral blood mononuclear cells (PBMCs).
- Nivolumab treatment had no clinically meaningful changes in activated T-cells in peripheral blood; no dose response was evident.
- Baseline measurements of select immune cell subsets were not associated with response to nivolumab.
- Mean ALC measured over time did not change at any nivolumab dose nor was it associated with response to nivolumab.
- Median percent increase from baseline to post-dose for CXCL9 and CXCL10 were consistent with demonstration of immunomodulatory activity of nivolumab on these chemokines.

To understand if the effect of nivolumab in combination with ipilimumab was distinct from that of either nivolumab or ipilimumab monotherapy, changes in immunomodulatory PD biomarkers with combination nivolumab and ipilimumab treatment was assessed in one study. ALC, activated CD4+ and CD8+ T cells in the periphery, and levels of inflammatory cytokines were measured in blood and serum. Results were as follows:

- No consistent rise in ALC was observed with combination nivolumab and ipilimumab therapy, similar to nivolumab monotherapy.
- Increases in activated CD4+ and CD8+ T cells were observed with the combination regimen, consistent with the pharmacodynamic effects of ipilimumab alone and distinct from the effects of nivolumab alone.
- Combination therapy resulted in increases in interferon-γ induced serum cytokines, such as MIG (CXCL9) and IP-10 (CXCL10), which are also increased with single agent nivolumab.

### 2.3.5 Clinical Efficacy

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

### 2.3.6 Clinical Safety

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 12,300 treated subjects.

For monotherapy, the safety profile is similar across tumor types. There is no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. In Phase 3 controlled studies, the safety profile of nivolumab monotherapy is acceptable in the context of the observed clinical

efficacy, and manageable using established safety guidelines. Clinically relevant AEs typical of stimulation of the immune system were infrequent and manageable by delaying or stopping nivolumab treatment and timely immunosuppressive therapy or other supportive care.

In several ongoing clinical trials, the safety of nivolumab in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies is being explored. Most studies are ongoing and, as such, the safety profile of nivolumab combinations continues to evolve. The most advanced combination under development is nivolumab with ipilimumab, which is approved in subjects with unresectable or metastatic melanoma, and being studied in multiple tumor types. Results to date suggest that the safety profile of nivolumab with 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.

### 2.3.7 Flat Dosing

The safety and efficacy of 240 mg Q2W flat dose of nivolumab is expected to be similar to 3 mg/kg Q2W dosing regimen. A flat dose of nivolumab 240 mg Q2W was selected since it is identical to a dose of 3 mg/kg for subjects weighing 80 kg, the observed median body weight in nivolumab treated cancer patients. Using a PPK model, the overall distributions of nivolumab exposures ($C_{avgss}$, $C_{minss}$, $C_{maxss}$, and $C_{min1}$) are comparable after treatment with either 3 mg/kg or 240 mg nivolumab. The predicted range of nivolumab exposures (median and 90% prediction intervals) resulting from a 240 mg flat dose across the 35 to 160 kg weight range is maintained well below the corresponding exposures observed with the well tolerated 10 mg/kg nivolumab Q2W dosage. Across the various tumor types in the clinical program, nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy and safety has been found to be relatively flat. Given the similarity of nivolumab PK across tumor types and the similar exposures predicted following administration of 240 mg flat dose compared to 3 mg/kg Q2W regimen, it is expected that the safety and efficacy profile of 240 mg Q2W nivolumab will be similar to that of 3 mg/kg nivolumab. Hence, a flat dose of 240 mg nivolumab is under investigation.

In addition, nivolumab 480 mg administered once every 4 weeks (Q4W) is currently under investigation. The less frequent dosing regimen is designed to afford more convenience to the target patient populations. The nivolumab dose of 480 mg Q4W was selected based on clinical data and modeling and simulation approaches using PPK and exposure-response analyses of data from studies in multiple tumor types (melanoma, NSCLC, and RCC) to provide an approximately equivalent dose of nivolumab 3 mg/kg Q2W. Exposures following nivolumab 480 mg Q4W regimen are predicted to be within the exposure ranges observed at doses up to 10 mg/kg Q2W used in the nivolumab clinical program, and are not considered to put participants at increased risk.

## 2.4 Ipilimumab with Nivolumab

### 2.4.1 Clinical Pharmacokinetics

The pharmacokinetics of nivolumab and ipilimumab were assessed using a PPK approach when nivolumab and ipilimumab were administered in combination. The %CV CL, $V_{ss}$, and $t_{1/2}$ of nivolumab were 10.0 mL/h (50.3%), 7.92 L (30.1%), and 24.8 days (94.3%), respectively. When ipilimumab 3 mg/kg (registrational dose) was administered in combination with nivolumab, the CL of nivolumab was increased by 24%, whereas there was no effect on the CL of ipilimumab. However, co-administration with ipilimumab 1 mg/kg did not appear to have an effect on nivolumab CL. This is unlikely to be clinically relevant given the observed efficacy with the nivolumab and ipilimumab combination regimen.

When administered in combination, the CL of nivolumab increased by 42% in the presence of anti-nivolumab antibodies. There was no effect of anti-ipilimumab antibodies on the CL of ipilimumab.

### 2.4.2 Immunogenicity

Of 394 patients who were treated with nivolumab in combination with ipilimumab and evaluable for the presence of anti-nivolumab antibodies, 149 patients (37.8%) tested positive for treatment-emergent anti-nivolumab antibodies by an ECL assay and 18 patients (4.6%) had neutralizing antibodies against nivolumab. Of the 391 patients evaluable for the presence of anti-ipilimumab antibodies, 33 patients (8.4%) tested positive for treatment-emergent anti-ipilimumab antibodies by an ECL assay and 1 patient (0.3%) had neutralizing antibodies against ipilimumab. There was no evidence of increased incidence of infusion reactions/hypersensitivity reactions with antinivolumab antibody development. There was no evidence of altered toxicity profile associated with anti-product antibody development and there was no apparent casual effect of neutralizing antibodies on loss of efficacy.

### 2.4.3 Clinical Efficacy

In trial CA209012 (NCT01454102; CheckMate 012), an ongoing multi-arm phase 1 safety study of nivolumab in chemotherapy-naive NSCLC subjects, 56 subjects were administered nivolumab in combination with chemotherapy (gemcitabine / cisplatin, pemetrexed / cisplatin, carboplatin / paclitaxel), 21 with nivolumab in combination with erlotinib, and 197 with nivolumab in combination with ipilimumab.

A summary of ORR and PFS rate at 12 months for subjects treated with nivolumab plus ipilimumab is provided in the table below. The original nivolumab plus ipilimumab combinations using the same dosing regimens as in the melanoma studies (n = 49) were found to be non-tolerable for the NSCLC population, and these regimens were not pursued further. The results from newer combination dosing regimens (arms N, O, P, Q; n = 148) with lower and less frequent dosing of ipilimumab are presented below. The cohorts containing the approved dose of nivolumab (3 mg/kg) demonstrated improved ORR and PFS compared to the cohorts containing the lower dose of nivolumab (1 mg/kg).

The regimens for these cohorts were:

- Arm N (n=31): nivolumab 1 mg/kg + ipilimumab 1 mg/kg every 3 weeks for 4 cycles, followed nivolumab 3 mg/kg every 2 weeks

- Arm O (n=40): nivolumab 1 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 6 weeks
- Arm P (n= 38): nivolumab 3 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 12 weeks
- Arm Q (n=39): nivolumab 3 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 6 weeks

**Table 2: Efficacy in Chemotherapy-Naive NSCLC Subjects Treated with Nivolumab and Ipilimumab**

| Treatment Group | N | Nivolumab (mg/kg) | ORR[a] | | PFS at 12 months | | Median OS | |
|---|---|---|---|---|---|---|---|---|
| | | | n (%) | 95% CI[b] | % | 95% CI[c] | Months | 95% CI[b] |
| Nivo 1 + Ipi 1 ×4 (arm N) | 31 | 1 | 6 (19) | 8, 38 | 30 | 14, 47 | NR | 11.5, NR |
| Nivo 1 + Ipi 1 (arm O) | 40 | 1 | 13 (33) | 19, 49 | 25 | 12, 42 | NR | 11.0, NR |
| Nivo 3 + Ipi 1 q12w (arm P) | 38 | 3 | 18 (47) | 31, 64 | 48 | 31, 63 | NR | 14.1, NR |
| Nivo 3 + Ipi 1 q6w (arm Q) | 39 | 3 | 15 (39) | 23, 55 | 35 | 20, 50 | 18.1 | 13.3, 18.1 |

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a. CR + PR; assessed according to RECIST v.1.1
b. Based on Kaplan-Meier method
c. Based on Greenwoods formula

Abbreviations: CI = confidence interval; Ipi = ipilimumab; Nivo = nivolumab; NR: not reached; ORR = objective response rate; PFSR = progression-free survival rate; OS = overall survival

### 2.4.4 Clinical Safety

The original nivolumab plus ipilimumab combinations using the same dosing regimens as in the melanoma studies were found to be non-tolerable for the NSCLC population, so 4 additional regimens were examined (arms N, O, P, Q), and the results from these newer cohorts are presented. The regimens for these cohorts were:

- Arm N (n=31): nivolumab 1 mg/kg + ipilimumab 1 mg/kg every 3 weeks for 4 cycles, followed nivolumab 3 mg/kg every 2 weeks
- Arm O (n=40): nivolumab 1 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 6 weeks
- Arm P (n= 38): nivolumab 3 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 12 weeks
- Arm Q (n=39): nivolumab 3 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 6

The most frequently reported drug-related adverse events (AEs) in the newer nivolumab plus ipilimumab cohorts were fatigue (29.0%), diarrhea (25.0%), pruritus (23.7%), and fatigue (23.1%) in arms N, O, P, Q, respectively. Drug-related serious adverse events (SAEs) reported in more than 2 subjects/cohort treated in the newer nivolumab plus ipilimumab cohorts were adrenal insufficiency, hypophysitis, pneumonitis, autoimmune hepatitis, diarrhea, colitis, and acute kidney injury.

