A Phase II Clinical Trial of Combination Nivolumab (Opdivo), Ipilimumab (Yervoy), and Paclitaxel in Patients with Untreated Metastatic Non-Small Cell Lung Cancer (NSCLC) (The OPTIMAL Trial) [TOP 1705] NCT03573947

DUKE CANCER INSTITUTE

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Principal Investigator
Jeffrey Clarke, MD
Duke Cancer Institute
Thoracic Oncology
[redacted]

Correlative Sciences Sub-Investigator
Kent Weinhold, PhD
Director, Immunology
Core Lab
Duke Translational Research Institute (DRTI)
[redacted]

Sub-Investigator(s)
Neal Ready, MD, PhD
Thomas Stinchcombe, MD
Scott Antonia, MD, PhD
Jeffrey Crawford, MD
Jennifer Tenhover, ANP
Yeshu Conn, ANP
Susan Blackwell, PA-C
Deborah Ballard, ANP
Jeana Schneider, PA-C

Correlative Sciences Sub-Investigator
Andy Nixon, PhD
Assoc Prof of Medicine
Medicine- Oncology Lab
[redacted]

Data Management
Thoracic Oncology Clinical Trials
[redacted]
Duke Cancer Institute
[redacted]

Statistician
Xiaofei, Wang, PhD
Department of Biostatistics
Duke Cancer Institute
[redacted]

Lin Gu, MS
[redacted]

Lead Study Coordinator
Carol Alonso, RN, MSN
Thoracic Oncology
[redacted]

Regulatory Coordinator
Lucas David, MHA
Thoracic Oncology
[redacted]

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Statement of Compliance and Signature Page

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This study will be conducted in compliance with the protocol approved by the Institutional Review Boards of Duke University Health System according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB as soon as possible. The signature below constitutes the approval (by the PI) of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local and state legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Duke Sponsor Investigator: Jeffrey Clarke, MD
Duke University Thoracic Oncology Program

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Jeffrey Clarke, MD, **Date**
Duke Sponsor Investigator

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PROTOCOL SYNPOSIS

Objectives

Primary Objective

1. To estimate the progression free survival for the combination nivolumab, ipilimumab, and paclitaxel in untreated, metastatic NSCLC

Secondary Objectives

1. To describe the safety and adverse events of combination nivolumab, ipilimumab, and paclitaxel in untreated, metastatic NSCLC.
2. To estimate the overall response rate with the study combination.

Exploratory Objectives

1. To explore correlation between baseline and treatment related changes in immune correlates and clinical outcome.
2. To explore any correlation between molecular/ histopathologic alterations and clinical outcome.
3. To estimate the objective response rate and median PFS to the study combination in PDL1 positive tumors

Patient Population

Subjects with histologically confirmed stage IV or recurrent non curable NSCLC of squamous or non-squamous histology, with no prior systemic anticancer chemotherapy or immunotherapy given as primary treatment for advanced or metastatic disease.

Study Design

This open-label, non-randomized, phase II trial designed to assess the safety and efficacy of nivolumab and ipilimumab in combination with weekly paclitaxel days 1 and 8 every 21 days in patients with treatment naïve NSCLC. All subjects with metastatic or recurrent non curable NSCLC will be enrolled at one of four participating cancer centers and will complete an extensive medical history, baseline physical examination and clinical assessment to ensure subject eligibility requirements (see Eligibility Criteria for key inclusion and exclusion criteria) prior to starting study treatment.

Patients will be treated with nivolumab, ipilimumab, and paclitaxel.

Number of Subjects

A cohort of up to 49 patients will be enrolled at Duke.

Estimated Length of Study Participation

Estimated duration of subject enrollment is 24 months.
Patients will continue to receive study treatment until they experience unacceptable drug-related toxicity, disease progression or 24 months. Subjects that discontinue study treatment with no documented disease progression and no subsequent anti-cancer treatment will be followed every 12 weeks with tumor evaluations until disease progression or start of new anti-cancer therapy is documented. All subjects will be followed for survival until death, loss to follow-up, or study completion.

Study completion is 2 years after the last subject starts study drug regimen.

Study Drug Regimen

The dosing regimen will be: nivolumab 360 mg every 3 weeks, ipilimumab 1 mg/kg every 6 weeks, and paclitaxel 80 mg/m2 on days 1 and 8 of a 21 day treatment cycle. Paclitaxel would be stopped after a total of 4-6 cycles of treatment.

Study Assessments

Safety assessments will be performed every 3 weeks, and as clinically indicated, and 35 days and 100 days after last dose of study drug (Section 7.0). These assessments will include vital signs, ECOG performance status, medical history, physical examination, complete blood count (CBC), biochemistry, creatinine, AST, ALT, and bilirubin. Thyroid stimulating hormone testing will be performed at regular intervals. Adverse events will be recorded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. General symptom management and supportive care as clinically indicated to ensure optimal patient care will be provided.

Tumor Assessments

Efficacy will be assessed by radiographic imaging (CT and/or MRI) every 2 cycles (i.e. every 6 weeks) using RECIST version 1.1.

Correlative Studies

Archived paraffin tumor and peripheral blood samples will be collected from each subject for correlative studies at specified time points. Refer to Correlates section for details of the correlative studies.

1. *Tumor Tissue*. An attempt will be made to get Archived FFPE tumor samples from all subjects. Allowable archival samples include surgical tissue or core needle biopsy. There will be no protocol violation if submitted specimen is not adequate for analysis.

2. *Circulating Immune Cells*. Subjects will have peripheral blood mononuclear cells (PBMC) collected at baseline, at first restaging, and at disease progression.

3. *Circulating Proteins*. Subjects will have plasma and serum collected at baseline, at first restaging, and at disease progression.

1. INTRODUCTION

1.1 Background

Lung cancer is the leading cause of cancer mortality in the United States with an estimated 225,000 new cases in 2017 and approximately 160,000 deaths annually in the US[1]. Non-small cell lung cancer (NSCLC) encompasses the vast majority of new lung cancer diagnoses. There remains an urgent unmet need for well tolerated, high efficacy therapies for frontline, treatment-naive NSCLC. Conventional first-line chemotherapeutic options alone have a very modest overall response rate of 25-35% and typical 1-year survival rates of approximately 30-60% in patients with a performance status of 0 or 1 [2,3]. Platinum combinations with bevacizumab and/or pemetrexed maintenance modestly improve survival [4-7]. Platinum-doublet chemotherapy regimens can be poorly tolerated with treatment-limiting fatigue, chemotherapy induced nausea and vomiting, cytopenias, and impairment of quality of life. Anti-PD1 immune checkpoint monotherapy with nivolumab in the 2nd line setting has superior survival compared to docetaxel chemotherapy and is FDA approved in that setting. Approximately ~20% of unselected patients with previously NSCLC have durable objective responses with nivolumab [8-9].

The movement of immune checkpoint therapies into the front-line setting in NSCLC recently is a strategy employed to improve clinical outcomes for NSCLC. Nivolumab monotherapy was found to safe with efficacy in untreated non-small cell lung cancer [10] Pembrolizumab monotherapy in patients with untreated NSCLC with PDL1 expressed on greater than 50% of tumor cells, resulted in a progression free survival of 10.3 months compared to 6.0 months with combination chemotherapy [11]. Pembrolizumab was associated with a superior response rate of 44.8% compared with 27.8% and median duration of response was not reached for patients receiving pembrolizumab. Combination immunotherapy with the addition of CTLA4 blockade with ipilimumab to nivolumab PD1 inhibition appears to further increase clinical activity [12]. Treatment with nivolumab plus ipilimumab in first-line NSCLC patients resulted in an overall response rate of 38-47% with a median duration of response not reached with minimum follow-up of about 7 months and a median follow up time of approximately 12 months. Standard dose nivolumab was combined with every 6 weeks ipilimumab 1 mg/kg in a phase 1 trial for untreated advanced NSCLC. Grade 3-4 toxicity occurred in 33-37% of patients, did not exceed maximum tolerated dose, and was deemed appropriate for phase 2 and 3 trials. Based on this data, the use of frontline immunotherapy and combinational approaches in NSCLC remains a potentially highly efficacious treatment approach for NSCLC patients. Checkmate 568 is a large phase 2 trial studying nivolumab plus ipilimumab in untreated advanced NSCLC that has completed enrollment and no excessive or unexpected toxicity has been reported.

Cytotoxic chemotherapy has several critical mechanisms to enhance tumor immunity and potentially improve efficacy of immunotherapeutics. Chemotherapy has demonstrated the ability to enhance T cell activation and tumor infiltration, increase dendritic cell activation, enhance tumor antigen processing and presentation, and inhibit regulatory T cells within the tumor microenvironment [13]. As proof of concept, nivolumab has been combined with platinum-doublet chemotherapy in patients with treatment naïve NSCLC, specifically using carboplatin with paclitaxel, gemcitabine, or pemetrexed [14]. The use of nivolumab with chemotherapy resulted in overall response rates ranging from 33-47% and occurred irrespective of PDL1 status. Importantly, toxicity rates were similar to the expected rates for combination chemotherapy regimens. Given these results,

the use of chemotherapy with immune checkpoint agents is feasible, is well tolerated, and can potentially increase response rates in untreated NSCLC.

1.2. Study Drugs

1.2.1 Nivolumab

PD-1 (or CD279), a 55-kilodalton Type 1 transmembrane protein, is a member of the CD28 family of T-cell co-stimulatory receptors that include immunoglobulin super family members CD28, CTLA-4, ICOS, and BTLA. PD-1 is highly expressed on activated T cells and B cells. PD-1 expression can also be detected on memory T-cell subsets with variable levels of expression. Two ligands specific for PD-1 have been identified: PD-L1 (also known as B7-H1 or CD274) and PD-L2 (also known as B7-DC or CD273). PD-L1 and PD-L2 have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems. The interaction of PD-1 with its ligands, PD-L1 and PD-L2, which are expressed on antigen-presenting cells (APCs) and DCs, transmits negative regulatory stimuli to down-modulate the activated T-cell immune response. The absence or inhibition of PD-1 in murine models has resulted in the development of various autoimmune phenotypes and autoimmune diseases. Taken together, these results suggest that inhibition of PD-1 binding to its ligands has the potential to activate T-cell responses. Since these responses are variable and dependent upon various host genetic factors, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance of self-antigens.

Tumors can express tumor-specific antigens as a result of non-synonymous gene mutations, and ongoing immune surveillance is believed to control the development of many tumors. Tumor progression may depend on the acquisition of mechanisms that permit them to evade an effective immune response. One such mechanism of evasion may be the expression of ligands, which engage inhibitory receptor(s) on anti-tumor T-cells of many tumors. PD-L1 expression has been found on a number of tumors and may be a mechanism by which tumors can directly engage PD-1 to evade an effective anti-tumor immune response. Expression of IFN-γ by activated T cells is known to induce PD-L1 expression in tumors. PD-L1 expression has been associated with poor prognosis in renal, esophageal, gastric, ovarian, pancreatic, and lung cancers. PD-1 engagement on T-cells by PD-L1-positive APC or PD-L1-positive tumor cells in the tumor microenvironment may limit effective immune responses. Conversely, PD-L1 expression may be a positive prognostic factor as it may indicate infiltration of tumor-specific T cells that secrete IFN-γ, which upregulates PD-L1 expression. Consistent with this hypothesis is the co-localization of lymphoid cell infiltrates and PD-L1 staining observed in human melanoma lesions.

Studies in multiple tumor models using a chimeric murine anti-mouse PD-1 antibody showed that PD-1 blockade has anti-tumor activity. Blocking PD-1 in PD-L1-positive tumors may reverse the inactivation of tumor-specific effector T-cells at the tumor site, as well as activate anti-tumor responses that are limited by PD-L1 expression on "host" DC or APC. The anti-tumor effects of anti-PD-1 observed in several murine models suggest that both PD-L1-positive and PD-L1-negative tumors may be targeted using this approach. In addition, in several tumor models in which anti-PD-1 has proved ineffective, PD-1 blockade can be combined with vaccines or other immunomodulatory antibodies for improved therapeutic efficacy.

Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 blockade by nivolumab is a promising avenue to pursue as an anti-tumor therapy for recurrent or treatment-refractory malignancies or as an anti-viral therapy for chronic viral infections.

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.

1.2.1.1. Preclinical and Clinical Trial Experience

For complete study information, refer to the current Nivolumab Investigator's Brochure (IB).

1.2.1.2. Non-Clinical Toxicology 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. 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.

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 (area under the concentration-time curve [AUC] from time zero to 168 hours [AUC(0-168 h)] 117,000 µ•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.

1.2.1.3. Clinical Trial Summary

The PK, clinical activity, and safety of nivolumab have been assessed in approximately 70 clinical studies sponsored by BMS, ONO, or other partners. Across these studies, approximately 12,300 subjects have received nivolumab monotherapy in single- or multiple-dose phase 1/2/3 studies or studies with

nivolumab in combination with other therapeutics (ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies). Results from the ongoing studies are preliminary and are subject to change.

Nivolumab has demonstrated clinical activity in NSCLC, melanoma, RCC, and cHL (approved indications) and other tumor types as monotherapy or in combination with ipilimumab. The majority of responses were durable and exceeded 6 months. In randomized, controlled studies, nivolumab monotherapy demonstrated statistically significant improvement in OS over standard of care in subjects with advanced or metastatic melanoma, in subjects with advanced or metastatic NSCLC, and in subjects with advanced RCC. In randomized, controlled studies, nivolumab in combination with ipilimumab demonstrated statistically significant improvement in PFS and ORR over ipilimumab monotherapy in subjects with advanced or metastatic melanoma.

All available data suggest that nivolumab monotherapy has a consistent AE profile across tumor types. The safety profile is generally consistent across completed and ongoing clinical trials, with no maximum tolerated dose (MTD) reached at any monotherapy dose tested up to 10mg/kg. There was no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. The safety profile of nivolumab in combination with ipilimumab was consistent with the mechanisms of action of nivolumab and ipilimumab. The nature of the AEs was similar to that observed with either agent used as monotherapy; however, both frequency and severity of most AEs were increased with the combination. A dose of 3 mg/kg nivolumab/3 mg/kg ipilimumab exceeded the MTD, and both 1 mg/kg nivolumab/3-mg/kg ipilimumab and 3 mg/kg nivolumab/1 mg/kg ipilimumab were identified as the MTD. Across all studies conducted to date, drug-related AEs have included pulmonary toxicity, renal toxicity (including acute renal failure), endocrine abnormalities, GI toxicity, dermatologic toxicity (including rash) and hepatotoxicity. For nivolumab monotherapy and combination therapy, the majority of these AEs have been managed successfully with supportive care and, in more severe cases, a combination of dose delay, permanent discontinuation, and/or use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in the management guidelines provided.

