Phase II Study of Consolidation Immunotherapy with Nivolumab and Ipilimumab or Nivolumab alone following Concurrent Chemoradiotherapy for Unresectable Stage IIIA/IIIB Non-small Cell Lung Cancer (NSCLC)

Big Ten Cancer Research Consortium: BTCRC-LUN16-081

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VERSION DATE: 28FEB2020

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

_____ _____
Signature of Site Investigator Date

_____
Site Investigator Name (printed)

_____
Site Investigator Title

_____
Name of Facility

_____
Location of Facility (City and State)

PLEASE EMAIL COMPLETED FORM TO BTCRC ADMINISTRATIVE HEADQUARTERS

SYNOPSIS

TITLE	Phase II Study of Consolidation Immunotherapy with Nivolumab and Ipilimumab or Nivolumab alone following Concurrent Chemoradiotherapy for Unresectable Stage IIIA/IIIB Non-small Cell Lung Cancer (NSCLC)
PHASE	Phase II
OBJECTIVES	Primary Objective: **Arm 1**- To determine if consolidation therapy with nivolumab alone following concurrent chemoradiation improves 18-month progression free survival (PFS) relative to a historical control of chemoradiation alone, in subjects with inoperable or unresectable stage IIIA or IIIB NSCLC **Arm 2**- To determine if consolidation therapy with nivolumab and ipilimumab following concurrent chemoradiation improves 18-month PFS relative to a historical control of chemoradiation followed by single agent checkpoint inhibitor, in subjects with inoperable or unresectable stage IIIA or IIIB NSCLC Secondary Objectives: • To determine if consolidation therapy with nivolumab alone following concurrent chemoradiation improves time to metastatic disease and overall survival (OS) relative to a historical control of chemoradiation alone in subjects with inoperable or unresectable stage IIIA or IIIB NSCLC (Arm 1). • To determine if consolidation therapy with nivolumab and ipilimumab following concurrent chemoradiation improves time to metastatic disease and overall survival (OS) relative to a historical control of chemoradiation followed by single agent checkpoint inhibitor in subjects with inoperable or unresectable stage IIIA or IIIB NSCLC (Arm 2). • To assess toxicity and tolerability of consolidation therapy with nivolumab plus ipilimumab or nivolumab alone following concurrent chemoradiation in subjects with inoperable or unresectable stage IIIA or IIIB NSCLC. Exploratory Objectives: • To assess PD-L1, CD4, CD8, expression levels in the tumor samples of subjects with inoperable or unresectable stage IIIA or IIIB NSCLC and correlate with PFS, OS, time to metastatic disease, and treatment toxicity. • To assess associations between DNA, RNA, microRNA, DNA methylation, protein expression, lipidomic profiling, immune markers, protein biomarker panels, and other markers and efficacy and toxicity of treatment. • To explore whether clinical characteristics may be associated with the development of pneumonitis and correlate with PFS, OS, time to metastatic disease, and treatment toxicity. • To explore whether radiation treatment plan deviation or lung dosimetric factors may be associated with the development of pneumonitis and correlate with PFS, OS, time to metastatic disease, and treatment toxicity.