Drug-related AEs leading to discontinuation reported in more than 1 subject treated in the new

nivolumab plus ipilimumab arms included ALT increased, AST increased, colitis, myalgia, pneumonitis, rash, autoimmune hepatitis, infusion-related reaction, facial nerve disorder, esophagitis, and transaminases increased.

Most deaths were due to disease progression. The only deaths reported due to study drug toxicity were in the nivolumab + ipilimumab original treatment groups (respiratory failure following Grade 3 colitis, pulmonary hemorrhage, and toxic epidermal necrolysis in a patient with history of ulcerative colitis).

### 2.5 Correlative Studies Background

Baseline and on-treatment tumor biopsies will be evaluated for all participants, as well as an optional time of progression tumor biopsy. Biopsies are planned pre-treatment, approximately 4 weeks post initiation of therapy, and at the time of disease progression. To perform immunoprofiling, tissue will be subjected to:

- **Flow cytometry**. This will assess for immune cell lineages (e.g. T cells, B cells, neutrophils, macrophages, dendritic cells, NK cells, etc.) as well as characterization of CD4+ and CD8+ T cells, including their differentiation status (e.g. FOXP3, CCR7, CD45RA, CD45RO), expression of activation markers (e.g. CD69, CD11a, CD38) and inhibitory receptors (e.g. PD-1, TIM-3, LAG-3, CTLA-4), and their proliferation (e.g. Ki-67).

If adequate tissue and resources are available, samples may also undergo:

- **Microfluidic culture**. Primary tumor spheroids in microfluidic culture will be exposed to CTLA-4 or PD-1 inhibitors and we will then observe whether engulfment of spheroids by macrophage-like cells occurs over time. We will also perform cytokine profiling of conditioned media from these samples.
- ***Ex vivo* cytokine analysis.** The cytokine release studies will study 15-20 different cytokines and their relationship with patient outcomes, with the overarching hypothesis that change in cytokines over time will be associated with outcome to therapy with immune checkpoint inhibition.

Additional biomarkers may be analyzed as deemed appropriate at the time of analysis. Furthermore, tumor and germline whole exome sequencing (WES) as well as single cell RNA sequencing will be performed. To perform WES, nucleic acid (DNA and RNA) will be obtained from tumor cellular material using standard operating procedures. For clinical tumor specimens, a "high-coverage" sequencing approach will be utilized, which should yield an average coverage of 150-200 fold; paired normal DNA will be sequenced to a depth of approximately 80-100-fold. WES data will be analyzed for base mutations, small insertions/deletions, and copy number alterations. RNA sequencing will be done to examine gene expression changes and pathway adaptation on-treatment as compared to pre-treatment.

Results from flow cytometry and cytokine analyses (if performed) will be compared to clinical outcomes. For the flow cytometric immunoprofiling on tumor and immune cells, t-distributed neighbor embedding (t-SNE) analyses will be performed, resulting in the identification of "hot"

and "cold" clusters[5,6]. Each of the immunologic markers/parameters will be analyzed individually and in compilation to form such clusters. We hypothesize that outcomes may vary according to the value of such markers and/or hot/cold cluster status.

Peripheral blood mononuclear cells (PBMCs) as well as plasma will be collected from whole blood to assess immune cell populations and cytokines and other biomarkers of interest as appropriate. Surface staining with a panel of antibodies and intracytoplasmatic cytokine staining followed by flow cytometry will be performed on the PBMC samples. Different T cell populations, their activation status, and the production of different cytokines as well as other immune cell populations including myeloid-derived suppressor cells (MDSCs) will be characterized. MDSCs are a heterogeneous group of immature cells which are greatly expanded in experimental models of cancer. Studies in humans have reported increased frequencies as well as immune-suppressive properties in some of the myeloid-derived subsets of MDSCs present in the peripheral blood of patients with various forms of cancer[14,15]. To further explore the relationship of immune cell populations and their potential correlation to clinical outcomes, peripheral blood levels will be serially collected from patients enrolled to the trial.

## 3. PARTICIPANT SELECTION

### 3.1 Eligibility Criteria

3.1.1 Histologically confirmed stage IV NSCLC, with no prior systemic anti-cancer therapy of any kind (including *EGFR* and *ALK* inhibitors). Prior definitive chemoradiation for locally advanced disease is permitted as long as the last administration of chemotherapy or radiation (whichever was given last) occurred at least 6 months prior to enrollment. Prior adjuvant or neoadjuvant chemotherapy for early stage lung cancer is permitted if completed at least 6 months prior to initiating study treatment.

3.1.2 Participants must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan, MRI, or calipers by clinical exam. See **Section 11** for the evaluation of measurable disease.
Note: presence of measurable disease must be in at least one lesions that has not been previously irradiated.

3.1.3 Age ≥ 18 years.

3.1.4 ECOG performance status ≤ 1 (see **Appendix A**)

3.1.5 Participants must have normal organ and marrow function as defined below:

- Absolute neutrophil count ≥ 1,500/mcL
- Platelets ≥ 100,000/mcL
- Total bilirubin ≤ 1.5 × institutional upper limit of normal (ULN)
- AST(SGOT)/ALT(SGPT) ≤ 2.5 × institutional ULN, **OR**

- AST(SGOT)/ALT(SGPT) ≤ 5 × institutional ULN if liver metastases are present
- Serum creatinine ≤ 1.5 × institutional ULN, **OR**
- Creatinine clearance ≥ 60 mL/min/1.73 $m^2$ for participants with serum creatinine levels above 1.5 × institutional ULN.

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

3.1.7 Participants must be able and willing to undergo a pre-treatment tumor tissue biopsy. Participants must also be willing to undergo an on-treatment tumor tissue biopsy if clinically feasible.

3.1.8 Participants must have a tumor tissue sample available (formalin-fixed paraffin embedded [FFPE] tissue block or unstained slides); may be newly obtained or obtained within 6 months prior to enrollment (without systemic therapy given after the sample was obtained). Participants without sufficient archival tissue may be enrolled following successful completion of the pre-treatment tumor tissue biopsy. Tissue must be a core needle biopsy, excisional, or incisional biopsy. Fine needle aspirates (FNA) or malignant effusions are not adequate. Bone biopsies without a soft tissue component are not adequate.

3.1.9 The effects of nivolumab and ipilimumab on the developing human fetus are unknown. For this reason, women of childbearing potential (WOCBP) must agree to follow instructions for acceptable contraception from the time of signing consent, and for 23 weeks after their last dose of protocol-indicated treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol who are not azoospermic who are sexually active with WOCBP must agree to follow instructions for acceptable contraception from the time of signing consent, and for 31 weeks after their last dose of protocol-indicated treatment.

## 3.2 Exclusion Criteria

3.2.1 Participants with known *EGFR* mutations or *ALK* rearrangements. All subjects must have been tested for *EGFR* mutation and *ALK* rearrangement prior to study entry, unless they are known to have a *KRAS* mutation.

Note: molecular testing is not required for squamous NSCLC.

3.2.2 Participants who have had prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

3.2.3 Participants who received prior non-CNS directed palliative radiation therapy within 7 days of the date of study entry.

3.2.4 Participants who are receiving any other investigational agents.

3.2.5 Participants with known untreated brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. Subjects are eligible if CNS metastases are adequately treated and subjects are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to study entry. Subjects must be either off corticosteroids, or on a stable or decreasing dose of ≤10 mg daily prednisone (or equivalent) for at least 2 weeks prior to first study treatment.

3.2.6 History of allergic reactions attributed to compounds of similar chemical or biologic composition to ipilimumab or nivolumab.

3.2.7 Participants with previous malignancies are excluded unless a complete remission was achieved at least 2 years prior to first treatment and no additional therapy is required or anticipated to be required during the study period as judged by the treating investigator. Exceptions include non-melanoma skin cancers, and *in situ* cancers of any type (e.g. bladder, gastric, colon, cervical/dysplasia, melanoma, or breast carcinoma *in situ*).

3.2.8 Participants with any other active malignancy requiring concurrent intervention.

3.2.9 Participants with an active, known, or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

3.2.10 Participants with a condition requiring systemic treatment with corticosteroids of > 10 mg daily prednisone (or equivalent), or subjects requiring other immunosuppressive medications within 14 days of first treatment. Inhaled, topical, ophthalmologic, local steroid injections, and adrenal replacement steroid > 10 mg daily prednisone or equivalent are permitted in the absence of active autoimmune disease.

3.2.11 Participants with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity in the opinion of the treating investigator.

3.2.12 Participants with a known history of testing positive for human immunodeficiency virus (HIV), or known acquired immunodeficiency syndrome (AIDS).