1.2.1.4. Safety Profile

The overall safety experience with nivolumab is based on experience in approximately 12,300 subjects as either monotherapy or in combination with other therapeutics. In general, for monotherapy, the safety profile is similar across tumor types. The only exception is pulmonary inflammation AEs, which may be numerically greater in subjects with NSCLC, possibly because in some cases, it can be difficult to distinguish between nivolumab-related and unrelated causes of pulmonary symptoms and radiographic changes. The most frequently reported treatment-related AE is fatigue, which is almost always of low grade.

Most related AEs are thought to be due to the effects of inflammatory cells on specific tissues. A variety of preferred terms (PTs) have been used to describe similar kinds of organ-related AEs, with the result being that AE frequency tables organized by PTs can lead to underestimation of the frequency of similar kinds of organ-related AEs. To address this issue, select AE categories were created. Select AE categories group together the most common and impactful PTs by organ category. These categories include the following: pulmonary, GI, hepatic, skin, endocrine, hypersensitivity/infusion reaction, and renal AEs. It is also useful to consider the management of nivolumab-related AEs by organ category as the diagnostic

work-up often requires excluding other potential diagnoses and, when appropriate, instituting specific management principles.

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. Nivolumab+ipilimumab is approved for the treatment of melanoma in multiple countries, including the US and EU, and is the most advanced combination under development in multiple other tumor types (see Section 5.5). The combination of both agents results in a safety profile with similar types of AEs as either agent alone, but in some cases, with a greater frequency. The optimal doses for nivolumab + ipilimumab combination continue to be evaluated and may vary by tumor type.

In general, the approach to suspected nivolumab-related AEs is similar across any involved organ system. Subjects should have a thorough diagnostic work-up to evaluate potential drug- and non-drug-related diagnoses. For suspected nivolumab-related AEs, based on the severity of the event, management with immunosuppressants may be necessary. In general, dose delays and observation are adequate for low-grade AEs. For moderate- and high-grade AEs, immunosuppression with corticosteroids should be utilized. Once the AE has begun to improve, corticosteroids can be tapered over approximately 3 weeks to 6 weeks (depending on the severity of the AE). The management of AEs considered related to any combination treatment is similar to the management of AEs caused by either agent alone and utilizes the same safety management algorithms.

It is rare for a patient receiving immunosuppression for nivolumab-related AEs to develop an opportunistic infection. Subjects with inflammatory events of any organ category expected to require more than 4 weeks of corticosteroid or other immunosuppressive agents to manage the AE should be considered for antimicrobial/antifungal prophylaxis, per institutional guidelines, to prevent opportunistic infections such as P. jiroveci (formerly P carinii) and fungal infections. Early consultation with an infectious disease specialist should be considered. Depending on the presentation, consultation with a pulmonologist for bronchoscopy or a gastroenterologist for endoscopy may also be appropriate. In addition, a concomitant opportunistic infection should be considered in the differential diagnosis if a patient develops recurrent AEs in the setting of ongoing or prior immunosuppressive use. Nivolumab should not be used in subjects with active autoimmune disease given the mechanism of action of the antibody.

1.2.1.5. Dose Selection

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 (Cavgss, Cminss, Cmaxss, and Cmin1) are comparable after treatment with either 3 mg/kg or 240 mg nivolumab. The predicted range of nivolumab exposures (median and 90% prediction intervals) resulting from a 240 mg flat dose across the 35 to 160 kg weight range is maintained well below the corresponding exposures observed with the well tolerated 10 mg/kg nivolumab Q2W dosage. 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 now a clinical standard of care.

Nivolumab 360 mg will be administered as an IV infusion over 30 minutes every 3 weeks (Q3W). Nivolumab has been shown to be safe and well tolerated up to a dose level of nivolumab 10 mg/kgQ2W. As population PK (PPK) analyses have shown that the PK of nivolumab are linear over a dose range of 0.1 to 10 mg/kg with no differences observed in PK across ethnicities and tumor types, the PPK model was used to simulate exposures at different dosing regimens, including nivolumab 360 mg Q3W. The simulated steady-state average concentration (Cavgss) following administration of nivolumab 360 mg Q3W are expected to be similar to those following administration of nivolumab 240 mg Q2W and nivolumab 3 mg/kg Q2W administered to participants weighing 80 kg. It should be noted that the steady-state peak concentrations (Cmaxss) following nivolumab 360 mg Q3W are predicted to be less than those following the administration of nivolumab 10 mg/kg Q2W, providing sufficient safety margins. Finally, nivolumab 360 mg Q3W in combination with platinum-doublet chemotherapy dosing is currently being studied for the treatment of NSCLC and gastric cancer in a phase 3 study.

1.2.2. Ipilimumab

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 (Treg) function, which may contribute to a general increase in T-cell responsiveness, including the anti-tumor response.

Yervoy (ipilimumab) 3 mg/kg has been approved for use in advanced melanoma in over 47 countries, including the United States (US, 25-Mar-2011), the European Union (EU, 13-Jul-2011), and Australia (Jul-2011). Yervoy 10 mg/kg is approved as adjuvant treatment of unresectable or metastatic melanoma in the US.

Ipilimumab has specificity and 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 g/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 g/mL, respectively.

1.2.2.1. Clinical Trial Experience

For complete study information, refer to the current ipilimumab Investigator's Brochure (IB).

The combination of nivolumab with ipilimumab 1 mg/kg every 6 weeks was found to be safe and effective

in patients with untreated advanced NSCLC [12]. Ipilimumab 1 mg/kg with nivolumab plus paclitaxel will be studied in the clinical trial. Checkmate 227 is a very large randomized phase 3 trial that studied multiple combinations of chemotherapy, nivolumab, nivolumab plus ipilimumab, and chemotherapy combined with nivolumab plus ipilimumab in untreated stage 4 lung cancer. Checkmate 227 has completed accrual and DSMB review did not identify significant safety concerns for the chemotherapy plus nivolumab plus ipilimumab combination that required alteration in accrual or therapy on that study arm.

1.2.2.2. Clinical Trial Summary

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, including 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 (and only approved) 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, completed Phase 3 studies (MDX010-20, CA184024, CA184029, and CA184169) have demonstrated a clinically meaningful and statistically significant survival benefit in pretreated advanced melanoma, in previously untreated advanced melanoma, and in adjuvant melanoma. Ipilimumab monotherapy or in combination with chemotherapy has not prolonged survival in prostate cancer, NSCLC, and SCLC (Studies CA184043, CA184095, CA184104, and CA184156). Outside melanoma, combination with other checkpoint inhibitors (e.g. PD-1 inhibitors) may be required to achieve clinically meaningful activity.

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 overall survival (OS).

1.2.2.3. Safety Profile

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 the 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. The management guidelines for general irAEs and ipilimumab-related GI toxicities, hepatitis, endocrinopathy, and neuropathy are described in this protocol.

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), previously untreated advanced melanoma (at 10 mg/kg in combination with dacarbazine [DTIC] compared to DTIC alone), and adjuvant melanoma. In addition, ipilimumab shows evidence of enhanced clinical activity when combined with nivolumab in melanoma and in other tumor types including NSCLC. 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.

1.2.3. Clinical Activity of Nivolumab in Combination with Ipilimumab and Chemotherapy

In CA209012, 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. Preliminary ORR and PFSR at 24 weeks for subjects treated with nivolumab + chemotherapy esd (N = 56, median follow-up 83.6 weeks), and nivolumab + erlotinib (N = 21, median follow-up 71.9 weeks) in CA209012. Among responders, the median durations of responses ranged from 25.4 weeks to 45 weeks for nivolumab + chemotherapy, while the median durations of responses for nivolumab + erlotinib were not reached at the time of analysis. Among the erlotinib patients, 20 of the 21 subjects had previously received an EGFR TKI for NSCLC. All had sensitizing EGFR mutations.

A summary of ORR and PFSR at 12 months for subjects treated with nivolumab + ipilimumab is provided below. The original nivolumab + 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 PFSR compared to the cohorts containing the lower dose of nivolumab (1 mg/kg).

The regimens for these cohorts were:

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

Treatment Group	N	Nivo	ORR[a]		PFSR at 12 months		Median OS	
		mg/kg	n (%)	95% CI[b]	%	95% CI[c]	Months	95% CI[b]
Nivo + Ipi								
Nivo1 + Ipi1 x4 (arm N)	31	1	6 (19)	8, 38	30	14, 47	NR	11.5, NR
Nivo1 + Ipi1 (arm O)	40	1	13 (33)	19, 49	25	12, 42	NR	11.0, NR
Nivo3 + Ipi1 q12w (arm P)	38	3	18 (47)	31, 64	48	31, 63	NR	14.1, NR
Nivo3 + Ipi1 q6w (arm Q)	39	3	15 (39)	23, 55	35	20, 50	18.1	13.3, 18.1

Source: Preliminary data for CA209012, database lock date 18-Feb-2016

[a] CR + PR; assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1

[b] Based on Kaplan-Meier method

[c] Based on Greenwoods formula

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

1.2.4 Chemotherapy and Immune therapy Combinations

Combinations of platinum based chemotherapy including paclitaxel with nivolumab have been studied in advanced stage NSCLC. The combination of carboplatin, paclitaxel, and nivolumab was found to be safe with promising efficacy. In study CA209012, patients with treatment naïve advanced stage NSCLC received nivolumab combined with platinum based chemotherapy doublets: gemcitabine, pemetrexed, or paclitaxel (10). Nivolumab 10 mg/kg or 5mg/kg was given every 21 days with 4 cycles of standard dose chemotherapy followed by nivolumab maintenance. In general, the 4 cycles of combined therapy were safe and feasible with the majority of treatment related adverse events leading to therapy discontinuation occurring during the nivolumab single agent maintenance phase. There was evidence of possible additive therapeutic benefit for the combination compared to what would be expected for chemotherapy or nivolumab alone with overall response rates of 40%, promising 1 year survival, and a number of durable responses. Checkmate 227 is a

large randomized phase 3 trial for untreated advanced lung cancer studying platinum based chemotherapy, versus nivolumab plus ipilimumab in one part of the study.

Paclitaxel is being incorporated into this treatment regimen given its' well established efficacy and safety in the treatment of NSCLC. Paclitaxel has been utilized extensively as a single agent therapy for both treatment naïve and refractory NSCLC [2, 3]. Furthermore, weekly dosing of paclitaxel has been studied in multiple large clinical trials and has a favorable toxicity profile and antitumor activity [2]. Importantly, paclitaxel has been investigated in NSCLC in combination with other immunotherapies. For example, a large phase III study recently evaluated combination carboplatin and paclitaxel with ipilimumab in squamous cell NSCLC with tolerable safety profile though no improvement in OS[4]. Additionally, nivolumab has demonstrated efficacy and safety in NSCLC in multiple clinical studies [5].

1.3 Study Rationale

Immune therapy with PD1 checkpoint antibodies has produced durable responses in advanced NSCLC that has transformed clinical care for lung cancer patients. Combination immune therapy with nivolumab plus ipilimumab has produced increased durable remissions in untreated advanced lung cancer compared to nivolumab alone in the arms of a large phase 1 trial. However one of the challenges that remains in immune therapy for lung cancer is the rate of rapid progression with inferior progression free survival compared to cytotoxic chemotherapy in some studies (8). The combination of chemotherapy plus PD1 checkpoint antibody has shown promising response rates, improvement in progression free survival compared to historical rates for immune therapy alone, and no apparent decrease in durable remissions. Despite promising efficacy, it would be highly desirable to avoid the toxicity of platinum chemotherapy for the initial treatment of lung cancer. Therefore we plan to study well tolerated, intermediate dose weekly paclitaxel in combination with nivolumab plus ipilimumab in order to try and avoid early cancer progression, provide synergy with immune therapy, and achieve the higher durable remissions rates that have been reported for combination immune therapy.

This is a multicenter, phase II clinical trial of nivolumab, ipilimumab, and paclitaxel in patients with metastatic treatment-naïve NSCLC to assess the efficacy and safety of combination immunotherapy plus single agent weekly chemotherapy days 1 and 8 every 21 days. Our hypothesis is that the combination nivolumab, ipilimumab, and single agent chemotherapy will have a superior progression free survival (PFS) compared to nivolumab and ipilimumab. The primary endpoint will determine the PFS of nivolumab and ipilimumab plus single agent chemotherapy and compare with previously reported outcomes for nivolumab and ipilimumab in untreated, advanced stage NSCLC. The sample size is 49 patients total across the participating institutions. The dosing regimen will be: nivolumab 360 mg every 3 weeks, ipilimumab 1 mg/kg every 6 weeks, and paclitaxel 80 mg/m2 on days 1 and 8 every 21 day treatment cycle. Patients will be eligible for enrollment regardless of PDL1 testing status or results. Paclitaxel would be stopped after a total of 4-6 cycles of treatment. Whole blood will be collected for each patient on protocol to enable potential extensive analysis circulating inflammatory proteins and immune cell subsets. Archival tumor specimens for each patient will be available for retrospective, exploratory correlative science analysis.

2. OBJECTIVES

2.1 Primary Objective

The primary objective of this trial is:

1. To estimate the progression free survival for the combination nivolumab, ipilimumab, and paclitaxel in untreated, metastatic NSCLC.

2.2. Secondary Objectives

The secondary objectives of this trial are:

1. To describe the safety and adverse events of combination nivolumab, ipilimumab, and paclitaxel in untreated, metastatic NSCLC.

2. To estimate the overall response rate with the study combination.

2.3. Exploratory Objectives

The exploratory objectives of this trial are:

1. To explore correlation between baseline and treatment related changes in immune correlates and clinical outcome.

2. To explore any correlation between molecular/ histopathologic alterations and clinical outcome.

3. To estimate the objective response rate and median PFS to the study combination in PDL1 positive tumors

3. STUDY DESIGN

3.1 Study Description

This open-label, non-randomized, phase II trial designed to assess the safety and efficacy of nivolumab and ipilimumab in combination with weekly paclitaxel days 1 and 8 every 21days in patients with treatment naïve NSCLC. All subjects with metastatic or recurrent and not curable non-small cell lung cancer will be enrolled at one of four participating cancer centers and will complete an extensive medical history, baseline physical examination and clinical assessment to ensure subject eligibility requirements (see Eligibility Criteria for key inclusion and exclusion criteria) prior to starting study treatment.

- Enrolled subjects are defined as subjects who give informed consent.
- Screen failures are defined as subjects who give informed consent and do not meet eligibility criteria.
- Accrued subjects are defined as subjects who give informed consent and meet eligibility criteria.

    a. Withdrawal: Subject accrued but later withdrawn from the study, either before or after receiving a study drug.
    b. Evaluable: All subjects who are accrued and receive any study treatment will be considered evaluable for toxicity. All subjects who are accrued and receive any study treatment will be considered evaluable for efficacy.

3.2. Dosing Regimen

The dosing regimen will be: nivolumab 360 mg every 3 weeks, ipilimumab 1 mg/kg every 6 weeks, and paclitaxel 80 mg/m2 on days 1 and 8 of an every 21 day treatment cycle. Patients will be eligible for enrollment regardless of PDL1 testing status or results. Paclitaxel would be stopped after a total of 4-6 cycles of treatment or unacceptable toxicity.

Table 2. Cohort. The cycle length for the study will be 3 weeks.

	Patients	**Nivolumab IV Every 3 weeks**	**Ipilimumab IV Every 6 weeks**	**paclitaxel IV On day 1 and 8 for 4-6 cycles**
Single Cohort	49	360 mg over 30 minutes	1 mg/kg over 30 minutes	80 mg/m^2 over 60 minutes

Patients may continue to receive nivolumab and ipilimumab until they experience unacceptable treatment-related toxicity, disease progression, or once they have been treated for 2 years. Paclitaxel will be stopped after a total of 4-6 cycles of treatment.

3.3. Safety and Efficacy

Safety assessments will be performed on every 3 weeks, as clinically indicated, 35 days after last dose of study drug, and 100 days after the last dose of study drug (section 7.0). These assessments will include vital signs, ECOG performance status, medical history, physical examination, complete blood count (CBC), biochemistry, creatinine, AST, ALT, and bilirubin. Thyroid stimulating hormone testing will be performed at regular intervals. Adverse events will be recorded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. General symptom management and supportive care as clinically indicated to ensure optimal patient care will provided.

Efficacy will be assessed by radiographic imaging (CT and/or MRI) every 6 weeks (± 7 days up to week 48, then every 12 weeks (± 7 days) until documented disease progression using RECIST version 1.1.

4. PATIENT RECRUITMENT

Patients will be recruited for this study as follows: Upon determination that a patient's tumor histology and radiographic findings are compatible with the eligibility criteria of this protocol, the clinical study will be briefly explained to the patient by the principal investigator (PI) or designee. If the patient indicates interest in study participation, patient education sheets (if available) and the approved protocol consent form will be provided to the patient as these provide the most comprehensive explanation of the study in lay terms. If the patient shows continued interest, the PI or designee will thoroughly explain the required elements of informed consent and all aspects of the study to the patient including inclusion/exclusion criteria, risks, possible benefits and alternatives to study participation.

5. SUBJECT SELECTION

The following guidelines are to assist physicians in selecting patients from whom protocol therapy is safe and appropriate. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate. For entry into the study, the following criteria **MUST** be met.

5.1. Inclusion Criteria

1. Histologically confirmed Stage IV or recurrent Non-small cell lung cancer squamous or non-squamous histology (Stage IV as diagnosed using the 7th edition of Lung Cancer Stage Classification), with no prior systemic anticancer therapy given as primary therapy for advanced or metastatic disease. Prior adjuvant chemotherapy, neoadjuvant chemotherapy, or chemoradiotherapy is permitted as long as the last administration of the prior regimen occurred at least 6 months prior to study enrollment. Patients with known EGFR, ALK, or ROS1 alterations must have received one prior TKI. If ROS1 not known for any reason, subject meets eligibility. (Greater than or equal to 1 week washout for those patients on a TKI)
2. Archived tumor tissue will be used for exploratory analysis. Archival samples must come from a core needle biopsy,surgical tissue, or FNA 19 guage needle or larger. Available tumor tissue is not required for eligibility. There is no protocol violation if submitted specimen is not adequate for analysis. Note: a bone biopsy is not an acceptable sample.

3. At least one site of disease that is measurable by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 that has not been previously irradiated; if the patient has had previous radiation to the marker lesion(s), there must be evidence of progression since the radiation. (Appendix A)
4. Age ≥ 18 years with ability and willingness to provide informed consent.
5. ECOG performance status 0 or 1. (Appendix B)
6. Negative pregnancy test done ≤72 hours (or per institutional policy) prior to treatment, for women of childbearing potential only. Female subjects should be using highly effective contraceptive measures, and must have a negative pregnancy test or must have evidence of non-child-bearing potential by fulfilling one of the following criteria at screening:
    a. Post-menopausal defined as aged more than 50 years and amenorrheic for at least 12 months following cessation of all exogenous hormonal treatments.
    b. Women under 50 years old would be consider postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with LH and FSH levels in the post-menopausal range for the institution
    c. Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation

7. Men and women of childbearing potential must agree to use medically accepted barrier methods of contraception (e.g. male or female condom) at the time of pregnancy test (women of childbearing potential only), during the course of the study and for 7 months after the last dose of study drug, even if oral contraceptives are also used. All subjects of reproductive potential must agree to use both a barrier method and a second method of birth control during the course of study and for 7 months after the last dose of study drug.
8. A concurrent diagnosis of a separate malignancy is allowed if clinically stable and does not require tumor-directed therapy.
9. Provision of written informed consent including HIPAA according to institutional guidelines prior to any study-specific procedures
10. Patients must agree to research blood sampling to participate in study;
11. Adequate organ and marrow function as defined by the following:
    a. Creatinine clearance ≥ 50 cc/min or serum Cr ≤ 1.5 x institutional ULN(Appendix C)
    b. Total bilirubin ≤ 1.5 x upper limit of normal (ULN)
    c. AST/ALT ≤ 2 x ULN without liver metastasis; ≤ 5 x ULN with liver metastasis
    d. Absolute neutrophil count (ANC) ≥ 1500 µl
    e. Hemoglobin (Hgb) ≥ 9 g/dL
    f. Platelets ≥ 100,000/µl

5.2. Exclusion Criteria

1. Subjects with known EGFR mutations which are sensitive to available targeted inhibitor therapy and must have received treatment with at least one prior tyrosine kinase inhibitor (TKI). (Greater than or equal to 1 week washout for those patients on a TKI).
2. Subjects with known ALK or ROS1 translocations which are sensitive to available targeted inhibitor therapy must have received treatment with at least one prior TKI. (Greater than or equal to 1 week washout for those patients on a TKI).
3. Radiation therapy within 14 days prior to day 1 of study drug.
4. Experimental agents within 28 days prior to day 1 of study drug.

5. Intolerance of nivolumab or other PD-1/PD-L1 axis drug(s), or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways, including prior therapy with anti-tumor vaccines or other immune-stimulatory anti-tumor agents.
6. Known auto-immune conditions requiring systemic immune suppression therapy other than prednisone ≤ 10 mg daily (or equivalent).
7. History of interstitial pneumonitis from any cause.
8. Concurrent severe and/or uncontrolled medical conditions which may compromise participation in the study, including impaired heart function or clinically significant heart disease.
9. Pregnant or breast feeding.
10. Not willing to use an effective method of birth control medically accepted barrier methods of contraception (e.g. male or female condom) at the time of pregnancy test (women of childbearing potential only), during the course of the study and for 7 months after the last dose of study drug.
11. Current use of medications specified by the protocol as prohibited for administration in combination with the study drugs. This includes patients with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days prior to day 1 of study drug. Inhaled or topical steroids and adrenal replacement doses >10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
12. Current active infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment on day 1 of study drug. Patients receiving prophylactic antibiotics (e.g., for prevention of urinary tract infection or chronic obstructive pulmonary disease) are eligible.
13. Known active CNS metastases which are symptomatic. Eligible if metastases have been locally treated 14 days prior to cycle 1 day 1, are clinically controlled, or asymptomatic on cycle 1 day
    1. Steroid dose must be equivalent of ≤ 2 mg decadron daily or equivalent dose steroid. Untreated, asymptomatic brain metastases allowed if subject does not require corticosteroids or anticonvulsant therapy.
14. History of myocardial infarction, NYHA class III or IV congestive heart failure, or unstable angina, cardiac or other vascular stenting, angioplasty, or surgery within 6 months prior to study enrollment.
15. Known history of HIV seropositivity or known acquired immunodeficiency syndrome (AIDS), hepatitis C virus (allowed if received curative therapy), acute or chronic active hepatitis B infection, or other serious chronic infection requiring ongoing treatment.
16. Inability to comply with protocol or study procedures.

5.3. Inclusion of Women and Minorities

There are no exclusions based on gender, race or ethnicity in this trial. There is no evidence to suggest that Outcomes will differ.

5.4. Protocol Eligibility Waivers

No waivers of inclusion or exclusion criteria will be granted. All prospective patients must meet all entry criteria. If there are any questions regarding the interpretation of a criterion for a potential patient, contact the principal investigator to discuss.

6. REGISTRATION PROCEDURE

Patient registration for all patients signing informed consent will be completed through the Duke Cancer Institute (DCI) Clinical Research Unit (CRU) into EPIC and ONCORE systems within 1 business day of obtaining consent. Patients will be enrolled only after all pre-treatment evaluations are completed and all eligibility criteria are met.

7. STUDY ASSESSMENTS

The Study Calendar (Appendix D) summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.
For the purpose of scheduling evaluations and to allow for patient and investigator schedules, holidays and weather or other emergencies requiring clinical facilities to be closed, a window of + 7 days will be applied to all day 1 study visits unless otherwise noted. Subjects may be dosed no less than 19 days from the previous dose of Nivolumab.
Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and or BMS for reasons related to subject safety.

7.1. Screening Period

During the Screening Period, subjects are consented and screened for the study. Informed consent must be obtained before initiation of any screening procedure that is performed solely for the purpose of determining eligibility for this study. Evaluations performed as part of routine care before informed consent can be considered as screening evaluations if done within the defined screening period, and if permitted by the local Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) policies. Study eligibility is based on meeting all of the inclusion criteria and none of the exclusion criteria (refer to Section 5) before the first dose of study drug on Cycle 1 Day 1.

The following study procedures must be done within 28 days prior to Cycle 1 Day 1 (unless otherwise specified). Baseline and Cycle 1 Day 1 procedures may be completed on the same day, however, screening assessment to confirm eligibility **MUST** have already been determined (Refer to Study Calendar- Appendix D for details):

- Informed Consent
- Eligibility criteria review (inclusion/exclusion)
- Demographics/baseline characteristics, smoking history
- Medical and cancer history
- Physical examination
- Height
- Vital signs (temperature, blood pressure, pulse and respiratory rate) and weight
- Concomitant medications
- ECOG performance status
- Adverse event assessment (review of baseline symptoms)

- Tumor assessment (CT and/or MRI) of Chest, Abdomen, Pelvis and all known or suspected sites of disease, MRI of brain or CT Brain with contrast is required for all subjects
    - For patients with **treated** brain metastases, if brain MRI falls outside of the 28 day screening window, a repeat brain MRI is not needed unless greater than 4 weeks from the completion date of radiation therapy.
- Circulating Immune Cells (PBMC) may be collected pre-dose on Cycle 1 Day 1
- Circulating proteins (may be collected pre-dose on Cycle 1 Day 1)

The following study procedures must be done within 14 days prior to Cycle 1 Day 1:

- CBC with differential
- Chemistries including liver function tests (LFTs)
- Thyroid Function (TSH, Free T4)

The following must be done within 72 hours (or institutional standards) of study drug administration

- Serum pregnancy test (women of childbearing potential)

Subject eligibility is determined using lab results obtained up to 14 days prior to Cycle 1 Day 1. Any laboratory assessments repeated on Cycle 1 Day 1 must meet eligibility requirements. The Screening Period ends upon receipt of the first dose of study drug or final determination that the subject is ineligible for the study.

7.2. Treatment Period

During the Treatment Period, subjects will receive nivolumab every 3 weeks, ipilimumab every 6 weeks, and paclitaxel* on Days 1 & 8 of an every 21-day treatment cycle until either: 1) disease progression; 2) the occurrence of unacceptable treatment-related toxicity; or 3) other reason(s) for subject discontinuation as described in Section 7.7. Toxicity-related dose modifications of nivolumab, ipilimumab, and Paclitaxel may occur during the Treatment Period. Dose modification guidelines are described in Section 9.1.

*Paclitaxel will be stopped after a total of 4-6 cycles of treatment or if unacceptable toxicity if prior to 4-6 cycles. For the purpose of day 8 treatment and to allow for patient and investigator schedules, holidays and weather or other emergencies requiring clinical facilities to be closed, a window of ±/-3 days will be applied to day 8 treatment, without a delay in the treatment cycle.

All subjects will have study procedures weekly (day 1 and 8) during the first cycle, then Day 1 of each cycle. After the completion of the first cycle, laboratory assessments may be obtained up to 3 days prior to Day 1. If clinically indicated, additional visits and/or safety assessments may be warranted.

The following study procedures must be completed **day 1 and 8 of cycle 1 then day 1 of each cycle thereafter (lab assessments may be obtained within 3 days)**:

- Physical examination
- Vital signs and weight
- Concomitant medications

- ECOG performance status
- Adverse event assessment
- CBC with differential
- Chemistries including LFTs
- Serum pregnancy test (for women of childbearing potential) or per institutional policy

The following study procedures are to be completed within 3 days of **day 8 of Cycles 2- 6 while receiving Paclitaxel**:

- Physical examination (optional)
- Vital signs and weight (optional)
- Concomitant medications
- ECOG performance status (optional)
- Adverse event assessment
- CBC with differential
- Chemistries including LFTs

The following study procedures must be completed **day 15, Cycles 3-6 (+3 days)**:

- Nursing phone call screening for symptoms of immune hypophysitis or adrenal insufficiency
- See Apppendix F for phone call template and action items

The following study procedures must be completed **every 6 weeks unless otherwise specified**:

- Thyroid profile (TSH and free T4)
- Tumor assessment (CT and/or MRI)**
- Circulating Immune Cells (PBMC) - first restaging only
- Circulating proteins- first restaging only

**Restaging scans will be performed every 6 weeks (± 7 days) up to week 48, then every 12 weeks (± 7 days). Disease response will be assessed using guidelines described in Section 8.6.

CT chest and known sites of disease are required for those subjects with metastases in those areas identified at baseline or if clinically indicated. Subjects with a history of brain metastasis to have surveillance MRI approximately every 12 weeks from first dose or sooner if clinically indicated.

The Treatment Period ends when a subject receives his or her last dose of study treatment; the subject then enters the Follow-up Period.