3.2.13 Participants with known positive test for hepatitis B or C indicating acute or chronic infection.

3.2.14 Participants with ≥ Grade 2 peripheral neuropathy.

3.2.15 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.16 Pregnant women are excluded from this study because ipilimumab and nivolumab are both agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with ipilimumab or nivolumab, breastfeeding should be discontinued if the mother is treated with ipilimumab or nivolumab. A negative serum pregnancy test is required prior to study entry.

### 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 protocol therapy. Any participant not registered to the protocol before protocol therapy 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 therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

### 4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

## 5. TREATMENT PLAN

### 5.1 Treatment Regimen

Nivolumab will be administered once every 2 weeks, on cycle days 1, 15, and 29. Ipilimumab will be administered once every 6 weeks, on cycle day 1. A treatment cycle is defined as 6 weeks or 42 days. Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in **Section 7**. Appropriate dose modifications are described in **Section 6**.

| Table 3: Regimen Description | | | | | |
|---|---|---|---|---|---|
| **Agent** | **Premedications** | **Dose[A]** | **Route[B]** | **Schedule** | **Cycle Length** |
| Ipilimumab | None | 1 mg/kg | IV over 60 minutes (± 5 minute infusion window) | Day 1 | 42 days (6 weeks) |
| Nivolumab | None | 3 mg/kg | IV over 60 minutes (± 5 minute infusion window) | Days 1, 15, 29 | |

A. Calculation of body surface area (BSA) should be performed per institutional standards of practice. Re-calculation of dosage for fluctuations in body weight should be made in accordance with institutional guidelines.
B. On days where both nivolumab and ipilimumab will be administered, nivolumab should be administered first. The ipilimumab infusion will start at least 30 minutes after completion of the nivolumab infusion.

## 5.2 Pre-Treatment Criteria

### 5.2.1 Cycle 1, Day 1

If screening laboratory values were completed ≤ 96 hours before Cycle 1 Day 1, laboratory tests do not need to be repeated on Cycle 1 Day 1 and the screening laboratory values may be used as the Cycle 1 Day 1 values.

If screening laboratory values were completed > 96 hours prior to Cycle 1 Day 1, laboratory tests must be repeated on Cycle 1 Day 1. Laboratory values drawn on Cycle 1 Day 1 must re-meet eligibility criteria, exceptions to this are possible following discussion with the principal investigator.

### 5.2.2 Subsequent Cycles

Management of specific toxicities considered at least possibly related to the study regimen is outlined in **Section 6**.

## 5.3 Agent Administration

### 5.3.1 Nivolumab

Nivolumab will be administered as an IV infusion over approximately 60 minutes (± 5 minute infusion window). Nivolumab will be administered every 2 weeks, on cycle days 1, 15, and 29. On days where both nivolumab and ipilimumab will be administered, nivolumab should be administered first. The ipilimumab infusion will start at least 30 minutes after completion of the nivolumab infusion.

### 5.3.2 Ipilimumab

Ipilimumab will be administered as an IV infusion over approximately 60 minutes (± 5 minute infusion window). Ipilimumab will be administered every 6 weeks, on cycle day 1. BSA for dosage calculations should be performed per institutional standards of practice. Re-calculation of dosage for fluctuations in body weight should be made in accordance with institutional guidelines. On days where both nivolumab and ipilimumab will be administered, nivolumab should be administered first. The ipilimumab infusion will start at least 30 minutes after completion of the nivolumab infusion.

## 5.4 General Concomitant Medication and Supportive Care Guidelines

No investigational or commercial agents or therapies other than ipilimumab and nivolumab may be administered with the intent to treat the participant's malignancy, with the exception of palliative radiation therapy with the principal investigator's agreement. As concurrent radiotherapy and nivolumab/ipilimumab have not been formally evaluated, in cases where palliative radiotherapy is required for a tumor lesion, then nivolumab/ipilimumab should be withheld for at least 1 week before, during, and 1 week after radiation. Bisphosphonate use is permitted.

Investigators should use appropriate supportive medications to address toxicities that arise during the study, including but not limited to antiemetics, corticosteroids, and blood product transfusion.

### 5.4.1 Infusion-Related Reactions

Infusion reactions, including high-grade hypersensitivity reactions, following administration of nivolumab or ipilimumab are uncommon. Participants should be monitored for fever, chills, rigors, itching, arthralgias, rash, hypertension, hypotension, bronchospasm, and dyspnea during and immediately after administration of the study agents.

In the event of any ≥ Grade 3 infusion-related reaction, protocol therapy should be permanently discontinued. Emergency care should be implemented as clinically appropriate and per local institutional standards of practice.

In the event of any Grade 1 infusion-related reaction, the patient should be monitored until recovery of symptoms to baseline. The following prophylactic premedications are recommended for future infusions: diphenhydramine 25 – 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg (or equivalent) at least 30 minutes before additional infusions.

In the event of any Grade 2 infusion-related reaction, the infusion should be stopped. The patient may be medicated with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen 325 – 1000 mg PO (or equivalent). Corticosteroids or bronchodilators may also be administered as clinically appropriate. The patient should be monitored until symptoms have resolved to baseline. After resolution of symptoms, the infusion may be restarted at 50% of the original infusion rate. If no further complications ensue after 30 minutes, the rate may be increased to

100% of the original infusion rate. If symptoms recur, no further administration of nivolumab or ipilimumab should occur at that visit. Administer 50 mg IV diphenhydramine (or equivalent) and monitor patient until the symptoms resolve to baseline.

For future infusions following a Grade 2 infusion-related reaction, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg (or equivalent), administered at least 30 minutes prior to the infusion. If necessary per the judgment of the treating investigator, corticosteroids (up to 25 mg SoluCortef or equivalent) may be used.

### 5.4.2 Drug-Drug Interaction Potential with Nivolumab

Although monoclonal antibodies are not direct inhibitors/inducers of metabolizing enzymes, recent literature reports suggest that therapeutic proteins that are modulators of cytokines may indirectly affect expression of cytochrome (CYP) enzymes. The indirect drug-drug interaction potential of nivolumab was assessed using systemic cytokine modulation data for cytokines known to modulate CYP enzymes, at single and multiple doses of 0.3 to 10 mg/kg Q3 weeks.

There were no meaningful changes in cytokines known to have indirect effects on CYP enzymes across all dose levels of nivolumab (0.3, 2 and 10 mg/kg) during the course of treatment. This lack of cytokine modulation suggests that nivolumab has no or low potential for modulating CYP enzymes, thereby indicating a low risk of therapeutic protein-drug interaction.

Nivolumab is an IgG4 monoclonal antibody, which is eliminated by mechanisms similar to that of other antibodies, namely by non-specific catabolism (mainly by enzymes in the reticuloendothelial system). These enzymes are not known to be inhibited or induced by drugs, and therefore it is unlikely that other drugs will have an impact on the PK of nivolumab.

### 5.4.3 Drug-Drug Interaction Potential with Ipilimumab

Ipilimumab is a human monoclonal antibody that is not metabolized by cytochrome P450 enzymes (CYPs) or other drug metabolizing enzymes.

A drug-interaction study of ipilimumab administered alone and in combination with chemotherapy (dacarbazine or paclitaxel/carboplatin) was conducted evaluating interaction with CYP isozymes (particularly CYP1A2, CYP2E1, CYP2C8, and CYP3A4) in patients with treatment-naive advanced melanoma. No clinically relevant pharmacokinetic drug-drug interaction was observed between ipilimumab and paclitaxel/carboplatin, dacarbazine or its metabolite, 5-aminoimidazole-4-carboxamide (AIC).

The use of anticoagulants is known to increase the risk of gastrointestinal hemorrhage. Since gastrointestinal hemorrhage is an adverse reaction with ipilimumab, patients who require concomitant anticoagulant therapy should be monitored closely.

## 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), treatment may continue for a maximum of 24 months or until one of the following criteria applies:

- Disease progression, unless the participant meets the requirements outlined in **Section 5.5.1**.
- Intercurrent illness that prevents further administration of treatment
- The patient becomes pregnant or plans to become pregnant
- Unacceptable adverse event(s)
- 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 relevant Off-Treatment/Off-Study information will be updated in OnCore.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Mark Awad MD, PhD at telephone number 617-632-3468.

### 5.5.1 Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease (PD)[16].

Subjects will be permitted to continue on nivolumab and ipilimumab for treatment beyond initial RECIST 1.1 defined PD as long as they meet all of the following criteria:

1. Investigator-assessed clinical benefit and no rapid disease progression or threat to vital organs/critical anatomical sites requiring urgent alternative medical intervention (e.g. spinal cord compression)
2. Subject is tolerating study treatment
3. Subject has a stable performance status
4. Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g. CNS metastases)
5. Subject provides written informed consent prior to receiving additional nivolumab and ipilimumab treatment.

The decision to continue treatment beyond initial investigator-assessed progression should be

discussed with the principal investigator and documented in the study records. A follow-up scan should be performed in six (6) weeks ± 7 days of original PD to determine whether there has been a decrease in the tumor size, or continued progression of disease. Subsequent scans should be performed as per protocol criteria.

If the investigator feels that the subject continues to achieve clinical benefit by continuing treatment, the subject should remain on the trial and continue to receive monitoring according to the Study Calendar located in **Section 10**.

For the subjects who continue study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/ or the diameters of new measurable lesions compared to the time of initial PD. Nivolumab and ipilimumab treatment should be discontinued permanently upon documentation of further progression.