7.3. Follow-up Period (Follow-up Visits 1 & 2)

Post study follow-up is of critical importance and is essential to preserving subject safety and integrity of the study. Subjects are to return 35 days after their last dose of study drug (±7 days) or coinciding with the date of discontinuation of study drug (±7 days) if the date of discontinuation is greater than 42 days from the last dose for an off-treatment f/u visit #1. Follow-up visit 2 to occur 80 days from Follow-up Visit 1 (±7 days). Subjects are to be monitored for at least 100 days after the last dose of study drug and complete the following study procedures:

- Physical examination

- Vital signs and weight
- Concomitant medications
- ECOG performance status
- Adverse event assessment
- CBC with differential
- Chemistries including LFTs

Additional follow-up may occur for subjects with adverse events (AEs) related to study drug that are ongoing at the time of this off-treatment visit unless AE is deemed unresolvable or subject has started a new anti-cancer treatment regimen.

For subjects that are discontinued from study treatment for reasons other than disease progression, subjects will have restaging scans per standard of care schedule, followed until disease progression or start of new anti-cancer treatment regimen. Disease status may be collected by personal interviews or review of medical records. Subjects will be followed for survival up to 2 years or until the study is closed (whichever comes first). Survival status may be collected by personal interviews or review of medical or public records.

7.3.1 Follow-up patients who discontinue treatment for reasons other than progression *and* started new therapy.

Follow up 1 & 2: Complete the following assessments:

- **Do** collect:
  - Adverse events *related to* treatment
  - Corticosteroid concomitant medications taken for treatment related adverse event.

Do not collect: Physical examination, Vital signs and weight, ALL Concomitant medications, ECOG, ALL Adverse event assessment, CBC with differential, Chemistries including LFTs

- **Do not** submit RECIST.
- **Do not** collect research blood at progression

Follow-up #1:

- Document all ongoing adverse events related to treatment
  - Continue to follow AE until it is resolved or deemed "unresolvable".
- Document any new treatment related adverse event.
- Document Corticosteroid concomitant medication taken for treatment related AE.
- Document/submit SAEs whether related or not study therapy through 100 days last dose whether or not related to treatment.

Follow-up #2: Same as Follow-up #1 with
Additional FU after 100 days for ongoing, treatment related adverse event until resolved or deemed unresolvable

7.4 Disease Progression

- Circulating proteins (research blood)
- Circulating Immune Cells (PBMC) research blood

- Note: Subjects who discontinue treatment for reasons other than progression, will have research blood drawn at progression unless they start a new anti-cancer treatment regimen.

7.5 Laboratory Assessments

Local laboratories will perform all clinical laboratory tests using standard procedures, and results will be provided to the Investigator. Abnormalities in clinical laboratory tests that lead to a change in subject management (e.g., dose modification, requirement for additional medication, treatment or monitoring) are considered clinically significant for the purposes of this study, and will be recorded on the case report form (CRF). If laboratory values constitute part of an event that meets criteria defining it as serious, the event (and associated laboratory values) must be reported as a serious adverse event (SAE).

Refer to Appendix E for details of laboratory tests for this study.

7.6 Tumor Assessments

Tumor response will be assessed using RECIST version 1.1. **Restaging scans will be performed every 6 weeks (± 7 days) up to week 48, then every 12 weeks (± 7 days). CT Chest and known sites of disease are required for those subjects with metastases in those areas identified at baseline or if clinically indicated. Subjects with a history of brain metastasis to have surveillance MRI or CT with contrast approximately every 12 weeks from first dose or sooner if clinically indicated. The same method for tumor assessment should be employed at every assessment.

7.7 Subject Discontinuation

Subjects will receive study treatment until treatment discontinuation for one of the reasons listed below. However, subjects may discontinue study treatment or withdraw their consent to participate in the study at any time without prejudice. All reasons for discontinuation or withdrawal from trial will be recorded.

The duration of treatment for nivolumab and ipilimumab will be until unacceptable drug-related toxicity or disease progression, or 24 month time. Reasons for subject discontinuation by the Investigator may include, but are not limited to, the following:

- Death
- ~~Confirmed~~ Radiographic disease progression (Note: With approval of the Lead PI, a subject may be granted an exception to continue on study treatment with confirmed radiographic progression if clinically stable or clinically improved.) Section 9.2
- There is toxicity deemed by the investigator or subject to be unacceptable
- Concurrent illness that prevents further administration of treatment
- Significant noncompliance with trial treatment or procedure requirements by subject or Investigator
- Investigator or Lead PI determination that it is no longer safe and/or no longer in the subject's best interest to continue participation
- Subject's legal representative withdraws consent
- Subject is lost to follow-up

- The subject, for any reason, requires treatment with another systemic agent potentially effective for treatment of the study indication. In this case, discontinuation from the study occurs immediately upon introduction of the new agent
- Sexually active subjects who refuse to use medically accepted methods of contraception during the course of the study and for 7 months following the last dose of study drug
- Women who become pregnant
- Request by regulatory agencies for termination of treatment of an individual subject or all subjects under the protocol

8. STUDY DRUGS

8.1. Treatment Compliance and Study Drug Accountability

The Investigator will maintain accurate records of nivolumab/ ipilimumab study drugs, including dates of receipt. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each subject in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. At completion of the study, to satisfy regulatory requirements regarding drug accountability, all unused study drug will be reconciled and destroyed in accordance with applicable state and federal regulations.

Administration guidelines:

Subjects will receive treatment starting day 1 cycle 1 with nivolumab 360 mg as a 30 minute infusion every 3 weeks, ipilimumab 1mg/kg as a 30 minute infusion every 6 weeks, paclitaxel 80mg/m2 as a 60 minutes infusion days 1 & 8 of a 21 day treatment cycle. Paclitaxel will be stopped after a total of 4-6 cycles. Treatment will continue until progression, unacceptable toxicity, withdrawal of consent, 24 months from the first dose, or the study ends, whichever comes first.

There are no premedications recommended for the first cycle prior to nivolumab & ipilimumab infusions. For cycles in which paclitaxel is administered, the nivolumab is to be administered first. The second infusion will always be ipilimumab (if applicable). The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion. Once immunotherapy infusion completed subject should be premedicated with dexamethasone 10 mg IV, diphenhydramine 50 mg IV, and famotidine 20 mg IV (or per local standard) 30 minutes before paclitaxel infusion.

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

There will be a window of -5/+15 minutes for the administration of Nivolumab Ipilimumab, and Paclitaxel.

Subjects may be dosed no less than 19 days from the previous dose of Nivolumab.

- Ipilimumab may not be resumed sooner than 6 weeks (± 5days) after the prior ipilimumab dose.

Dosing calculations for all drugs should be based on the body weight assessed as per Study Calendar (Appendix D). All doses should be rounded to the nearest milligram. The dose may remain the same if the subject's weight is within 10% of the baseline weight or prior dose weight.

8.2. Nivolumab

Nivolumab 10mg/ml vials will be supplied by BMS packaged 5 vials per carton. Nivolumab injection is a clear to opalescent, colorless to pale yellow liquid, which may contain light (few) particles. 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, 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.

8.2.1. Storage and Handling

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

8.2.2. Administration

Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding (polyethersulfone membrane) in-line filter at the protocol-specified doses and infusion times. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL. During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

8.3. Ipilimumab

8.3.1. Recommended Storage and Use Conditions

Ipilimumab 5mg/ml vials will be supplied by BMS packaged 4 vials per carton. Ipilimumab injection (5 mg/mL) can be used for intravenous (IV) administration without dilution 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 8°C or room temperature/room light. Ipilimumab injection may be diluted in 0.9% Sodium Chloride Injection, United States Pharmacopeia (USP) or 5% Dextrose Injection, USP to concentrations between 1 and 4 mg/mL and stored 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. The product may be infused using a volumetric pump at the protocol-specific dose(s) and rate(s) through a PVC IV solution infusion set with an in-line, sterile, nonpyrogenic, low-protein-binding filter (pore size of 0.2 to 1.2 m). 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.

Ipilimumab injection, 50 mg/10 mL (5 mg/mL) or 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, USP 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.

Recommended safety measures for preparation and handling include protective clothing, gloves, and safety cabinets.

8.4. Paclitaxel

8.4.1. Storage and Handling

Paclitaxel is commercially available as a sterile solution concentrate, 6 mg/ml in 5 ml vials (30 mg/vial) in poluxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. Paclitaxel must be prepared in glass or polyolefin containers due to leaching of diethylexlphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized. Each bag/bottle should be prepared immediately before administration. Formulation of a small number of fibers in collation (within acceptable limits established by the USP Particulate Matter Test for LVP's) has been observed after preparation of paclitaxel. Therefore, in line filtration is necessary for administration of paclitaxel solution. In line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g., IVEX-II or IVEX-HP or equivalent) into the IV fluid pathway distal to the infusion pump. Although particulate formulation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used. The intact vials should be stored under refrigeration (2-8 °C). All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of Paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable for 24 hours.

Paclitaxel should be diluted in 250ml of 0.9% Sodium Chloride Injection, USP; 5% Dextrose Injection, USP; 5 % Dextrose and 0.9% Sodium Chloride Injection, USP: or 5% Dextrose in Ringer's Injection and infused over 1 hour. Paclitaxel will be administered via an infusion control device (pump) using non-PVC tubing and connectors, such as the IV administration sets (polyethylene or polyolefin) which

are used to infuse parenteral Nitroglycerin. Nothing else is to be infused through the line where paclitaxel is being administered. Medications for acute management of anaphylaxis should be readily available in the location where the patient is being treated.

Please see local prescribing information (package insert) for detailed instructions on the reconstitution, storage conditions and IV administration of paclitaxel.

8.5. Concomitant Medications/Vaccinations

Concomitant medications will be documented throughout the study. Medications specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The Investigator should discuss any questions regarding this with the Lead PI.

8.5.1. Acceptable Concomitant Medications

All treatments that the Investigator considers necessary for a subject's welfare may be administered at the discretion of the Investigator in keeping with the local standards of medical care. All concomitant medication received from the date of signed informed consent through 30 days after the last dose of study drug should be recorded on the CRF including all prescription, over-the-counter (OTC), herbal supplements, and IV medications.

8.5.2. Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Period of this study:

- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive non-pallative radiation therapy, or standard or investigational agents for treatment of NSCLC)
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Systemic immunosuppresive agents > equivalent dose of 2 mg decadron daily or equivalent.
- Other investigational agents
- Radiation therapy (Note: Radiation therapy to a symptomatic solitary lesion may be allowed with the approval of the Lead PI.)
- Live vaccines within 30 days prior to the first dose of study drug and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from a suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Lead PI. Condition requiring systemic treatment with corticosteroids (Prednisone less than or equal to 10mg daily or equivalent is allowable. Adrenal replacement

doses greater than 10mg daily prednisone equivalent are permitted in the absence of active autoimmune disease.

Subjects who, in the assessment by the Investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the Investigator deems to be medically necessary.

There are no prohibited therapies during the Follow-up Period.

9 Dose Modification and Toxicity Management

Subjects will be monitored continuously for AEs throughout the study and for 35 and 100 days after the last dose of study drug. Subjects will be instructed to notify their treating physician of any and all AEs. Toxicity will be graded according to NCI-CTCAE version 4.03.

All AEs should also be managed with supportive care at the earliest signs of toxicity considered related to study drug(s).

9.1. Dose Modifications

Subjects experiencing one or more AEs due to the study drug(s) may require dose modification(s) as described in this section. At the discretion of the Investigator, dose modifications are permitted outside of the those provided in the protocol if the Investigator feels it is in the interest of the subject's safety (e.g., due to multiple toxicities, persistent toxicities, intercurrent illness, or short term compliance or monitoring issues, etc.).

Subjects may need to be followed at least weekly when any study drug is held for toxicity until the toxicity returns to Grade ≤ 1 or is determined to be chronic or irreversible. Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 6 weeks of the scheduled interruption, unless otherwise discussed with the Lead PI. The time between doses should be as close as possible to the intended schedule, trying always to minimize the delay. The start of the dose delay count is from the first dose delayed, not the last dose given.

The reason for interruption should be documented in the patient's study record.

Dosing of all drugs should be delayed if any criteria for nivolumab and ipilimumab modifications or paclitaxel modifications are met. That is, nivolumab and or ipilimumab should be delayed if criteria for delay of paclitaxel are met, and paclitaxel should be delayed if criteria for delay of nivolumab and/or ipilimumab are met. Nivolumab, ipilimumab and paclitaxel must be administered together until paclitaxel treatment discontinuation (4-6 cycles). For subjects in which paclitaxel is discontinued before cycle 4 due to toxicity, subjects may continue to receive nivolumab and Ipilimumab.

Study drug cycles 1-6 while receiving Taxol with Ipilimumab and Nivolumab

a. C1-C6 do not skip cycles if a cycle is delayed. If a cycle is delayed, that same cycle will begin when subject meets protocol parameters to resume treatment,
b. C1, C3, C5. Ipilimumab is to be administered C1, C3, C5 only on these cycles during C1-C6 with Taxol. C7 and beyond, do not skip cycles. If a cycle is delayed, that same cycle will begin when subject meets protocol parameters to resume treatment.

All dose modifications and reasons for modification must be recorded in the CRF.

9.1.1. Nivolumab and Ipilimumab Dose Modifications

Recommendations for nivolumab and ipilimumab modifications are provided below. **The current dose modificationss are guidance. Defaulting to the ASCO and/or NCCN guidedlines is acceptable alternative after approval from PI. The reason for dose modification should be documented in patient's study record.**
There are no recommended dose modifications for hypothyroidism or hyperthyroidism. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions. There will be no dose escalations or reductions of the nivolumab or ipilimumab. Doses may be interrupted, delayed or discontinued. Discontinue nivolumab and/or ipilimumab in patients with severe or life-threatening infusion reactions. In circumstances where the ipilimumab is felt to be the primary cause of the toxicity, nivolumab may be restarted without ipilimumab.

Subjects should receive appropriate supportive care measures as deemed necessary by the Investigator. It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested supportive care measures for the management of adverse events are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care.

9.1.2. Pulmonary Adverse Events

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

- For **Grade 1 events**, consider delay of therapy. Monitor for symptoms every 2-3 days, consider pulmonary and ID consults. Re-image at least every 3 weeks.

- For recurrent **Grade 2 events**, delay therapy per protocol. Consider bronchoscopy, lung biopsy, and pulmonary and ID consults. Monitor symptoms daily, consider hospitalization. 1.0 mg/kg/day methylprednisolone IV or oral equivalent. Re-image every 1-3 days. If symptoms return to near baseline, taper steroids over at least 1 month and then resume therapy per protocol and consider prophylactic antibiotics.

- For **Grade 3-4 events**, discontinue therapy per protocol. Hospitalize, get pulmonary and ID consults. Give 2-4 mg/kg/day methylprednisolone IV or IV equivalent. Add prophylactic antibiotics for opportunistic infections. Consider bronchoscopy, lung biopsy. If symptoms return to baseline, taper steroids over at least 6 weeks. If not improving after 48 hours or worsening, 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.

9.1.3. GI Adverse Events

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

- For **Grade 1** diarrhea/colitis, continue therapy per protocol and administer symptomatic treatment. Monitor closely for worsening symptoms and educate patient to report worsening immediately.

- For **Grade 2** diarrhea/colitis, delay therapy per protocol and administer symptomatic treatment. If it improves to grade 1, resume therapy per protocol. If it persists > 5-7 days or recurs, give 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent. When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume therapy per protocol.

- For **Grade 3 or 4** diarrhea/colitis, discontinue therapy per protocol. Administer 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent. Add prophylactic antibiotics for opportunistic infections, consider lower endoscopy. If it improves, continue steroids until grade 1, then taper over at least 1 month. If it persists > 3-5 days or recurs after improvement, add infliximab 5 mg/kg (if no contraindication).

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.

9.1.4. Renal Adverse Events

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

- For **Grade 1** events, continue therapy per protocol, monitor creatinine weekly. If it returns to baseline, resume routine creatinine monitoring per protocol.

- For **Grade 2-3** events, delay therapy per protocol, and monitor creatinine every 2-3 days. Administer 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent. Consider a renal biopsy with nephrology consult. If it returns to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume therapy and routine creatinine monitoring per protocol.

- For **Grade 4** events, discontinue therapy per protocol, and monitor creatinine daily. Administer 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent. Consult a nephrologist and renal biopsy. If it returns to grade 1, 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 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.

9.1.5. Hepatic Adverse Events

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

- For **Grade 1** events, continue therapy per protocol, and continue LFT monitoring per protocol.

- For **Grade 2** events, delay therapy per protocol and increase frequency of monitoring to every 3 days. If symptoms return to baseline, resume routine monitoring and resume therapy per protocol. If elevations persist > 5-7 days or worsen, administer 0.5-1.0 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 therapy per protocol.

- For **Grade 3-4** events, discontinue therapy (may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN), and increase frequency of monitoring to every 1-2 days. Administer 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent (recommended starting dose for grade 4 hepatitis is 2 mg/kg/day IV). Add prophylactic antibiotics for opportunistic infections and consult a gastroenterologist. If symptoms return to grade 2, resume routine monitoring and resume therapy per protocol. If they do not improve in >3-5 days, worsen or rebound, add mycophenolate mofetil 1 g BID. 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.

9.1.6. Endocrinopathy Adverse Events

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

- For **Asymptomatic TSH Elevation,** continue therapy per protocol. If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements, include fT4 at subsequent cycles as clinically indicated; consider endocrinology consult.

- For **Symptomatic Endocrinopathy,** evaluate endocrine function and consider a pituitary scan. For subjects who are symptomatic with abnormal lab/pituitary scan, delay nivolumab therapy per protocol, administer 1-2 mg/kg/day methylprednisolone IV or PO equivalent, and initiate appropriate hormone therapy. If there are no abnormal labs or pituitary MRI scan, but symptoms persist, repeat labs in 1-3 weeks and repeat MRI in 1 month. If the symptoms improve with or without hormone replacement, taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections, and resume nivolumab therapy per protocol. Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component.

- **Suspicion of Adrenal Crisis** – delay or discontinue therapy per protocol and rule out sepsis. Administer stress dose of IV steroids with mineralocorticoid activity and IV fluids. Consult endocrinologist. If adrenal crisis is 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.

9.1.7. Skin Adverse Events

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

- For **Grade 1-2** events, continue nivolumab therapy per protocol and administer symptomatic therapy. If symptoms persist > 1-2 weeks or recur, consider a skin biopsy and delay therapy per protocol. Consider 0.5-1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper the steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume therapy per protocol.

- For **Grade 3-4** events, delay or discontinue therapy per protocol. Get a dermatology consult and consider a skin biopsy. Administer 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent. If signs improve to grade 1, taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections, and resume therapy per protocol.

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. If SJS/TEN is suspected, withhold therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue therapy.

9.1.8. Neurologic Adverse Events

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

- For **Grade 1** events, continue therapy per protocol. Continue to monitor the patient.

- For **Grade 2** events, delay therapy per protocol. Treat symptoms per local guidelines. Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent. If signs improve to baseline, resume therapy per protocol.

- For **Grade 3-4** events, discontinue therapy per protocol, and obtain neurology consult. Treat symptoms per local guidelines. Administer 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent and add prophylactic antibiotics for opportunistic infections. If signs improve to grade 2, taper steroids over at least 1 month. If they worsen, or atypical presentation, 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.

9.1.9. Infusion Reactions

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. Infusion reactions should be graded according to NCI CTCAE (Version 4.03) guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

For Grade 1 symptoms: (mild reaction; infusion interruption not indicated; intervention not indicated)

- Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphehhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab or ipilimumab administrations.

For Grade 2 symptoms: (moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours)

- Stop the nivolumab or ipilimumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab or ipililumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF).

- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000mg should be administered at least 30 minutes before nivolumab or ipililumab infusions. If necessary, corticosteroids (up to 25 mg of Solucortef or equivalent) may be used.

For Grade3 or 4 symptoms: (severe reaction, Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]. Grade 4: Life threatening; pressor or ventilator support indicated)

- Immediately discontinue infusion of nivolumab or ipililumab. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not

recur. Nivolumab or ipililumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

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

9.2 Treatment Beyond Progression

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.

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

- Investigator-assessed clinical benefit and no rapid disease progression
- Subject is tolerating study treatment
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g. CNS metastases)
- **Subject provides written informed consent prior to receiving additional nivolumab and or ipilimumab treatment using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options.**

The decision to continue treatment beyond initial investigator-assessed progression should be discussed and approved by the Lead PI and documented in the study records.

Treatment should be not be delayed > 6 weeks for intervention per protocol dose delay. If treatment is not able to resume within 6 weeks, treatment continuation should be discussed with Lead PI.

Tumor assessments are to continue on Q6 week schedule during treatment beyond progression.
A radiographic assessment/scan should be performed within 6 weeks of initial investigator-assessed progression to determine whether there has been a decrease in the tumor size or continued progressive disease unless > 6 weeks approved by Lead PI.
If subject is on Q12 week schedule when progresses (after 48 weeks), restaging schedule returns to Q6 week schedule. **If pts have had stable findings for 2 scans after TBP, then interval can be lengthened to Q12weeks per treating provider discretion.**

For subjects who continue study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden with a minimum 5 mm absolute increase from time of initial progressive disease.from the 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/or ipililumab 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 10mm (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.

9.3 Criteria to resume nivolumab

Participants may resume treatment with nivolumab when the drug-related AE(s) resolve(s) to Grade ≤ 1 or baseline, with the following exceptions:

- Participants may resume treatment in the presence of Grade 2 fatigue.
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Participants with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin.
- Participants with combined Grade 2 AST/ALT and total bilirubin values meeting discontinuation parameters (Section 9.1.5) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the ~~BMS Medical Monitor.~~ Lead PI.
- Participants who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≤ 10 mg/day.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.

- Participants who delay study treatment due to any Grade ≥ 3 amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis, and that is assessed by the investigator to be related to ipilimumab and not to nivolumab, may resume nivolumab when the amylase or lipase abnormality has resolved to Grade < 3.
  - If Nivolumab is delayed for > 6 weeks, Nivolumab will be discontinued.

9.4 Criteria to resume ipilimumab

Participants may resume treatment with nivolumab and ipilimumab when drug-related AE(s) resolve(s) to Grade 1 or baseline value, with the following exceptions:

- Participants may resume treatment in the presence of Grade 2 fatigue.
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.

- Participants with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT or total bilirubin.
- Participants with combined Grade 2 AST/ALT and total bilirubin values meeting discontinuation parameters (Section 7.7) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed.
- Participants who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≤ 10 mg/day.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the Lead PI.
- Dose delay of ipilimumab which results in no ipilimumab dosing for > 12 weeks requires ipilimumab discontinuation, with exceptions as noted in Section 9.1.
- Ipilimumab may not be resumed sooner than 6 weeks (± 5days) after the prior ipilimumab dose.
- In general, participants who meet criteria to resume ipilimumab will also have met criteria to resume nivolumab, so it should be feasible to synchronize dosing of both drugs when resuming ipilimumab. In order to facilitate this, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted ± 5 day window, as long as consecutive nivolumab doses are given at least 19 days apart.

  One exception to note is when ipilimumab and nivolumab doses are delayed due to drug-related Grade ≥ 3 amylase or lipase abnormalities not associated with symptoms or clinical manifestations of pancreatitis. If the investigator assesses the Grade ≥ 3 amylase or lipase abnormality to be related to ipilimumab and not related to nivolumab, nivolumab may be resumed when the amylase or lipase abnormality resolves to Grade < 3 but ipilimumab may only be resumed when the amylase or lipase abnormality resolves to Grade 1 or baseline. Investigator attribution of this toxicity to the ipilimumab dosing must be clearly noted in the participant's medical chart.

9.5 Paclitaxel Dose Modifications

If multiple adverse events are seen, administer dose modification based on greatest reduction required for any single adverse event observed. Reductions apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

Paclitaxel will not be re-escalated once reduced. If more than 2 dose reductions for paclitaxel are required, paclitaxel will be discontinued.

Dose Level	Drug Name	Dose
0	Paclitaxel	80 mg/m2
-1	Paclitaxel	60 mg/m2

-2	Paclitaxel	40 mg/m2

In the event of severe reaction necessitating discontinuation of paclitaxel, the patient may remain in the clinical trial and continue to receive both nivolumab and ipilimumab.

9.5.1 Hematologic Adverse Event

Paclitaxel dose guidelines for Day 1 hematologic adverse events

For ANC < 1500 or platelets < 100,000 on Day 1, delay treatment and repeat CBC weekly. Resume treatment when ANC improves to ≥ 1500 platelets improve to ≥ 100,000.

- If treatment was delayed for 1 week, resume treatment at the previous doses of paclitaxel.
- If treatment was delayed for more than one week and less than six weeks, reduce paclitaxel by one dose level for this and all subsequent cycles.

For delays of 6 weeks or greater, discontinue paclitaxel for this and all subsequent doses.

Paclitaxel dose modifications for Day 8 hematologic adverse event

For ANC 500-999 or platelets 50,000 – 74,999, decrease paclitaxel by one dose level for this and all subsequent doses.

For ANC < 500 or platelets < 50,000, skip paclitaxel and decrease paclitaxel by one dose level for all subsequent doses.

9.5.2 Febrile neutropenia

For febrile neutropenia (defined as temperature ≥ 38.5° C [101° F] sustained for more than one hour concomitant with ANC < 500/mm3), reduce paclitaxel by one dose level for this and subsequent cycles.

9.5.3 Gastrointesinal Adverse Event
Paclitaxel dose modifications for gastrointestinal adverse event
For grade 3 or 4 nausea or vomiting despite maximal antiemetic therapy (including 5HT-3 antagonist, corticosterious, and aprepitant), discontinue Paclitaxel.
If the gastrointestinal adverse event is not consistent with autoimmune inflammatory bowel syndrome, continue nivolumab at the previous dose when symptoms resolve to ≤ grade 1.

9.5.3 Neurotoxicity

For grade 3 sensory or motor neuropathy, skip Paclitaxel until the adverse event

resolves to ≤ grade 1 and then resume therapy with one dose level reduction of paclitaxel on Day 1 of the next scheduled cycle. If paclitaxel is skipped for two Consecutive cycles, discontinue paclitaxel. Treatment with nivolumab may continue. For grade 4 sensory or motor neuropathy, skip all therapy until resolution to ≤ grade 2, discontinue paclitaxel; resume nivolumab at the previous dose.

9.5.4 Cardiotoxicity

Cardiotoxicity may include events of cardiac disorders, myocardial disorders, cardiac failure, angina, tachycardia, bradyarrhythmias, or ventricular arrhythmias. In clinical studies, the frequency of cardiotoxicity was 4% for paclitaxel in monotherapy studies/indications; and was reported in 6% for paclitaxel in combination with gemcitabine.

Cardiac events are not uncommon in the indicated population, especially those who have previously received anthracyclines or have underlying cardiac or pulmonary disease. Therefore, patients receiving paclitaxel should be vigilantly monitored for the occurrence of cardiac events.

9.5.5 Paclitaxel Hypersensitivity and/or Infusion Reactions

Paclitaxel can rarely induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms of allergic-like reactions.

All **Grade 3 or 4** infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE Version 4.0 guidelines. Treatment recommendations are provided below and may be modified based on local Treatment standards and guidelines as appropriate:

For **Grade 1** symptoms: Mild reaction; infusion interruption not indicated; intervention not indicated. Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional paclitaxel administrations.

For **Grade 2** symptoms: Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g. antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for 24 hours.

Stop the paclitaxel infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes,

the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further paclitaxel will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional paclitaxel administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For **Grade 3 or Grade 4** symptoms: (Severe reaction, Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelac [e.g., renal impairment, pulmonary infiltrates]). Grade 4: (life threatening; pressor or ventilatory support indicated).

Immediately discontinue infusion of paclitaxel. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1: 1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1: 10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur.

Paclitaxel will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine or corticosteroids).

10 CORRELATIVES

Tissue and blood based biomarker studies will be performed to better understand the role of factors that may be associated with efficacy or toxicity from study treatment and/or cancer biology. Additional markers related to efficacy, toxicity, and/or cancer biology may be analyzed. Anticipated analyses are listed below and focus on factors associated with angiogenesis, inflammation, immunity, and tumor growth. However, final analytic lists and technology platforms will be based upon best science and available funding at the time of analysis.

10.1 Tumor Tissue Biomarkers

Archived formalin fixed paraffin embedded (FFPE) tumor samples may be used to perform pre-treatment analyses. Tumor samples will be tested by IHC for CD8 and PDL1 staining, the primary biomarker endpoints for this study. Expression of additional proteins that may be associated with sensitivity or resistance to nivolumab and ipilimumab including but not limited to, TGFβ1, BMPs, and various immune cell populations, including CD3, CD4, CD8, Treg, (FoxP3), Th17 T-cells and monocyte/macrophage and neutrophil populations. PCR may also be performed for analyses of factors that may be associated with sensitivity or

resistance to these agents including but not limited to CD3, CD4, CD8, EOMES, IFNγ, FOXP-3, Granzyme-A, Granzyme-B, Perforin, IL1β, IL6, IL7, IL10, IL11, IL12, IL17A, IL17E, IL22, and IL23.