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

### 5.6 Duration of Follow Up

Participants will be followed for a minimum of 90 days following their last dose of ipilimumab and 100 days following their last dose of nivolumab for serious adverse event (SAE) reporting. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed at minimum until resolution or stabilization of the adverse event. Participants who are removed before documented disease progression should be followed for RECIST response criteria until disease progression or death. Following documentation of disease progression, participants will continue to be followed for a maximum of 3 years or until death for survival status only.

### 5.7 Criteria for Taking a Participant Off Study

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

- Lost to follow-up
- Withdrawal of consent for data submission
- Death
- Completion of required 3 years follow-up

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

The research team will update the relevant Off Study information in OnCore.

## 6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays will be made as indicated in the following tables. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

### 6.1 Toxicity Management

**Table 4: Gastrointestinal Adverse Event Management**

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

| Grade of Diarrhea / Colitis | Management | Follow-Up |
|---|---|---|
| Grade 1 | Continue protocol therapy.<br><br>Treat symptoms as clinically appropriate. | Monitor patient closely for worsening symptoms.<br><br>Educate patient to report worsening immediately.<br><br>**If worsens:**<br>Treat as Grade 2 or ≥ Grade 3. |
| Grade 2 | Delay protocol therapy.<br><br>Treat symptoms as clinically appropriate. | **If improves to Grade 1:**<br><br>Resume protocol therapy<br><br>**If persists > 5-7 days or recurs:**<br><br>Administer 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent<br><br>When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume therapy per protocol.<br><br>**If worsens or persists > 3-5 days with oral steroids:**<br><br>Treat as ≥ Grade 3. |

| **Table 4: Gastrointestinal Adverse Event Management** | | |
|---|---|---|
| *Note: Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue protocol therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.* | | |
| **Grade of Diarrhea / Colitis** | **Management** | **Follow-Up** |
| ≥ Grade 3 | Permanently discontinue protocol therapy<br><br>Administer 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent<br><br>Add prophylactic antibiotics for opportunistic infections<br><br>Consider lower endoscopy as clinically appropriate | **If improves:**<br><br>Continue steroids until grade 1, then taper over at least 1 month<br><br>**If persists > 3-5 days, or recurs after improvement:**<br><br>Add infliximab 5 mg/kg (if no contraindication)<br><br>**Note:** Infliximab should not be used in cases of perforation or sepsis |
| Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids. | | |

| **Table 5: Renal Adverse Event Management** | | |
|---|---|---|
| *Note: Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy.* | | |
| **Grade of Creatinine Elevation** | **Management** | **Follow-Up** |
| Grade 1 | Continue protocol therapy.<br><br>Monitor creatinine weekly. | **If returns to baseline:**<br><br>Resume routine creatinine monitoring per protocol<br><br>**If worsens:**<br><br>Treat as Grade 2-3 or 4 |

| **Table 5: Renal Adverse Event Management** | | |
|---|---|---|
| *Note: Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy.* | | |
| **Grade of Creatinine Elevation** | **Management** | **Follow-Up** |
| Grade 2 – 3 | Delay protocol therapy<br><br>Monitor creatinine every 2-3 days<br><br>Administer 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent<br><br>Consider renal biopsy with nephrology consult as clinically appropriate | **If returns to Grade 1:**<br><br>Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume protocol therapy and routine creatinine monitoring per protocol<br><br>**If elevations persist > 7 days or worsens:**<br><br>Treat as Grade 4 |
| Grade 4 | Permanently discontinue protocol therapy<br><br>Monitor creatinine daily<br><br>Administer 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent<br><br>Consult nephrologist and consider renal biopsy as clinically appropriate | **If returns to Grade 1:**<br><br>Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections |
| Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids. | | |

| **Table 6: Pulmonary Adverse Event Management** | | |
|---|---|---|
| *Note: Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy. Evaluate with imaging and pulmonary consultation as clinically appropriate.* | | |
| **Grade of Pneumonitis** | **Management** | **Follow-Up** |
| Grade 1 | Consider delay of protocol therapy<br><br>Monitor for symptoms every 2-3 days<br><br>Consider Pulmonary and ID consults | Re-image at least every 3 weeks<br><br>**If worsens:**<br><br>Treat as Grade 2 or ≥ Grade 3. |
| Grade 2 | Delay protocol therapy<br><br>Obtain Pulmonary and ID consults as clinically appropriate<br><br>Monitor symptoms daily, consider hospitalization<br><br>Administer 1.0 mg/kg/day methylprednisolone IV or oral equivalent<br><br>Consider bronchoscopy, lung biopsy as clinically appropriate | Re-image every 1-3 days<br><br>**If improves:**<br><br>When symptoms return to near baseline, taper steroids over at least 1 month and then resume protocol therapy and consider prophylactic antibiotics<br><br>**If not improving after 2 weeks or worsening:**<br><br>Treat as ≥ Grade 3. |

| **Table 6: Pulmonary Adverse Event Management** | | |
|---|---|---|
| *Note: Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy. Evaluate with imaging and pulmonary consultation as clinically appropriate.* | | |
| **Grade of Pneumonitis** | **Management** | **Follow-Up** |
| ≥ Grade 3 | Permanently discontinue protocol therapy<br><br>Hospitalize as clinically indicated<br><br>Obtain pulmonary and ID consults as appropriate<br><br>Administer 2-4 mg/kg/day methylprednisolone IV or IV equivalent<br><br>Add prophylactic antibiotics for opportunistic infections<br><br>Consider bronchoscopy, lung biopsy | **If improves to baseline:**<br><br>Taper steroids over at least 6 weeks.<br><br>**If not improving after 48 hours or worsening:**<br><br>Add additional immunosuppression. |
| Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids. | | |

| **Table 7: Hepatic Adverse Event Management** | | |
|---|---|---|
| *Note: Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy. Consider imaging for obstruction.* | | |
| **Grade of Liver Test Elevation** | **Management** | **Follow-Up** |
| Grade 1 | Continue protocol therapy | Continue LFT monitoring per protocol<br><br>**If worsens:**<br><br>Treat as Grade 2 or ≥ Grade 3. |

**Table 7: Hepatic Adverse Event Management**

*Note: Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy. Consider imaging for obstruction.*

| Grade of Liver Test Elevation | Management | Follow-Up |
|---|---|---|
| Grade 2 | Delay protocol therapy<br><br>Increase frequency of monitoring to every 3 days | **If returns to baseline:**<br><br>Resume routine monitoring, resume protocol therapy<br><br>**If elevations persist > 5-7 days or worsen:**<br><br>Administer 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume protocol therapy |
| ≥ Grade 3 | Permanently discontinue protocol therapy[A]<br><br>Increase frequency of monitoring to every 1-2 days<br><br>Administer 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent[B]<br><br>Add prophylactic antibiotics for opportunistic infections<br><br>Consult gastroenterologist as clinically appropriate | **If returns to grade 2:**<br><br>Taper steroids over at least 1 month<br><br>**If does not improve in >3-5 days, worsens or rebounds:**<br><br>Add mycophenolate mofetil 1 g BID<br><br>If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines |

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

A. Protocol therapy may be delayed rather than discontinued if AST/ALT ≤ 8 × institutional ULN or total bilirubin ≤ 5 × institutional ULN.
B. The recommended starting dose for Grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

| **Table 8: Endocrinopathy Adverse Event Management** | | |
|---|---|---|
| *Note: Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy. Consider visual field testing, endocrinology consultation, and imaging.* | | |
| **Event** | **Management** | **Follow-Up** |
| Asymptomatic TSH Elevation | Continue protocol therapy.<br><br>If TSH < 0.5 × lower limit of normal (LLN), or TSH > 2 × ULN, or consistently out of range in 2 subsequent measurements: include free T4 at subsequent cycles as clinically indicated; consider endocrinology consult. | |
| Symptomatic Endocrinopathy | Evaluate endocrine function<br><br>Consider pituitary scan<br><br>**Symptomatic with abnormal lab/pituitary scan:**<br><br>Delay protocol therapy<br><br>Administer 1-2 mg/kg/day methylprednisolone IV or PO equivalent<br><br>Initiate appropriate hormone therapy<br><br>**No abnormal lab/pituitary MRI scan but symptoms persist:**<br><br>Repeat labs in 1-3 weeks / MRI in 1 month | **If improves (with or without hormone replacement):**<br><br>Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections<br><br>Resume protocol therapy<br><br>Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component |

| **Table 8: Endocrinopathy Adverse Event Management** | | |
|---|---|---|
| *Note: Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy. Consider visual field testing, endocrinology consultation, and imaging.* | | |
| **Event** | **Management** | **Follow-Up** |
| Suspicion of adrenal crisis (e.g. severe dehydration, hypotension, shock out of proportion to current illness) | Permanently discontinue protocol therapy<br><br>Rule out sepsis<br><br>Stress dose of IV steroids with mineralocorticoid activity<br><br>Administer IV fluids<br><br>Consult endocrinologist as clinically appropriate<br><br>If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy | |
| Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids. | | |

| **Table 9: Skin Adverse Event Management** | | |
|---|---|---|
| *Note: Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy.* | | |
| **Grade of Rash[A]** | **Management** | **Follow-Up** |
| Grade 1 – 2 | Continue protocol therapy.<br><br>Administer symptomatic therapy (e.g. antihistamines, topical steroids) | **If persists > 1-2 weeks or recurs:**<br><br>Consider skin biopsy<br><br>Delay protocol therapy<br><br>Consider 0.5-1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume protocol therapy<br><br>**If worsens:**<br><br>Treat as Grade 3-4 |
| Grade 3 – 4 | Delay or discontinue protocol therapy<br><br>Consider skin biopsy<br><br>Dermatology consult as clinically appropriate<br><br>Administer 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent | **If returns to Grade 1:**<br><br>Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections.<br><br>Resume protocol therapy if appropriate. |
| Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.<br><br>A. If Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN) is suspected, withhold protocol therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue protocol therapy. | | |