Genetic alterations, including both gene mutation and copy number alteration, may be characterized using a customized Next Gen Sequencing platform. Samples evaluated will be archived FFPE tumor samples.

10.2 Circulating Immune Cells (PBMC)

Polychromatic flow cytometry (PFC) panels will be used to assess the following circulating immune cell subsets in patient samples collected at three times points, including at baseline, after 6 weeks of combination therapy (first restaging) and at time of progression. Examples of the multiparameter panels to identify immune cell types and related markers are listed in Table 8.2, and include lymphoid markers focused on T-cell activation, maturation, regulation, and exhaustion, regulatory T cells, and myeloid derived dendritic cells (MDSC). The markers included in each respective panel have been reported to be of value in the context of prognostic or predictive immune markers in cancer studies[30-33]. Additional markers for each panel will be included to allow for panel refinement based on best scientific evidence at the time of funding. Data will be analyzed using novel computational methods developed at Duke that can be used to identify multi-dimensional populations and evaluate changes in these populations across treatment[34,35]. Refer to *Study Manual* for collection and submission details.

PBMCs will be processed and stored by the Duke Immune Profiling Core facility under the direction of Dr. Kent Weinhold. Polychromatic flow cytometry (PFC) panels will be used to assess the following circulating immune cell subsets in patient samples. Examples of the multiparameter panels to identify immune cell types and related markers are listed in Table 2, and include lymphoid markers focused on T-cell activation, maturation, regulation, and exhaustion, regulatory T cells, and myeloid derived dendritic cells (MDSC). The markers included in each respective panel have been reported to be of value in the context of prognostic or predictive immune markers in cancer studies. Additional markers for each panel will be included to allow for panel refinements based on best scientific evidence at the time of funding. Data will be analyzed using novel computational methods developed at Duke that can be used to identify multi-dimensional populations and evaluate changes in these populations across treatment.

Table Expanded FACS panels for flow based analysis of circulating immune cell subpopulations

	Marker	Stain	Purpose	Clone	Fluorophore
Tumor Reactive T cells (13c)	**amine**	**Surface**	**Dead cell exclusion**	***na***	**near IR**
	CD3	**Intracellular**	**T- cells**	***SK7***	**PerCP-Cy5.5**
	CD4	**Intracellular**	**CD4+ (helper) T cells**	***SK3***	**BUV737**
	CD8	**Intracellular**	**CD8+ (cytotoxic) T cells**	***SK1***	**BV510**
	Lag3 (CD223)	Surface	Exhaustion	*Polyclonal*	BV711
	CD38	Surface	Activation	HB7	BUV395
	CCR7 (CD197)	Surface	Maturation	*150503*	PE-CF594
	CD45RA	Surface	Maturation	HI100	FITC
	TIM3	Surface	Regulation	344823	*BV421*
	PD1 (CD279)	Surface	Exhaustion	*MIH4*	PE
	CTLA4 (CD152)	**Intracellular**	**Regulation**	**BNI3**	**BV786**
	Ki67	**Intracellular**	**Proliferation**	**B56**	**APC**
	ICOS (CD278)	Surface	Co-stimulation	**DX29**	**BV650**
Treg & MDSC (12c)	**amine**	**Surface**	**Dead cell exclusion**	***na***	**near IR**
	CD3	**Intracellular**	**T- cells**	***SK7***	**PerCP-Cy5.5**
	CD4	**Intracellular**	**CD4+ (helper) T cells**	***SK3***	**BUV737**
	CD8	**Intracellular**	**CD8+ (cytotoxic) T cells**	***SK1***	**BV510**
	CD16	Surface	Lineage exclusion channel	NKP15	PE-Cy7
	CD19			SJ25C1	
	CD20			L27 or 2H7 or H1	
	CD56			NCAM16.2 or B159	
	CD25	Surface	Tregs	M-A251 or 3G10	(3G10) FITC
	CD127	Surface	Tregs	HIL-7R-M21	BV421
	Ki67	**Surface**	**T-regs**	**B56**	**APC**
	CTLA4 (CD152)	**Intracellular**	**Regulation**	**BNI3**	**BV786**
	FoxP3	Intranuclear	Tregs	*PCH101*	PE
	CD14	Surface	MDSC's	M5E2	BV570
	HLA-DR	Surface	MDSC's	G46-6	BUV395
ICS Panel	**amine**	**Surface**	**Dead cell exclusion**	***na***	**near IR**
	CD3	**Intracellular**	**T- cells**	***SK7***	**PerCP-Cy5.5**
	CD4	**Intracellular**	**CD4+ (helper) T cells**	***SK3***	**BUV737**
	CD8	**Intracellular**	**CD8+ (cytotoxic) T cells**	***SK1***	**BV510**
	CD69	Surface	Activation	FN50	BV711
	IFN-g	Intracellular	Function (Ag specific)	B27	FITC
	IL-2	Intracellular	Function (Ag specific)	5344.111	PE
	TNFa	Intracellular	Function (Ag specific)	MAb11	APC
	CD107a	*Intracellular	Function (Ag specific)	H4A3	BV421
Key:	*CD107a is added at the time of stimulation				
	Fixed clones				

All immune cell correlates will be performed in collaboration with the Duke Immune Profiling Core (DIPC) laboratory. This will include studies requiring the analysis of immunological reactivity *in vivo* and immune response *in vitro*. Cells to be used in flow-based assays will be obtained from individual patient acid citrate dextrose anti-coagulated fresh whole blood that have been processed to isolate PBMC, cryopreserved, and stored in LN2 freezers for batch processing. Cell thawing and overnight resting will be performed for all flow cytometry assays according to standardized and optimized procedures (SOPs). After the overnight rest, cells will be counted, assessed for viability and recover, and then aliquoted for flow cytometry assays. Flow cytometry assays will be performed following SOPs. For efficiency and to minimize assay variability, all

visits from a single patient will be assayed in the same batch. To assess variability across assays, cells from a normal donor (drawn, processed and cryopreserved from a single visit), will be used as a control across all assay batches.

10.3 Circulating Protein Analysis

Plasma and serum samples will be obtained from subjects at baseline, 6 weeks of combination therapy, (first restaging), and at the time of progression Samples will be stored at -80°C until analyzed. Under the direction of Dr. Andrew Nixon, the Duke Phase I Biomarker Laboratory has developed a multiplex ELISA approach to analyze over 25 tumor angiogenesis and tumor growth factors in less than 0.5 ml of plasma. Coefficients of variation for most analytes are <20%. This platform has been successfully applied to several in-house phase I and II studies as well as several phase III, Alliance-conducted studies with bevacizumab in colorectal and other cancers. Markers of inflammation will be analyzed in the Duke Phase I Biomarker Laboratory, which serves as a core lab for these analyses for the US Cooperative Group Alliance. Analyses will be performed on pre-treatment and on-treatment samples. Analyte levels, and changes in analyte levels, will be correlated with clinical outcome (PFS, OS). Plasma and serum samples may be evaluated for protein markers that may be associated with sensitivity or resistance to these agents. These may include but are not limited to IFNγ, IL1β, IL6, sILR6R, sGP130, IL4, IL7, IL10, IL11, IL12, IL17A, IL17E, IL22, and IL23.

10.4 Intracytoplasmic Cytokine Analysis

The Intra-Cellular Staining (ICS) assay is the only assay capable of simultaneously determining the type of cytokine(s) produced by a single cell, the phenotype of each respective cytokine-producing cell, and the breadth or profile of the functional responses. The breadth of the functional response is defined by the number of functional markers produced simultaneously, for example IFNγ, IL-2+TNFα+CD107+Perforin+. The degree of polyfunctionality, or ability to perform multiple functions simultaneously, is critical for mediating effective immune responses[36]. Polyfunctional T cells have been associated with favorable immune responses in the context of vaccination[37-39] and infection[40-42]. More recently, polyfunctional responses have been associated with favorable outcomes in the context of cancer immunology. Jianda et al reported that CTLA-4 blockade with ipilimumab resulted increased polyfunctional NY-ESO-1 specific T cell responses and correlated polyfunctional cells with clinical benefit in melanoma patients[43]. Ding et al demonstrated the importance of polyfunctional cells for eradicating advanced B-cell lymphoma[44], Imai et al described how polyfunctional T cells might be inhibited by tumor progression[45].

We propose to utilize the ICS assay to stimulate production of cytokines IFN-α, IL-2, TNF-α and degranulation markers (CD107a (LAMP-1) and Perforin) in $CD4^+$ and $CD8^+$ T-cells (Table 2). These cells will be thawed, rested overnight, and activated *ex vivo* in the presence of protein transport inhibitors (PTI). PTIs are required to block secretion and accumulate sufficient cytokines and degranulation markers within the cell to be measured by flow cytometry. The specific *ex vivo* stimuli that will be used in the ICS assay will vary by tumor type and will be based on further optimization and the best science at the time of the program. Potential tumor associated antigens (TAAs) being considered for use as stimuli in the ICS assay include CEA for metastatic gastric cancer and colorectal cancer (CRC), and Alpha-Feto Protein (AFP) for hepatocellular carcinoma (HCC). MAGE3 and p53 are also being considered for use across malignancies. Final determination of optimal TAAs for each tumor type will be made at time of funding based on the best scientific evidence available. Control stimulations will include anti-CD3 + anti-CD28, as a positive control, and no specific antigen will be used as a background measure of endogenous production of cytokines and

degranulation markers. A minimum of 6 hours stimulation will be required for detection of cytokines since cytokine levels are typically too low in resting cells. After stimulation, cells will be stained for surface antigens, fixed to stabilize the cell membrane, permeabilized to allow anti-cytokine antibodies to stain intracellularly, and acquired within 6 hours of staining.

10.5 Future Use of Patient Samples

Any remaining biological materials at the end of the study will be de-identified, these de-identified samples may be retained for possible use in biomarker research with the consent of the patient.

11 STATISTICAL ANALYSIS

11.1 General Analysis Considerations

This is a single arm phase II clinical trial of combination nivolumab (Opdivo), ipilimumab (Yervoy), and paclitaxel (Taxol) in patients with untreated metastatic non-small cell lung cancer (NSCLC). The primary objective of the study is to determine whether the combination regimens will improve progression-free survival (PFS) relative to historical control, The PFS is measured from the date of registration to the date of progression or death from any cause, whichever comes first.

The median PFS (mPFS) for untreated stage IV NSCLC patients treated with nivolumab and ipilimumab were reported to be 4 months. If the combination of nivolumab (Opdivo), ipilimumab (Yervoy), and paclitaxel (Taxol) can improve the median PFS r to 9 months or more, then we conclude that the combination regimens are of interest for further investigation. On the other hand, if median PFS is less than 6 months, then we conclude that the combination regimens are not worthy of further investigation. The hypothesis which is being tested is:

$$H0: mPFS \leq 6 \text{ month versus } H1: mPFS \geq 9 \text{ months},$$

Where mPFS is the true median PFS for the combination regimen. Using one-sided one-sample log-rank test at a significant level of 0.1, the study with 46 subjects has approximately 85% power to test the alternative hypothesis. The sample size calculation is based on the following assumptions: 1) it will take 12 months to accrue 46 subjects on the evenly pace, that is, the average accrual rate is 3.5 patients per month; 2) the follow-up time after the last enrollment is 12 months. Taking 5% of ineligibility or dropout into consideration, 49 patients will be enrolled in the multicenter.

The product limit estimator developed by Kaplan and Meier will be used to graphically describe PFS. From these product limit estimates, the median PFS and the rate of PFS at 6 months will be estimated. The proportion of patients who respond (completely or partially) to the combination regimen will be estimated and exact binomial confidence intervals will be computed for the estimate. One-sample log rank test [ref2] will be used to compare survival of the combination regimen against that of similar population treated with nivolumab and ipilimumab.

The toxicity associated with the treatment regimen will be summarized. For each type of toxicity, a patient's worst treatment-related toxic episode will be used to summarize distribution of toxicity grade experienced.

Given the limited sample size, all biomarker analyses will be considered exploratory. For analysis of the immune monitoring data from the 2 polychromatic flow cytometry panels, we will perform initial analysis using statistical graphics (e.g. box-plots) of the cell subset relative frequencies and trend over time. To assess the impact of cell subsets of interest (listed above) at baseline and on-treatment and on treatment outcome, we will perform a Kruskal–Wallis one-way ANOVA with cell subset relative frequency as dependent variable and the RECIST 1.1 response categories as independent factors to identify the cell subsets whose unadjusted p-values are statistically significant. Given the exploratory aim of research, no correction for the number of independent variables will be performed, and a ranked list of cell subsets with uncorrected p-values will be tabulated. This list will be used for hypothesis generation, and to select candidates for independent validation studies. To evaluate the multivariate contributions of the candidate biomarkers, we will perform step-wise Cox regression against survival time using the adjusted R-squared value to evaluate goodness-of-fit. Potential demographic confounders will be evaluated in the regression model as appropriate.

11.1.1 Endpoints

Objectives	Endpoints
<u>Primary Objective</u> 1. To estimate the progression free survival for the combination nivolumab, ipilimumab, and paclitaxel in untreated, metastatic NSCLC	• Progression-free survival (PFS) defined as the time from first dosing date to the date of the first documented tumor progression, as determined by investigators (per RECIST v1.1), or death due to any cause, whichever occurs first. PFS is measured from the start date of protocol treatment to the date of progression or death, whichever comes first. A patient will be censored if he/she is terminated from the study earlier, such as withdrawn/lost to follow-up, or is alive when the final analysis is being conducted.
<u>Secondary Objectives</u> 1. To describe the safety and adverse events of combination nivolumab, ipilimumab, and paclitaxel in untreated, metastatic NSCLC. 2. To estimate the overall response rate with the study combination.	• The study will assess the number and percentage of participants who experience high grade (Grade 3-4 and Grade 5) treatment-related select and immune-mediated adverse events. The select adverse events of interest are the following: pneumonitis, interstitial nephritis, diarrhea/colitis, hepatitis, rash, endocrinopathies, and hypersensitivity/infusion reaction events. • Objective Response Rate (ORR) defined as the number and percentage of participants with a best overall response (BOR) of confirmed complete response (CR) or partial response (PR). Best overall response (BOR) is defined as the best response designation, recorded between the date of first dose and the date of the initial objectively documented tumor progression per RECIST v1.1

	or the date of subsequent therapy, whichever occurs first.
Exploratory Objectives 1. To explore correlation between baseline and treatment related changes in immune correlates and clinical outcome.	• Tumor and peripheral blood specimens will be collected for future exploratory multiplex flow cytometric analysis and ELISA based testing.

12 SAFETY MONITORING AND REPORTING

Refer to *Study Manual* for required reporting forms.

The PI is responsible for the identification and documentation of adverse events and serious adverse events as defined below. At each study visit, the PI or designee must assess, through non-suggestive inquiries of the subject or evaluation of study assessments, whether an AE or SAE has occurred.

12.1 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the supporting company product(s), is also an AE.

AEs may occur during the course of the use of supporting company product(s) in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Progression of the cancer under study is not considered an AE unless it is considered to be drug related by the Investigator.

AEs will be documented from the date of first dose of study drug through 30 days after the last dose of study drug. All Grade 2-5 AEs as well as special reporting circumstances, such as exposure via a parent during pregnancy or breast-feeding, overdose, medication error, misuse, abuse, off-label use or occupational exposure must be recorded on the CRF.

AEs will be assessed according to the CTCAE version 4.03. If CTCAE grading does not exist for an AE, the severity of the AE will be graded as mild (1), moderate (2), severe (3), life-threatening (4), or fatal (5).

Attribution of AEs will be indicated as follows:

- Definite: The AE is clearly related to the study drug
- Probably: The AE is likely related to the study drug
- Possible: The AE may be related to the study drug
- Unlikely: The AE is doubtfully related to the study drug
- Unrelated: The AE is clearly NOT related to the study drug

12.2 Reporting Adverse Events

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 also be reported in routine study data submissions.

Abnormal laboratory results are to be records as AEs if any of the following conditions are met:

- The abnormal laboratory value leads to a therapeutic intervention (e.g., corrective therapy).
- The abnormal laboratory value is considered to be clinically significant by the Investigator.
- Any lab test result that is clinically significant or meets the definition of an SAE.
- Any laboratory test result abnormality that required the subject to have study treatment discontinued or interrupted

12.3 Serious Adverse Events

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

1) Results in death.2) Is immediately life-threatening (i.e., in the opinion of the Investigator, the AE places the subject at immediate risk of death; it does not include a reaction that, had it occurred in a more severe form, might have caused death).

1) 3) Requires inpatient hospitalization or results in prolongation of an existing hospitalization. Hospitalizations do not include:

   a) Preplanned (prior to the study) hospital admissions unless the hospitalization is prolonged
   b) Planned admissions (as part of a study – e.g., routine biopsies).
   c) 23-hour re-hospitalizations
   d) Hospitalization for elective procedures or procedures unrelated to study treatment
   e) Emergency room visits unless considered life threatening event. See SAE definition #2.

4) Results in persistent or significant disability or incapacity. (Note: The term "disability" refers to events that result in a substantial disruption of a subject's ability to conduct normal life function.)

5) Is a congenital anomaly or birth defect.

6) Is an important medical event (Note: The term "important medical event" refers to an event that, based upon appropriate medical judgment, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require intervention to prevent one of the other serious outcomes listed under the definition of SAE. Examples of important medical events include intensive

treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of product dependency or product abuse.)

SAEs and/or follow up to SAEs including death due to any cause other than progression of the cancer under study, that occurs from the date of the first dose of study drug through 100 days following the last dose of study drug, whether or not related to study drug(s), must be recorded on the CRF and must be reported within 24 hours of learning of the event to Thoracic-multisite coordinator and Thoracic regulatory coordinator and within 2 working days to supporting companies.

For Duke, complete the DCI SAE Report form for Investigator Initiated Trials which can be found on the Duke Cancer Institute Intranet. Submit form to at thoracic-multisite@dm.duke.edu and thoracic-regulatory-multisite@dm.duke.edu within 24 hours of learning of event.

Participating sites will complete the DCI SAE Report Form for Investigator-Initiated Trials (pages 1-4) and submit to Thoracic-multisite@dm.duke.edu and thoracic-regulatory-multisite@dm.duke.edu within 24 hours of learning of event.

All SAEs must be followed until resolution, return to baseline condition, or deemed unresolveable. Any SAEs that are ongoing at the time the clinical database is locked will be reported to supporting companies as unresolved.

The initial report for each SAE or death should include at minimum the following information:

- **protocol number and title**
- **patient initials, study identification number, sex, age**
- **date the event occurred**
- **description of the event**
- **seriousness criteria**
- **event causality or causal relationship**
- **study drug name(s)**
- **dose level and cycle number at the time the event occurred**
- **description of the patient's condition**
- **study status of patient at time of report**
- **responsible investigator name and contact details**

The Investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The Investigator should separate a primary AE considered as the foremost untoward medical occurrence from secondary AEs which occurred as complications. Whenever possible, the Investigator should also provide the batch or lot number of the study drug(s).

De-identified source documentation (i.e. admission notes, discharge summary, applicable laboratory results, radiology/diagnostic testing results, etc.) must be sent with the SAE Report Form.

Follow-up information should be communicated to Duke as soon as possible.

SAE Reporting Procedure for Principal Investigator and Thoracic multisite team:

The Principal Investigator will review the report form with accompanying source documents and complete page 5 of the SAE Report Form, the Principal/Medical Monitor Review Assessment.

If the event meets the Duke University Health System (DUHS) IRB reporting requirements, the Thoracic regulatory coordinator will submit information about the SAE including the Lead PI's assessment as a safety event to the DUHS IRB.

Within-24 hours of receipt, the Thoracic multisite coordinator will submit the SAE report form and other relevant safety information to the following supporting companies:

BMS Worldwide Safety
Email: worldwide.safety@BMS.com
Fax: 1-609-818-3804

Expedited Reporting Procedure for Duke Cancer Institute (Coordinating Center):

Duke Cancer Institute as the coordinating center for this study is responsible for reporting SAEs to the FDA in accordance with 21CFR 312.32. Any SAE that is possibly related and unexpected must be submitted to the FDA attached to the IND. If the SAE meets criteria for reporting to the FDA, the Thoracic multisite coordinator will complete the Form FDA 3500A (MedWatch) and send to the Lead PI and supporting companies. The Thoracic multisite team will forward FDA 3500A MedWatch form to FDA and the supporting companies that are noted above. This submission of the Form FDA 3500A to the FDA attached to the IND will be completed by the Duke Thoracic Oncology Clinical Trials Regulatory Coordinator.

1. **All unexpected, drug related SAEs that are fatal or life-threatening will be reported to the FDA by phone or fax within 7 calendar days of initial receipt of the information and will provide a complete report within 8 days of the initial report submission (by calendar day 15).**
2. **All unexpected, treatment-related SAEs that are not fatal or life-threatening will be reported in a written report to the FDA within 15 days of initial receipt of the information.**

Our Thoracic regulatory team will forward all expedited reports to all participating investigators in the form of an Investigator Alert.

12.4 Events of Clinical Interest

Select (non-serious and serious) adverse events called Events of Clinical Interest (ECI) that occur from the date of the first dose of study drug through 30 days following the last dose of study drug, must be recorded on the CRF and must be reported within 24 hours to the Thoracic-multisite coordinator and thoracic regulatory coordinator and within 2 working days to BMS using the DCI SAE Report Form for Investigator-Initiated Trials.
Participating sites will complete the DCI SAE Report Form for Investigator-Initiated Trials (pages 1-4) and submit to Thoracic-multisite@dm.duke.edu

Pregnancy, overdose, potential drug-induced liver injury and cancer are ECIs for this study and must be handled as SAEs

ECI Reporting Procedure Lead PI and Thoracic multisite team:

The Lead PI will review the SAE report form with accompanying source document(s), complete page 5 of the SAE Report Form, Principal/Medical Monitor Review Assessment .

Within 2 business days of receipt, the Thoracic multisite coordinator will submit the SAE report form and other relevant safety information to the following supporting company:

BMS Worldwide Safety
Email: worldwide.safety@BMS.com
Fax: 1-609-818-3804

12.5 Other Safety Considerations

The Investigator must also report in the same timelines as SAEs any incidence of medication error, occupational exposure, abuse or misuse that is associated with or result in an adverse event. All related fatal outcomes must also be reported in the same timeline as a SAE.

Refer to SAE reporting procedures in Section 13.

12.5.1 Pregnancy and Lactation

Although pregnancy and lactation are not considered adverse events, it is the responsibility of Investigator or designee to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 90 days of cessation of treatment. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (important medical events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported in the same procedure as an SAE. Refer to SAE reporting procedures in Section 13.

12.5.2 Medication Overdose and Error

No specific information is available on the treatment of overdose of either nivolumab or ipilimumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Monitoring should be based upon good medical judgment, taking into account the level of overdose, evolving toxicities, and other relevant medical and social factors specific to the patient. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of study drug(s), the adverse event(s) is reported as a SAE, even if no other seriousness criteria are met. Refer to SAE reporting procedures in Section 13.

13 ADMINISTRATIVE RESPONSIBILITIES

13.1 Institutional Review Board/Independent Ethics Committee

Before study initiation, the Investigator must have written and dated approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects.

The Investigator should provide the IRB/IEC with reports, updates, and other information (e.g., Safety Updates, Amendment IRB/IECs, and Administrative Letters) according to regulatory requirements and institution procedures.

Copies of all IRB/IEC approvals, as well as annual re-approvals and approved/stamped informed consent forms must be submitted to Duke Thoracic Oncology Clinical Trials Office.

13.2 Protocol and Protocol Revisions

All revisions to the protocol will be provided to the supporting companies by the Lead PI or designee(s) at the Duke Thoracic Oncology Clinical Trials Office. The Lead PI must have written and dated approval/favorable opinion from the Duke University Health System (DUHS) IRB of revised protocol.

Investigators must obtain written and dated and approval/favorable opinion from the IRB/IEC before conducting any updated protocol version. Study must be conducted as described in the approved protocol. The Investigator must not implement changes of the approved protocol without prior written agreement by the Lead PI and prior review and documented approval/favorable agreement by the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the changes involve only logistical or administrative aspects of the study (e.g., changes in research personnel or change in phone numbers).

Documentation of approval(s) from the IRB/IEC must be sent to Duke Thoracic Oncology Clinical Trials Office.

13.3 Protocol Deviations and Violations

A protocol deviation is non-adherence to protocol specific study procedures or schedules that does not involve inclusion/exclusion criteria, primary objective evaluation criteria, and/or Good Clinical Practice (GCP) guidelines.
A protocol violation is any significant divergence from the protocol such as non-adherence on the part of the subject, the Investigator, or the sponsor to protocol specific inclusion/exclusion criteria, primary objective evaluation criteria, and/or GCP guidelines.

As a matter of policy, the Lead PI (i.e. sponsor) will not grant exceptions to protocol specific entry criteria to allow subjects to enter a study. If it is found that a subject who did not meet protocol eligibility criteria was entered in a study (a protocol violation), the Lead PI and/or designee(s) at the Duke Thoracic Oncology Clinical Trials Office must be informed immediately. Such subjects will be discontinued from the study, except in an exceptional instance following review and written approval by the Lead PI and the responsible IRB/IEC.

Protocol deviations and violations must be documented and reported to the Lead PI and/or designee(s) at the Duke Thoracic Oncology Clinical Trials Office.

In accordance with applicable regulations, Investigators must report protocol deviations and violations to their local IRB/IEC according to their institutional guidelines.

13.4 Informed Consent

The Investigator must ensure that subjects or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and their IRB. A copy of the proposed informed consent document must be submitted to the Lead PI or designee(s) at the Duke Thoracic Oncology Clinical Trials Office for review and comment prior to submission to the local IRB/IEC.

Informed consent must be obtained prior to performing any study-related procedures that are not part of normal subject care, including screening and changes in medications. A copy of the signed informed consent form must be given to the study subject.

13.5 Source and Study Documentation

Source documents include all original recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. Accordingly, source documents include, but are not limited to, laboratory reports (including normal and abnormal results), radiology reports, subject diaries, biopsy reports, ultrasound photographs, subject progress notes, hospital charts or pharmacy records and any other similar reports or records of any procedure performed in accordance with the protocol.

Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original certified document.

When clinical observations are entered directly into an electronic medical record system (i.e. in lieu of original hardcopy records), the electronic record can serve as the source document if the system has must be validated to meet the FDA requirements for electronic records and signatures (i.e. meets 21 CFR Part 11 compliant).

Regulations require that Investigators maintain information in the study subject's medical records which corroborate data recorded on the CRF. In order to comply with these regulatory requirements, the following information will be maintained and made available as required by the Lead PI or designee(s), monitors, and/or regulatory inspectors:

- Medical history/physical condition of the study subject prior to involvement in the study sufficient to verify protocol entry criteria.
- Dated note that informed consent was obtained for the subject's participation in the study.
- Dated and signed notes for each subject visit including results of examinations.
- Notations on abnormal lab results and their resolution.
- Dated reports of special assessments (e.g., ECG reports).
- Dated and signed notes regarding adverse events (including event description, severity, onset date, duration, relation to study treatment, outcome, and treatment for adverse event).
- Dated notes regarding concomitant medications taken during the study (including start and stop dates).
- Subject condition upon completion of or withdrawal from the study.

Study documentation includes all CRFs, data correction forms, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence and regulatory documents (e.g., protocol and amendments, IRB/IEC correspondence and approvals, approved and signed subject consent forms, Statement of Investigator form, and clinical study supplies receipts and distribution records).

The Investigator will prepare and maintain complete and accurate study documentation in compliance with GCP guidelines and applicable federal, state, and local laws, rules and regulations; and, for each subject participating in the study, promptly complete all CRFs and such other reports as required by this protocol following completion or termination of the clinical study or as otherwise required pursuant to any agreement with the Lead PI and Duke Cancer Institute (DCI).

The Investigator acknowledges that, within legal and regulatory restrictions and institutional and ethical considerations, study documentation will be promptly and fully disclosed to Lead PI or designee(s) by the Investigator upon request and also shall be made available at the Investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of the Lead PI and DCI or responsible government agencies as required by law.

The Investigator agrees to promptly take any reasonable steps that are requested by the Lead PI or designee(s) as a result of an audit to cure deficiencies in the study documentation and case report forms.

13.6 Case Report Forms

Subject data will be entered (i.e. CRFs completed) into an electronic data capture (EDC) system called Medidata RAVE. This database is maintained on a secure Duke University server and is accessible via internet with login and password.

CRFs should be completed by trained study personnel according to guidelines provided by the Lead PI or designee(s) at the Duke Thoracic Oncology Clinical Trials Office. The Investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. The Investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the Investigator confirms that all recorded data have been verified as accurate.

In the event of discrepant data, the study monitor or study designee will request data clarification from the Investigator or designee for which may be resolved electronically in the EDC system.