| **Table 10: Neurological Adverse Event Management** | | |
|---|---|---|
| *Note: Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy.* | | |
| **Grade of Neurological Toxicity** | **Management** | **Follow-Up** |
| Grade 1 | Continue protocol therapy. | Continue to monitor the patient.<br><br>**If worsens:**<br><br>Treat as Grade 2 or ≥ Grade 3. |
| Grade 2 | Delay protocol therapy<br><br>Treat symptoms per local guidelines<br><br>Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent | **If improves to baseline:**<br><br>Resume protocol therapy.<br><br>**If worsens:**<br><br>Treat as ≥ Grade 3. |
| ≥ Grade 3 | Permanently discontinue protocol therapy<br><br>Obtain neurology consult as clinically appropriate<br><br>Treat symptoms per local guidelines<br><br>Administer 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent<br><br>Add prophylactic antibiotics for opportunistic infections | **If returns to Grade 2:**<br><br>Taper steroids over at least 1 month.<br><br>**If worsens or atypical presentation:**<br><br>Consider IVIG or other immunosuppressive therapies per local guidelines. |
| Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids. | | |

| **Table 11: Pancreatic Adverse Event Management** | | |
|---|---|---|
| *Note: Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy.* | | |
| **Grade of Amylase or Lipase Elevation, Pancreatitis** | **Management[B]** | **Follow-Up** |
| Asymptomatic Grade 1[A] | Continue protocol therapy.<br><br>Monitor amylase and lipase weekly until resolution to baseline. | Resume routine protocol monitoring.<br><br>**If worsens:**<br><br>Treat as Grade 2-3 or 4. |
| Asymptomatic Grade 2-3[A] | Delay protocol therapy.<br><br>Monitor amylase and lipase weekly until resolution to baseline. | **If improves to baseline:**<br><br>Resume protocol therapy and routine protocol monitoring.<br><br>**If worsens:**<br><br>Treat as Grade 4. |
| Asymptomatic Grade 4[A] | Permanently discontinue protocol therapy.<br><br>Monitor amylase and lipase weekly until resolution. | Monitor patient until resolution to baseline. |
| Any Symptomatic Elevations in Amylase/Lipase, Pancreatitis | Permanently discontinue protocol therapy.<br><br>Consider GI consult as clinically appropriate.<br><br>Administer supportive care. | Monitor patient until resolution to baseline. |
| A. Patients should be monitored for signs/symptoms consistent with pancreatitis, including abdominal pain and vomiting.<br>B. Corticosteroids do not seem to alter the natural course of amylase/lipase elevations. | | |

| Table 12: Ocular Adverse Event Management | | |
|---|---|---|
| *Note: Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy. Work-up for ocular adverse events should also consider pituitary inflammation as a potential cause.* | | |
| **Event Grade** | **Management[A]** | **Follow-Up** |
| Grade 1 | Continue protocol therapy.<br><br>Monitor patient for worsening symptoms.<br><br>Consider ophthalmologist consult as clinically appropriate.<br><br>Administer topical corticosteroids as clinically indicated. | **If worsens:**<br><br>Treat as Grade 2 or ≥ Grade 3. |
| Grade 2 | Delay protocol therapy.<br><br>Obtain ophthalmologist consult.<br><br>Administer topical corticosteroids as clinically indicated. | **If improves to baseline:**<br><br>Resume protocol therapy.<br><br>**If worsens:**<br><br>Treat as ≥ Grade 3. |
| ≥ Grade 3 | Permanently discontinue protocol therapy.<br><br>Obtain ophthalmologist consult.<br><br>Administer systemic corticosteroids as clinically indicated. | Monitor patient until resolution to baseline.<br><br>Taper systemic corticosteroids as clinically appropriate. |
| Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids. | | |

| Table 13: Infusion-Related Reactions | | |
|---|---|---|
| **Event Grade** | **Management** | **Follow-Up** |
| Grade 1 | Monitor patient until recovery of symptoms to baseline. | Prophylactic premedications are recommended for future infusions: diphenhydramine 25 – 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg (or equivalent) at least 30 minutes before additional infusions. |

| Table 13: Infusion-Related Reactions | | |
|---|---|---|
| **Event Grade** | **Management** | **Follow-Up** |
| Grade 2 | Stop infusion.<br><br>Administer diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen 325 – 1000 mg PO (or equivalent).<br><br>Corticosteroids or bronchodilators may also be administered as clinically appropriate.<br><br>Monitor patient until symptoms have resolved to baseline.<br><br>After resolution of symptoms, the infusion may be restarted at 50% of the original infusion rate. If no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. If symptoms recur, no further administration of nivolumab or ipilimumab should occur at that visit. Administer 50 mg IV diphenhydramine (or equivalent) and monitor patient until the symptoms resolve to baseline. | Prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg (or equivalent), administered at least 30 minutes prior to the infusion.<br><br>If necessary per the judgment of the treating investigator, corticosteroids (up to 25 mg SoluCortef or equivalent) may be used as well. |
| ≥ Grade 3 | Permanently discontinue protocol therapy.<br><br>Emergency care should be implemented as clinically appropriate and per local institutional standards of practice. | Monitor patient until resolution to baseline. |

### 6.2 Dose Delays

Dosing of ipilimumab or nivolumab may be held at the treating investigator's discretion for any toxicity of any grade. Additionally, holding of the study agents may be required as indicated in the tables in **Section 6.1**.

A treatment delay of up to six weeks for nivolumab and up to 12 weeks for ipilimumab is allowable. Participants requiring a longer hold should be removed from protocol therapy. Exceptions for participants exhibiting clinical benefit may be possible with approval from the principal investigator.

If study agent dosing is held due to toxicity, the counting of cycle days and assessment schedule will continue without interruption. For example, a participant who does not receive their Cycle 3

Day 15 dose of nivolumab due to toxicity will proceed with their next regularly scheduled clinic visit (Cycle 3 Day 29) as previously planned. Additional interim clinic visits may be scheduled to manage toxicity, however the cycle will not restart due to dosing delays due to adverse events and the assessment schedule (including tumor imaging evaluations) will continue as originally planned.

### 6.3 Dose Reductions

There will be no dose reductions for nivolumab or ipilimumab allowed. Participants who cannot tolerate the assigned doses of nivolumab or ipilimumab should be removed from protocol therapy.

### 6.4 Overdose Management

There is no available information concerning overdose with nivolumab or ipilimumab. In case of overdose, patients must be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted. There are no specific antidotes.

## 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** and **Section 7.3**) will determine whether the event requires expedited reporting **in addition** to routine reporting.

### 7.1 Expected Toxicities

#### 7.1.1 Adverse Events List

In addition to the list below, please also refer to the investigator's brochure (IB) for both nivolumab and ipilimumab for comprehensive adverse event information.

##### 7.1.1.1 Adverse Event List for Nivolumab combined with Ipilimumab

Common adverse events associated with combination treatment include:

- Fatigue
- Fever
- Chills
- Flu-like symptoms
- Infusion-related reactions
- Headache
- Dizziness
- Hyperthyroidism or hypothyroidism
- Cough
- Dyspnea

- Pneumonitis
- Hypotension
- Dry mouth
- Anorexia
- Diarrhea
- Nausea
- Vomiting
- Dehydration
- Abdominal pain
- Colitis
- Elevated liver transaminases
- Elevated lipase and/or amylase
- Rash
- Pruritus
- Vitiligo
- Joint pain or stiffness
- Muscle soreness, weakness, stiffness, or spasms

### 7.2 Adverse Event Characteristics

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

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

- **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.

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

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

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

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

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

### 7.2.1 NON-SERIOUS ADVERSE EVENTS

Non-serious adverse events are to be provided to BMS in aggregate via a final study report as specified in the research agreement or, if a regulatory requirement [e.g. IND US trial] as part of an annual reporting requirement.

A non-serious adverse event is an AE not classified as serious (see **Section 7.3** below).

### 7.2.2 Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE information should begin at initiation of study drug. All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 30 days following the last dose of study treatment.

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

### 7.2.3 Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs (see **Section 7.3** below) should be documented and reported as such.

The following laboratory abnormalities should be documented and reported appropriately:

- Any laboratory test result that is clinically significant or meets the definition of an SAE (located in **Section 7.3**).
- Any laboratory abnormality that required the participant to have study drug discontinued or interrupted.
- Any laboratory abnormality that required the subject to receive specific corrective therapy.

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

### 7.2.4 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see **Section 7.3**).

Potential drug induced liver injury is defined as:

- AT (ALT or AST) elevation > 3 × ULN,
  **AND**
- Total bilirubin > 2 × ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),
  **AND**
- No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

For protocols involving participants with known abnormalities at baseline, or with other clinical confounders, the clinical team should establish and document an agreed upon definition for events considered to be potential DILI cases. Wherever possible, timely confirmation of initial liver related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see **Section 7.3**).