Accurate and reliable data collection will be ensured through verification and crosscheck of the CRFs against the Investigator's study records (source document verification) by the study monitor or study designee.

13.7 Monitoring and Audits/Inspections

The study will be monitored both internally by the Lead PI and externally by the Duke Cancer Institute (DCI) Monitoring Team in accordance with their NCI-approved plan.

In terms of internal review, the Lead PI and/or designee(s) will continuously monitor and tabulate adverse events. Appropriate reporting to the DUHS IRB will be made. If an unexpected frequency of Grade 3 or 4 adverse events occurs, depending on their nature, action appropriate to the nature and frequency of these adverse events will be taken. This may require a protocol amendment, dose de-escalation, or potentially closure of the study. The Lead PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

1. Interim analyses occur as scheduled (if applicable);
2. Stopping rules for toxicity and/or response are met;
3. Risk/benefit ratio is not altered to the detriment of the subjects;
4. Appropriate internal monitoring of adverse events and outcomes is done;
5. Over-accrual does not occur;
6. Under-accrual is addressed with appropriate amendments or actions;
7. Data are being appropriately recorded on the CRF in a reasonably timely manner.

The Duke Cancer Institute (DCI) Monitoring Team will conduct monitoring visits to ensure subject safety and to ensure that the protocol is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, GCP, and applicable regulatory requirements. As specified in the DCI Data and Safety Monitoring Plan, the DCI Monitoring Team will conduct routine monitoring after the third subject is enrolled, followed by annual monitoring of 1-3 subjects until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk.

Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns and may be initiated upon request of DUHS and DCI leadership, the DCI Cancer Protocol Committee, the Safety Oversight Committee (SOC), the sponsor, the Principal Investigator, or the IRB. All study documents must be made available upon request to the DCI Monitoring Team and other authorized regulatory authorities, including but not limited to the National Institute of Health, National Cancer Institute, and the FDA. Every reasonable effort will be made to maintain confidentiality during study monitoring.

The DCI Safety Oversight Committee (SOC) will perform annual reviews on findings from the DCI Monitoring Team visit and additional safety and toxicity data submitted by the Principal Investigator.

Regulatory authorities may also audit an Investigator during or after the study. The Investigator should contact the Lead PI and designee(s) at the Duke Thoracic Oncology Clinical Trials Office as well as their local IRB, immediately if this occurs, and must fully cooperate with governmental (e.g., FDA) audits conducted at a reasonable time in a reasonable manner.

The Duke University Compliance Program - Human Subject Research Compliance (HSRC) section may conduct confidential audits to evaluate compliance with the protocol and the principles of GCP. The Lead PI agrees to allow the HSRC auditor(s) direct access to all relevant documents and to allocate his/her time and the time of the study team at the Duke Thoracic Oncology Clinical Trials Office to the auditor(s) in order to discuss findings and any relevant issues.

13.8 Study Closeout

Upon completion of the study (defined as all subjects have completed all follow-up visits, all CRFs are complete, and all queries have been resolved) the Lead PI or designee(s) at the Duke Thoracic Oncology Clinical Trials Office will notify the Investigator of closeout and a study closeout visit will be performed.

The study monitor or study designee will ensure that the Investigator's regulatory files are up to date and complete, and that any outstanding issues from previous visits have been resolved. Other issues to be reviewed at the closeout visit include: retention of study files, possibility of site audits, publication policy, and study closure with local IRB.

13.9 Records Retention

The Investigator will maintain the records of study drug disposition, worksheets and all other study-specific documentation (e.g., study files, source documentation) until notified by the Lead PI or designee(s) at the Duke Thoracic Oncology Clinical Trials Office that records may be destroyed. If the application is not filed or is withdrawn, the Investigator will maintain the records for at least two (2) years after the formal discontinuation of the clinical development program for this product(s).

To avoid error, the Investigator will contact the Lead PI or designee(s) at the Duke Thoracic Oncology Clinical Trials Office before the destruction of any records pertaining to the study to ensure they no longer need to be retained. In addition, the Lead PI or designee(s) will be contacted if the Investigator plans to leave the institution so that arrangements can be made for the transfer of records.

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15 LIST OF APPENDICES

Appendix A RECIST 1.1

Appendix B ECOG Performance Status

Appendix C Standard Cockcroft and Gault Formula for Calculated Creatinine Clearance

Appendix D Study Calendar

Appendix E Laboratory Tests

Appendix A. RECIST 1.1

RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

Definitions
Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (version 1.1). Changes in only the largest diameter (uni-dimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease
Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10mm)
- 10mm caliper measurement by clinical exam (when superficial)
- 20mm by chest X-ray (if clearly defined and surrounded by aerated lung)

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15mm 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 to <15 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques are all non-measurable.
Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- 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 noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, 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 organ, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20mm x 30mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed.

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 as noted above, 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 pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Guidelines for Evaluation of Measurable Disease

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start 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 should always be done rather than 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 and >10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

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 date 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, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Response Criteria

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 diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of 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 progression).
- 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.

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of Non-target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
- 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): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concept apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in 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). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

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:

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

Evaluation of Best Overall Response
The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response."
The best overall response is determined once all the data for the patient is known. Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Appendix B. ECOG Performance Status

The ECOG Scale of Performance Status, developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair*, describes a patient's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability (walking, working, etc.).

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

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
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.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix C. Standard Cockcroft and Gault Formula for Calculated Creatinine Clearance

Standard Cockcroft and Gault Formula for Calculated Creatinine Clearance
For serum creatinine concentration in mg/dL:

Creatinine clearance (CrCl) will be calculated using the Cockroft-Gault equation as follows:

$$\text{CrCl (ml/min)} = \frac{(140 - \text{age}) \times (\text{actual weight in kg})}{72 \times \text{serum creatinine (mg/dl)}} \times 0.85 \text{ for females}$$

For serum creatinine concentration in mol/L:
CrCl = [(140 - age) x (wt in kg)] / [0.81 x serum creatinine (mol/L)]
Females: Multiply the result x 0.85
Units: age in years, weight in kilograms.

Source: Cockcroft DW, Gault MH. 1976. Prediction of creatinine clearance from serum creatinine. *Nephron* 16:31-4.

Appendix D Study Calendar

Study Procedures	Screening Period	Cycle 1		Cycle 2		Cycle 3			Cycle 4			Cycle 5			Cycle 6			Cycle 7+
	Days -28 to -1	Day 1	Day 8	Day 1	Day 8	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1
Informed Consent	X																	
Inclusion/Exclusion Criteria	X																	
Demographics/Baseline characteristics, Smoking History	X																	
Medical and Cancer History	X																	
Concomitant Medications[1]	X	X	X	X	X	X	X		X	X		X	X		X	X		X
Physical Examination	X	X	X	X	X[13]	X	X[13]		X	X[13]		X	X[13]		X	X[13]		X
Height	X																	
Vital Signs & Weight[2]	X	X	X	X	X	X	X		X	X		X	X		X	X		X
ECOG Performance Status	X	X	X	X	X[13]	X	X[13]		X	X[13]		X	X[13]		X	X[13]		X[13]
irAE Screening Phone Call[14]								X			X			X			X	
CBC With Differential [3]	X[3]	X[3]	X	X	X	X	X		X	X		X	X		X	X		X
Chemistries Including LFTs[3]	X[3]	X[3]	X	X	X	X	X		X	X		X	X		X	X		X
Serum Pregnancy Test [5]	X[5]	X[5]		X[5]		X[5]			X[5]			X[5]			X[5]			X[5]
Thyroid (free T4 & TSH)[3,4]	X[3,4]					X[4]						X[4]						X[4]
Nivolumab **		X		X		X			X			X			X			X
Paclitaxel **		X	X	X	X	X	X		X	X		X	X		X	X		
Ipilimumab **		X				X						X						X
Adverse Event Assessment[1]	X	X	X	X	X	X	X		X	X		X	X		X	X		X

Tumor Assessment [6]	X[6]					X[6]						X[6]						X[6]
Brain MRI[7]	X[7]								X[7]									X[7]
Archived Tumor Tissue[8]	X[8]																	
Circulating Immune Cells (PBMC)[9]	X[9]					X[9]												
Circulating Proteins[9]	X[9]					X[9]												
Survival[10,11]																		

Study Procedures – 21 Day Cycle Unless otherwise indicated	Progression	Follow-up #1 [12]	Follow-up #2 [12]	Survival
Concomitant Medications[1]		X[1]	X[1]	
Physical Examination		X	X	
Height				
Vital Signs & Weight[2]		X	X	
ECOG Performance Status		X	X	
CBC With Differential[13]		X	X	
Chemistries Including LFTs[13]		X	X	
Thyroid Function (Free T4 & TSH)[3,4]				
Serum Pregnancy Test [5]				
Nivolumab**				
Paclitaxel **				
Ipilimumab **				
Adverse Event Assessment[1]		X	X	
Tumor Assessment[6]				
Brain MRI or CT[7]				
Archived Tumor Tissue[8]				
Circulating Immune Cells (PBMC)[9]	X[9]			
Circulating Proteins[9]	X[9]			
Survival[10,11]		X[10,11]	X[10,11]	X[10,11]

1. Document this data throughout study when changes or events occur.
2. Obtain temperature (^{O}C), blood pressure, heart rate, and weight
3. Must perform within 14 days prior to Cycle 1 Day 1. If completed within 14 days of Cycle 1 Day 1, no need to repeat. If repeated on Cycle 1 Day 1, must wait for results to confirm eligibility prior to starting study drug. After the completion of the first cycle, laboratory assessments may be obtained up to 3 days prior to day 1.
4. Thyroid profile (TSH & Free T4) to be performed every 6 weeks.
5. Only for women of childbearing potential. To be performed within 72 hours of study drug administration (or per institutional policy)
6. Tumor assessment at baseline must include CT and/or MRI of Chest, Abdomen, Pelvis and all known or suspected sites of disease. Restaging scans will be performed every 6 weeks (± 7 days) for the first 48 weeks and then every 12 weeks (± 7 days) thereafter. CT of Chest and known cites of disease are required for restaging scansfor those subjects with metastasis in those areas identified at baseline or if clinically indicated. Same method for tumor assessment should be employed at every assessment Appendix A).
7. MRI of brain or Brain CT with contrast required for all subjects at baseline. For patients with **treated** brain metastases, if brain MRI falls outside of the 28 day screening window, a repeat brain MRI is not needed unless greater than 4 weeks from the completion date of radiation therapy. Subjects with a history of brain metastasis to have surveillance MRI/CT approx. every 12 weeks from first dose or sooner if clinically indicated.
8. FFPE tumor tissue (Fresh or archived specimen) should be submitted. Note: a bone biopsy is not an acceptable sample,
9. Peripheral blood collection for Circulating Immune Cells (PBMC), and Circulating Proteins are to be done at the following time points: Baseline (or Pre-dose C1D1), at first restaging, and at disease progression. Subjects who discontinue treatment for reasons other than progression, will have research blood drawn at progression, unless they start a new anti-cancer treatment regimen.
10. Subjects that are discontinued from study treatment for reasons other than disease progression, subjects will have restaging scans per standard of care scheduled followed until disease progression or start of new anti-cancer treatment regimen. Disease status may be collected by personal interviews or review of medical records.
11. Subjects are followed for survival up to 2 years or until the study is closed (whichever comes first). Survival status may be collected by personal interviews or review of medical or public records (Section 7.3).

12. Subjects to return for follow-up visit #1 at 35 days after last dose of study drug (+/- 7 days) or coinciding with the date of discontinuation of the study drug if the date of discontinuation is > 42 days from last dose for an off treatment visit. Follow-up visit #2 to occur 80 days from Follow-up #1 (+/- 7 days) or 100 days from discontinuation of the study drug. See **7.3.1** Follow-up patients who discontinue treatment for reasons other than progression *and* started new therapy
13. The following study procedures are **optional** day 8 for cycles 2 – 6 while receiving Paclitaxel: Physical Exam, and ECOG.
14. Nursing phone call screening for irAE hypophysitis or adrenal insufficiency. Cycles 3-6, Day 15 (+3 days)

***A window of +7 days can be applied to Day 1 study visits unless otherwise noted. A window of +/- 3 days can be applied to Day 8 study visits unless otherwise noted.**The dosing regimen will be: Nivolumab 360 mg every 3 weeks, Ipilimumab 1 mg/kg every 6 weeks, and paclitaxel 80 mg/m^2 on days 1 and 8 of a 21 day treatment cycle. Paclitaxel to be administered for a total of 4-6 cycles of Treatment.**

****Study drug cycles 1-6 while receiving Taxol with Ipilimumab and Nivolumab**

c. ***C1-C6 do not skip cycles if a cycle is delayed. If a cycle is delayed, that same cycle will begin when subject meets protocol parameters to resume treatment.
d. C1, C3, C5. Ipilimumab is to be administered C1, C3, C5 only on these cycles during C1-C6 with Taxol.
e. C7 and beyond do not skip cycles if a cycle is delayed.

Appendix E. Laboratory Tests

CBC with differential		
• hematocrit • hemoglobin • platelet count	• WBC (total and differential) • red blood cell (RBC) count	• absolute neutrophil count • absolute lymphocyte count
Chemistries with liver function tests (LFTs)		
• albumin • alkaline phosphatase (ALP) • ALT • AST • Bicarbonate	• blood urea nitrogen (BUN) • chloride • creatinine • glucose • calcium	• potassium • sodium • total bilirubin • total protein
Pregnancy Test		
• serum β-HCG pregnancy test		
Thyroid Function		
• TSH, Free T4		

Appendix F. Day 15, Cycle 3-6 Phone Call

The following study procedures must be completed day 15, Cycles 3-6 (+3 days):

What: Nursing phone call screening for symptoms of immune hypophysitis or adrenal insufficiency

Why: The intent of day 15 phone call is early detection of IH/AI with diagnostic endocrine labs collected at the optimal time (0800 ACTH/Cortisol and Cort Stim prior to steroids).

Question: Have you experience these symptoms since your last infusion?
Solicited symptoms:

- Persistent Headaches (new or different)
- Vision changes
- Fatigue: more than usual fatigue; worst fatigue of my life

Action items:
If one solicited symptom is positive:
Screening action items: Suspected

- Notify medical oncology provider, Dr. Clarke, and Dr. Shariff
- If patient is stable, recommend a screening *0800* ACTH and Cortisol and Cort Stim test (ACTH stimulation test) at Duke prior to next visit or initiation of steroids including Taxol dexamethasone premed.
- Consider additional diagnostic labs (thyroid and gonadal) and pituitary MRI. Refer to Dr. Shariff's algorithm.
- Labs/imaging billed to insurance.
- Results to Med Onc provider and Dr. Shariff.