### 7.2.5 Pregnancy

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

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

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

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

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

### 7.2.6 Overdose

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

### 7.2.7 Other Safety Considerations

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

## 7.3 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

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

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

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

**NOTE:** The following hospitalizations are not considered SAEs:

- A visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)

- Elective surgery, planned prior to signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anti-cancer therapy in the absence of any other SAEs

## 7.4 Expedited Adverse Event Reporting

7.4.1 Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 90 days of the last dose of ipilimumab or 100 days of the last dose of nivolumab on the local institutional SAE form.

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

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI 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 Expedited Reporting to Hospital Risk Management

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

## 7.7 Expedited Reporting to Bristol-Myers Squibb (BMS)

All SAEs that occur following the subject's written consent to participate in the study through 90 days of discontinuation of dosing of ipilimumab and 100 days of discontinuation of nivolumab must be reported to BMS Worldwide Safety. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up biopsy).

The BMS SAE form should be used to report SAEs. The BMS protocol ID number must be included on the form that is submitted by the Investigator.

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure. For drugs with potential for delayed SAEs (e.g., delayed excretion of the parent or active metabolites), a longer follow-up period may be warranted to allow collection of these SAEs, laboratory tests, and other

assessments.

For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection.

The Principal Investigator will reconcile the clinical database SAE cases transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com). Frequency of reconciliation should be every 3 months and prior to the database lock or final data summary. BMS GPV&E will email, upon request from the Investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to aepbusinessprocess@bms.com. The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS.

In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the IB). In the European Union (EU), an event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of an expedited safety report (ESR).

- Other important findings which may be reported by BMS as an ESR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a non-clinical (e.g., animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.
- Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.
- In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

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

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

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

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

All SAEs should be followed to resolution or stabilization.

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

SAEs should be reported on MedWatch Form 3500A.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection in the protocol.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

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

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

### 7.8 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

## 8. PHARMACEUTICAL INFORMATION

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

### 8.1 Ipilimumab (Yervoy)

#### 8.1.1 Description

Ipilimumab (BMS-734016, MDX-010) is a fully human IgG1κ consisting of 4

polypeptide chains; 2 identical heavy chains primarily consisting of 447 amino acids each with 2 identical kappa light chains consisting of 215 amino acids each linked through inter-chain disulfide bonds.

| Table 14: Physical and Chemical Properties of Ipilimumab | |
|---|---|
| Other Names | BMS-734016, MDX-010, YERVOY |
| Molecular Weight | 147,991 daltons |
| Appearance | Clear to slightly opalescent, colorless to pale yellow liquid, may contain particles |
| Solution pH | 7.0 |
| pI | The isoelectric focusing analysis generates a banding pattern in the pI range of 8.5 to 8.8, with the major isoform at an approximate pI of 8.7 |

8.1.2 **Form**

Ipilimumab injection, 200 mg/40 mL (5 mg/mL), is formulated as a clear to slightly opalescent, colorless to pale yellow, sterile, nonpyrogenic, single-use, isotonic aqueous solution that may contain particles. Ipilimumab injection, 50 mg/10 mL and 200 mg/40 mL, is supplied in 10-cc or 50-cc Type I flint glass vials, respectively, stoppered with gray butyl stoppers and sealed with aluminum seals. The drug product is formulated at a concentration of 5 mg/mL at a pH of 7.0.

8.1.3 **Storage and Stability**

Ipilimumab Injection, 200 mg/40 mL (5 mg/mL), must be stored refrigerated (2°C to 8°C) and protected from light. Ipilimumab injection must not be frozen.

Partially used vials or empty vials of ipilimumab injection should be discarded at the site according to appropriate drug disposal procedures.

Ipilimumab injection may be stored undiluted (5 mg/mL) or following dilution in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection in PVC, non-PVC/non-DEHP or glass containers for up to 24 hours (at 2°C to 8°C) or room temperature/room light.

8.1.4 **Compatibility**

Ipilimumab injection may be diluted in 0.9% Sodium Chloride Injection, United States Pharmacopeia (USP) or 5% Dextrose Injection. .

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.

### 8.1.6 **Availability**

Ipilimumab will be supplied as an investigational agent by Bristol-Myers Squibb (BMS).

### 8.1.7 **Preparation**

Ipilimumab injection (5 mg/mL) can be used for intravenous (IV) administration after transferring to a polyvinyl chloride (PVC), non-PVC/non-di-(2-ethylhexyl)phthalate (DEHP), or glass container and is stable for 24 hours at 2°C to 8ºC or room temperature/room light (RT/RL). Ipilimumab injection may be diluted in 0.9% Sodium Chloride Injection, United States Pharmacopeia (USP) or 5% Dextrose Injection. Preparation will follow institutional standard. The product may be infused using a volumetric pump at the protocol-specific dose(s) and rate(s) through a infusion set with an inline, sterile, nonpyrogenic, low-protein-binding filter (pore size of 0.2 to 1.2 micrometer).

Ipilimumab injection must not be administered as an IV push or bolus injection. Care must be taken to assure sterility of the prepared solutions since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents.

### 8.1.8 **Administration**

Ipilimumab will be administered as an IV infusion over approximately 60 minutes (± 5 minute infusion window). Ipilimumab will be administered every 6 weeks, on cycle day 1. Calculation of BSA should be done per institutional standards of practice. Re-calculation of dosage for fluctuations in body weight should be made in accordance with institutional guidelines. On days where both nivolumab and ipilimumab will be administered, nivolumab should be administered first. The ipilimumab infusion will start at least 30 minutes after completion of the nivolumab infusion.

### 8.1.9 **Ordering**

Ipilimumab will be ordered by site pharmacy personnel from BMS.

### 8.1.10 **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

### 8.1.11 **Destruction and Return**

Expired or unused supplies of ipilimumab should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

## 8.2 Nivolumab

### 8.2.1 Description

Nivolumab, also referred to as BMS-936558-01, BMS-936558, or Opdivo, is a soluble protein consisting of 4 polypeptide chains, which include 2 identical heavy chains and 2 identical light chains.

| Table 15: Physical and Chemical Properties of Nivolumab | |
|---|---|
| Other Names | Nivolumab, BMS-936558, MDX1106, ONO-4538, BMS-936558-01 |
| Molecular Weight | 146,221 daltons (143,619.17 daltons, protein portion) |
| Appearance | Clear to opalescent, colorless to pale yellow liquid, light (few) particulates may be present |
| Solution pH | 5.5 to 6.5 |

### 8.2.2 Form

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) is a clear to opalescent, colorless to pale yellow liquid, which may contain light (few) particulates. The drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), and polysorbate 80 (Tween$^{TM}$ 80), pH 6.0 and includes an overfill to account for vial, needle, and syringe holdup. It is supplied in 10-cc Type I flint glass vials, stoppered with butyl rubber stoppers and sealed with aluminum seals. The only difference between the two drug product presentations is the vial fill volume.

### 8.2.3 Storage and Stability

#### 8.2.3.1 Nivolumab Injection, 100 mg/10 mL (10 mg/mL)

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

#### 8.2.3.2 Undiluted Nivolumab Injection and Diluted Nivolumab Injection in the IV Container

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

8.2.4 **Compatibility**

Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

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.

8.2.6 **Availability**

Nivolumab will be supplied as an investigational agent by Bristol-Myers Squibb (BMS).

8.2.7 **Preparation**

Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding (polyethersulfone membrane) in-line filter at the protocol-specified doses and infusion times. It is not to be administered as an IV push or bolus injection.

When the dose is based on patient weight (ie mg/kg), nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL. When the dose is fixed (e.g. 240 mg, 360 mg, or 480mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 120 mL. During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

8.2.8 **Administration**

Nivolumab will be administered as an IV infusion over approximately 60 minutes (± 5 minute infusion window). Nivolumab will be administered every 2 weeks, on cycle days 1, 15, and 29. On days where both nivolumab and ipilimumab will be administered, nivolumab should be administered first. The ipilimumab infusion will start at least 30 minutes after completion of the nivolumab infusion.

8.2.9 **Ordering**

Nivolumab will be ordered by site pharmacy personnel from BMS.

8.2.10 **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug

Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

#### 8.2.11 Destruction and Return

Expired or unused supplies of nivolumab should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

## 9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

### 9.1 Archival Tumor Tissue Collection

Archival tissue obtained from a core needle biopsy, excisional, or incisional biopsy is required for enrollment to the trial. Archival tissue may be either a FFPE block or unstained slides, and must have been obtained from a biopsy procedure performed within 6 months prior to enrollment. Participants without sufficient archival tissue may be enrolled following successful completion of the pre-treatment tumor tissue biopsy.

Archival tissue will be submitted for whole exome sequencing (WES). Please refer to the separate laboratory manual for specific sample collection and handling details.

A germline blood sample will be obtained from participants during screening (any time prior to cycle 1 day 1) for WES analysis. **The germline blood sample should be sent for analysis at the same time as the archival tissue sample.**

### 9.2 Collection of Fresh Tumor Tissue

Fresh tumor tissue biopsies will be obtained from patients enrolling to the trial at the following times:

- Baseline - any time following signing of the informed consent form but prior to cycle 1 day 1
- On-treatment - between cycle 1 day 22 and cycle 1 day 36
- Optionally at the time of disease progression per RECIST 1.1 criteria - time of progression biopsies should be obtained prior to the initiation of another cancer treatment. In the event that it is not possible to perform the biopsy before another treatment is begun, biopsies can be obtained up to 30 days after the date at which disease progression was determined.

The pre-treatment biopsy is mandatory for all participants for enrollment to the trial. The on-treatment biopsy is mandatory unless it would pose a significant medical risk to the participant as judged by the treating investigator and clinician performing the procedure. Time of progression biopsy is optional for participants when clinically feasible. Additionally, if clinically feasible participants may undergo fluid collection procedures (e.g. pleural effusion drainage) **in addition** to tumor tissue biopsy collection. If the participant undergoes a surgical resection for standard of

care needs at any point during the trial, the resected tissue may also be collected for analysis as clinically appropriate. Please refer to the laboratory manual for specific collection and handling guidelines.

### 9.2.1 Pre-Treatment Specimens

Biopsy specimens obtained pre-treatment will be sent for single cell RNA sequencing, immunoprofiling via flow cytometry, multiplexed immunofluorescence and immunohistochemistry (IHC), and if adequate specimens are collected cytokine analysis/microfluidic culture. Please refer to the separate laboratory manual for specific collection and handling instructions.

In the event sufficient archival tissue is not available, WES will be performed on the pre-treatment biopsy sample in addition to the above testing. In this case, the germline blood sample obtained from participants during screening (any time prior to cycle 1 day 1) for WES should be sent for analysis **at the same time as the pre-treatment tissue sample.** Please refer to the laboratory manual for more detail.

### 9.2.2 On-Treatment Specimens

Biopsy specimens obtained on-treatment will be sent for single cell RNA sequencing immunoprofiling via flow cytometry, , multiplexed immunofluorescence and IHC, and if adequate specimens are collected cytokine analysis/microfluidic culture. Please refer to the laboratory manual for specific collection and handling instructions.

### 9.2.3 Time of Progression Specimens

Biopsy specimens obtained at the time of disease progression will be sent for WES, single cell RNA sequencing, immunoprofiling via flow cytometry, and multiplexed immunofluorescence and IHC. Please refer to the laboratory manual for specific collection and handling instructions.

### 9.2.4 Prioritization of Analyses

In the event that insufficient tumor tissue is obtained (e.g. the collected tumor tissue is scant, or the participant did not tolerate the biopsy procedure and it was aborted prior to collection of all of the core samples), priority of analyses will be as follows:

1. Performance of single cell RNA sequencing
2. Performance of immune profiling via flow cytometry
3. Performance of WES (applicable only to pre-treatment and time of progression samples)
4. Performance of multiplexed immunofluorescence and IHC
5. Performance of cytokine analysis/microfluidic culture

Collection of insufficient tumor tissue for analysis will not be considered a protocol violation.

### 9.3 Plasma Cytokine Analysis

Blood for performance of cytokine analysis will be collected from participants at the following time points:

- Baseline, to be collected any time prior to administration of the study drugs
- On day 1 of each subsequent cycle prior to administration of the study drugs
- At the off treatment visit

### 9.4 Peripheral Blood Mononuclear Cell Collection

Peripheral blood mononuclear cells (PBMCs) will be collected to examine T-cell responses in blood. Collection will occur at the following time points:

- Baseline, to be collected any time prior to administration of the study drugs
- On Cycle 2 Day 1 any time prior to administration of the study drugs
- At the off treatment visit

A total of 60 mL of blood will be collected at each time point. Please refer to the separate laboratory manual for specific collection and handling instructions.

## 10. STUDY CALENDAR

Baseline evaluations are to be conducted within 14 days prior to the start of protocol therapy. The informed consent and baseline tumor imaging may be obtained up to 28 days prior to the start of protocol therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Assessments must be performed prior to administration of any study agent.

## Table 16: Study Calendar

| | Pre-Study | Cycle 1 Day 1 | Cycle 1 Day 15[A] | Cycle 1 Day 29[A] | Cycle 2+ Day 1[B] | Cycle 2+ Day 15[A] | Cycle 2+ Day 29[A] | Off Treatment[C] | Long-term Follow Up[D] |
|---|---|---|---|---|---|---|---|---|---|
| Informed consent | X | | | | | | | | |
| Demographics | X | | | | | | | | |
| Medical history | X | | | | | | | | |
| Physical exam | X | X | X | X | X | X | X | X | |
| Vital signs[E] | X | X | X | X | X | X | X | X | |
| Height | X | | | | | | | | |
| Weight | X | X | X | X | X | X | X | X | |
| ECOG Performance Status | X | X | | | X | | | X | |
| CBC w/diff, plts | X | X | X | X | X | X | X | X | |
| Serum chemistry[F] | X | X | X | X | X | X | X | X | |
| TSH | X | | | | X | | | | |
| ACTH | X | | | | X | | | | |
| Amylase and Lipase | X | | | | X | | | | |
| Adverse event evaluation | X | X---------- | | | | | ----------X | X | |
| Radiologic evaluation | X | CT or MRI imaging of any disease-involved site. Imaging evaluations to be obtained at baseline and then every 6 weeks × 6 cycles (-3 day/+7 day scheduling window). Brain MRI is required for all patients at baseline, and every 12 weeks on study for patients with CNS disease. At the completion of 6 cycles of therapy, at the treating investigator's discretion, imaging may be moved to every 12 weeks (-14 day/+7 day scheduling window). Participants who discontinue treatment prior to documented disease progression should continue to be followed for radiologic response every 12 weeks until documented disease progression or death. | | | | | | X | X |
| Serum β-HCG[G] | X | | | | | | | | |
| Nivolumab Infusion[H] | | X | X | X | X | X | X | | |
| Ipilimumab Infusion[H] | | X | | | X | | | | |

## Table 16: Study Calendar

| | Pre-Study | Cycle 1 Day 1 | Cycle 1 Day 15[A] | Cycle 1 Day 29[A] | Cycle 2+ Day 1[B] | Cycle 2+ Day 15[A] | Cycle 2+ Day 29[A] | Off Treatment[C] | Long-term Follow Up[D] |
|---|---|---|---|---|---|---|---|---|---|
| Fresh Tumor Tissue Biopsy[I] | X | | | X[I] | | | | X | |
| Archival Tumor Tissue Collection | X | | | | | | | | |
| Plasma Collection | X | | | | X | | | X | |
| PBMC Collection[J] | X | | | | X | | | X | |
| Telephone or Care Provider Contact | | | | | | | | | X |

A. A ± 3 day scheduling window exists for this visit to accommodate vacations, holidays, adverse weather, or other scheduling difficulties.
B. The start of a subsequent cycle may be delayed by 7 days (+7 day window) to accommodate vacations, holidays, adverse weather, or other scheduling difficulties. The start of a subsequent cycle may also be moved up by 3 days (-3 day window) for scheduling issues.
C. Off-treatment evaluation. Note: follow up visits or other contact is required in order to identify SAEs during the 90 days following the last dose of ipilimumab and 100 days following the last dose of nivolumab. Participants removed from therapy due to adverse events must be followed at minimum until resolution or stabilization of the adverse event. Please refer to **Section 5.6** for more detail.
D. Long-term follow up evaluation via telephone or care provider contact is required for survival status only for 3 years following documentation of disease progression, or until death. Contact to be performed every 3 months following the last dose of study treatment (± 1 month window).
E. Vital signs to include heart rate, blood pressure, temperature, and respiratory rate.
F. Serum chemistry to include sodium, potassium, chloride, $CO_2$, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, SGOT [AST], and SGPT [ALT]. Other tests may be ordered as clinically indicated.
G. Serum pregnancy test only required for women of childbearing potential. Childbearing potential defined as any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea >12 consecutive months; or women with a documented plasma follicle-stimulating hormone level >35µIU/mL).
H. Nivolumab and ipilimumab infusions to be administered as described in **Section 5**.
I. Fresh tumor tissue biopsy as described in **Section 9**. Biopsy required at baseline prior to the administration of any study agents, and again on Cycle 1 Day 29 (± 7 day scheduling window). An optional biopsy at the time of disease progression will also be offered to all participants. Note that a germline blood sample is required with the pre-treatment tumor biopsy as described in **Section 9**.
J. PBMC collection to occur at baseline (any time prior to the first study drug administration), on Cycle 2 Day 1, and at the off treatment visit as described in **Section 9**.

# 11. MEASUREMENT OF EFFECT

## 11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every 6 weeks for the first 6 cycles of therapy. Following completion of 6 cycles, imaging may be performed every 12 weeks at the discretion of the treating investigator. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response. Participants who discontinue treatment prior to documented disease progression should continue to be followed for RECIST response evaluation until progression.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

### 11.1.1 Definitions

Evaluable for Target Disease response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

Unevaluable patients will be included in the analysis of response as non-responders assuming they were eligible and received study drug.

### 11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area are not considered measurable unless there has been demonstrated growth in the lesion.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice

thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up.

### 11.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm in diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

FDG-PET. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

(a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

(b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

(c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a

biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

MIBG (meta-iodobenzylguanidine).The following is recommended, to assure high quality images are obtained.

Patient preparation: Iodides, usually SSKI (saturated solution of potassium iodide), are administered to reduce thyroidal accumulation of free radioiodine, preferably beginning the day prior to injection and continuing for 3 additional days (4 days total). For infants and children, one drop t.i.d. is sufficient, for adolescents 2 drops t.i.d., and for adults 3 drops t.i.d. Participants and/or parents are asked about exposure to potential interfering agents. If none is noted, an indwelling intravenous line is established. The dose of MIBG is administered by slow intravenous injection over 90 seconds.

Images from the head to the distal lower extremities should be obtained.

I-123MIBG scintigraphy is performed to obtain both planar and tomographic images.

Planar: Anterior and posterior views from the top of the head to the proximal lower extremities are obtained for 10 minutes at 24 hours and occasionally at 48 hours following injection of 10 mCi/1.7 square meters of body surface area (~150 μCi/kg, maximum 10 mCi). Anterior views of the distal lower extremities are adequate. A large field of view dual head gamma camera with low energy collimators is preferred.

SPECT: Most participants receiving I-123 MIBG also undergo SPECT at 24 hours, using a single or multi-headed camera with a low energy collimator. The camera is rotated through 360 degrees, 120 projections at 25 seconds per stop. Data are reconstructed using filtered back projections with a Butterworth filter and a cut off

frequency of 0.2-0.5. SPECT/CT may be performed at institutions with this capacity.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later data and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure from CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

#### 11.1.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note:

the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.1.3.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.3.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

11.1.3.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

| **Table 17: For Participants with Measurable Disease (*i.e.*, Target Disease)** | | | | |
|---|---|---|---|---|
| **Target Lesions** | **Non-Target Lesions** | **New Lesions** | **Overall Response** | **Best Overall Response when Confirmation is Required*** |
| CR | CR | No | CR | ≥4 wks Confirmation** |
| CR | Non-CR/Non-PD | No | PR | ≥4 wks Confirmation** |
| CR | Not evaluated | No | PR | |
| PR | Non-CR/Non-PD/not evaluated | No | PR | |
| SD | Non-CR/Non-PD/not evaluated | No | SD | Documented at least once ≥4 wks from baseline** |
| PD | Any | Yes or No | PD | no prior SD, PR or CR |
| Any | PD*** | Yes or No | PD | |
| Any | Any | Yes | PD | |

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

| **Table 18: For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)** | | |
|---|---|---|
| **Non-Target Lesions** | **New Lesions** | **Overall Response** |
| CR | No | CR |
| Non-CR/non-PD | No | Non-CR/non-PD* |
| Not all evaluated | No | not evaluated |
| Unequivocal PD | Yes or No | PD |
| Any | Yes | PD |

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.1.4 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.

#### 11.1.5 Response Review

Imaging will be reviewed at the Tumor Imaging Metrics Core (TIMC).

## 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 within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality in accordance with DF/HCC SOPs.

### 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 clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. 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; summary of all deaths occurring with 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.

## 13. STATISTICAL CONSIDERATIONS

### 13.1 Study Design/Endpoints

This is an open label phase II study evaluating potential immunologic biomarkers of response and resistance to first-line ipilimumab and nivolumab therapy in non-small cell lung cancer (NSCLC). The primary objective of the trial is to determine whether combination therapy with ipilimumab and nivolumab confers a promising best overall objective response rate per RECIST 1.1 in this patient population. Secondary objectives include estimation of progression-free survival, overall survival, and toxicity.

#### 13.1.1 Study Endpoints

Best objective response will be evaluated via RECIST1.1 criteria. Progression-free survival (PFS) is defined as the time from registration to documented disease progression or death from any cause, whichever occurs first. Patients who have not experienced an event of interest by the time of analysis will be censored at the date they are last known to be alive and progression-free. Overall survival is defined as the time from registration to death from any cause, and patients who are thought to be alive at the time of final analysis will be censored at the last date of contact. Duration of response is defined as the time from tumor response to documented disease progression or death from any cause, whichever occurs first. Patients who have not experienced an event of interest by the time of analysis will be censored at the date they are last known to be alive and progression-free. Toxicity will be determined using the CTCAE version 4.0 criteria.

#### 13.1.2 Sample Size Considerations

The primary comparison will include all eligible and treated patients, of whom 80 will be accrued. Whereas traditional chemotherapy confers a response rate (CR + PR) of roughly 30%, the goal of this trial is to target a response rate of 44%, which will be taken as evidence of activity of combination therapy with ipilimumab and nivolumab. We will employ a Simon two stage design for this trial. In the first stage, a total of 43 eligible and treated patients will be enrolled. Accrual will proceed to the second stage if at least 15 patients achieve a CR or PR among those first 43 patients. In the second stage, an additional 37 patients will be enrolled. If at least 29 responses are observed among all 80 patients enrolled, then the combination of ipilimumab and nivolumab will be deemed worthy of additional study. This trial has 88% power against the null hypothesis while testing at the one-sided level of 0.109, and the probability that the study stops early under the null is 0.71.

We note that per RECIST 1.1, these responses must be confirmed with a second scan after the

initial response is determined. We also note that patients who are deemed unevaluable for response will not be replaced, and will be included as non-responders in the assessment of the best objective response rate.

### 13.1.3 Statistical Analysis Plan

The primary and some secondary analyses will include all eligible and treated patients. Exceptions to this include: analysis of toxicity data, which will include all patients who received study drug regardless of eligibility.

Time-to-event data, such as PFS and OS, will be estimated using the Kaplan-Meier method, and Cox proportional hazards models will be used to estimate hazard ratios. Comparisons of groups will be made using the logrank test and Cox modeling.

Categorical data, such as response rates (CR+PR) and toxicity, will be compared using Fisher's exact tests with a one-sided type I error rate of 10%; multivariable logistic regression modeling will be used to adjust for the effect of any covariates that are associated with these categorical outcomes. Though none are currently planned, any continuous outcomes will be analyzed using Wilcoxon rank sum test, and multivariable linear regression models may be used to adjust for multiple associations with outcome.

Modeling procedures will implement backward selection; variables significant at the 0.10 level in the univariate setting will be chosen for inclusion in an initial full model, and at each step the least significant variable will be removed from the model. Only those covariates with $p<0.05$ will remain in any final models, unless there are factors identified by the study team as crucial to model interpretation.

Point estimates of all endpoints will be accompanied by the corresponding two-sided 80% confidence intervals. The method of Atkinson and Brown will be used for the estimation of the confidence interval for response.

In the event that there are missing data, no imputation of the missing data will be conducted. We will assume that data are missing at random and will conduct all analyses as originally planned because we do not anticipate an excess of missing data.

Subset analyses of all variables, including correlatives, are considered to be exploratory in nature.

### 13.1.4 Correlative Analysis

The correlative studies planned for this trial include evaluation of flow cytometry, RNA seq, and cytokine release data with outcomes on this trial. Biopsies are planned pre-treatment, 4 weeks post initiation of therapy, and at the time of disease progression.

For the flow cytometric immunoprofiling on both tumor and immune cells, t-distributed neighbor embedding (t-SNE) analyses will be performed, resulting in the identification of "hot" and

"cold" clusters as previously described[5,6]. Each of the immunologic markers/parameters will be analyzed individually and in compilation to form such clusters. We hypothesize that outcomes may vary according to the value of such markers and/or hot/cold cluster status.

With respect to the single-cell RNA sequencing analyses, we hope to determine wither or not single cell expression profiles can distinguish malignant and non-malignant cell types, and whether or not bulk tumors can segregate to distinct clusters on the basis of their inferred cell type composition. We hope to evaluate the association of profile and/or cluster type with outcomes.

Lastly, the cytokine release studies will study 15-20 different cytokines and their relationship with patient outcomes, with the overarching hypothesis that change in cytokines over time will be associated with outcome to therapy with immune checkpoint inhibition.

We may employ a variety of statistical techniques for the analyses of these data. The rate of change at a particular time point such as 4 weeks may be compared to baseline measures and will be analyzed for association with patient demographics and/or disease characteristics using the Kruskal Wallis test. Presence or absence of mutations in plasma will be analyzed for association with other variables using Fisher's exact test. To account for the repeated measures over time, we may potentially use these data as time varying covariates in multivariable Cox models to study their impact on outcomes like PFS and OS.

With a given sample size of 80 patients in this study, we expect that at least 80% of patients (n=64) will yield analyzable laboratory results for a given endpoint. For a given marker or abnormality occurring at a rate of 50%, the marker can then be used to define two patient cohorts with n=32 patients in each group. This sample size provides 91% power to detect differences in the rate of another binary variable (such as progression, response, or presence of a resistance mutation) with frequencies of 25% and 60%, respectively, while testing with a one-sided 0.10-level Fisher's exact test.

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

A maximum total of 80 participants will be enrolled to the trial. We anticipate accruing approximately 3 – 4 subjects per month. Up to an additional three years of follow-up will be required on the last participant to observe response to trial therapy, for a total study length of approximately 6 years.

**Table 19: Accrual Targets**

| Ethnic Category | Sex/Gender | | | | |
|---|---|---|---|---|---|
| | Females | | Males | | Total |
| Hispanic or Latino | 2 | + | 1 | = | 3 |
| Not Hispanic or Latino | 39 | + | 38 | = | 77 |
| **Ethnic Category: Total of all subjects** | 41 (A1) | + | 39 (B1) | = | 80 (C1) |
| **Racial Category** | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| American Indian or Alaskan Native | 0 | + | 0 | = | 0 | |
| Asian | 1 | + | 0 | = | 1 | |
| Black or African American | 0 | + | 2 | = | 2 | |
| Native Hawaiian or other Pacific Islander | 0 | + | 0 | = | 0 | |
| White | 40 | + | 37 | = | 77 | |
| **Racial Category: Total of all subjects** | 41 (A2) | + | 39 (B2) | = | 80 (C2) | |
| | (A1 = A2) | | (B1 = B2) | | (C1 = C2) | |

## 13.3 Reporting and Exclusions

13.3.1 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first dose of study medication.

## 14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the 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. |