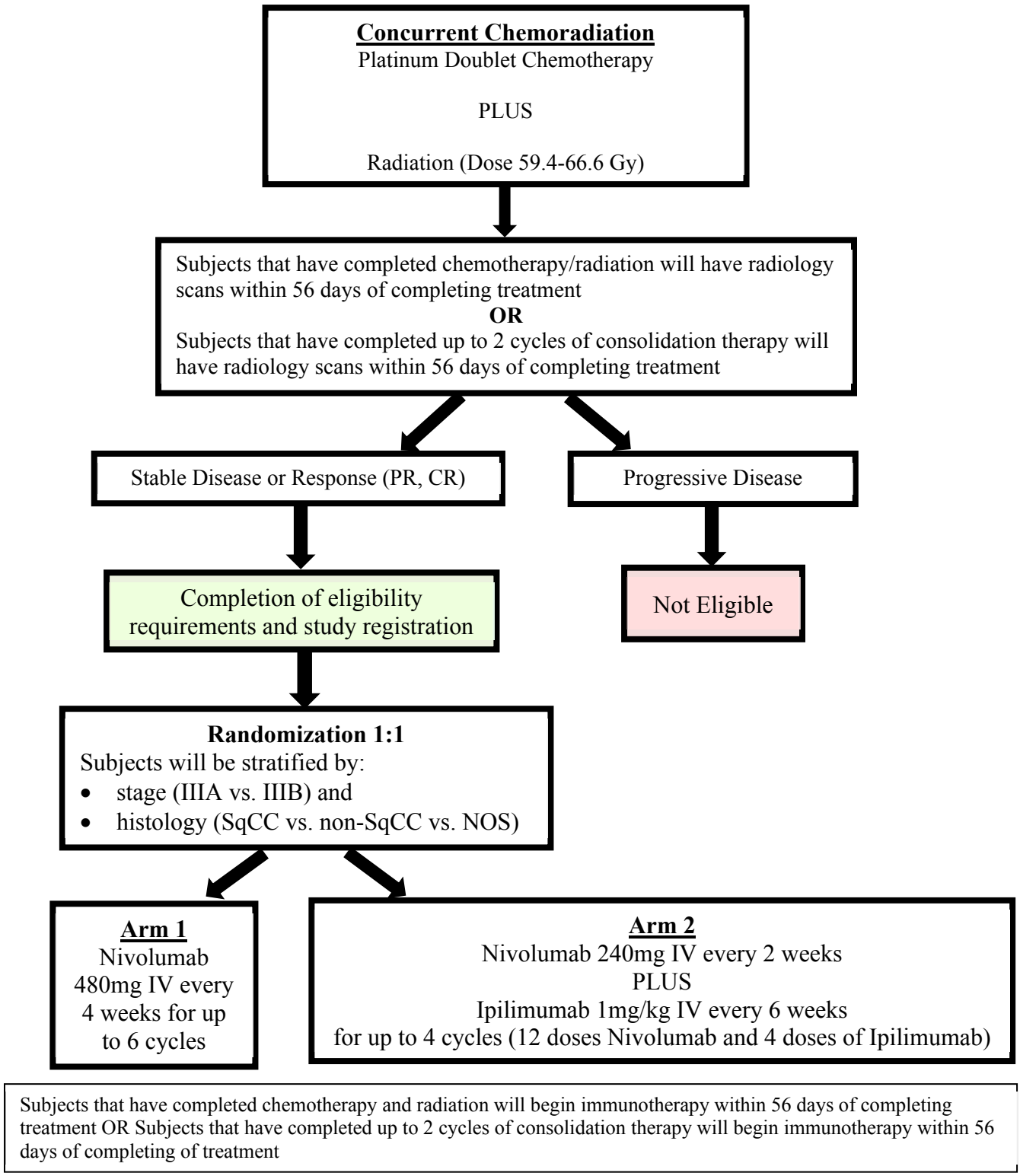
	• To examine characteristics of BAL samples (e.g cytokines and chemokines) in patients who develop pneumonitis.
STUDY DESIGN	This is an open label, multi-institutional, randomized, non-comparative two-arm phase II trial of consolidation therapy with either nivolumab plus ipilimumab or nivolumab alone following initial treatment with concurrent chemoradiation in subjects with inoperable or unresectable stage IIIA or IIIB NSCLC. Subjects will be randomized 1:1 following chemoradiation and prior to initiation of consolidation therapy.
KEY ELIGIBILITY CRITERIA	**Inclusion Criteria:** 1. Written informed consent and HIPAA authorization for release of personal health information. 2. Age ≥ 18 years at the time of consent. 3. Histological or cytological evidence of NSCLC. 4. Must have unresectable or inoperable stage IIIA or IIIB disease according to the 7th edition IASLC stage classification for lung cancer. Subjects are considered unresectable or inoperable based on the judgment of the treating physician. 5. Subjects must have completed concurrent chemoradiation with a platinum doublet and a dose of radiation ranging from 59.4-66.6 Gy. Subjects must have stable disease or disease response as evidenced on CT or PET scan evaluation. For those eligible, nivolumab or nivolumab/ipilimumab should begin within 56 days following the completion of chemoradiation. **OR** Subjects must have completed up to 2 cycles of consolidation therapy started within 8 weeks of completion of radiation. After completion of consolidation therapy, subjects must have stable disease or disease response as evidenced by CT or PET scan evaluation. For those eligible, nivolumab or nivolumab/ipilimumab should begin within 56 days after the last cycle of chemotherapy. 6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 within 14 days prior to registration for protocol therapy. 7. Adequate laboratory values obtained within 14 days prior to registration for protocol therapy (see protocol for details) 8. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 7 days prior to registration. **NOTE:** Women are considered of childbearing potential unless they are surgically sterile (have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or are post-menopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. In addition, women under the age of 62 must have a documented serum follicle stimulating hormone (FSH) level greater than 40 mIU/mL to be considered post-menopausal. 9. Women of childbearing potential must be willing to abstain from heterosexual activity or use an effective method of contraception from the

	time of informed consent until 23 weeks after treatment discontinuation. See Section 5.5.2 for adequate methods of contraception. 10. Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men receiving study drug and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product. See section 5.5.2 for methods of contraception. **Exclusion Criteria:** 1. Pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 23 weeks (female) or 31 weeks (male) after the last dose of trial treatment. 2. Active central nervous system (CNS) metastases. If symptomatic or without prior brain imaging, subjects must undergo a head computed tomography (CT) scan or brain MRI within 28 days prior to registration for protocol therapy to exclude brain metastases. 3. Treatment with any investigational agent within 28 days prior to registration for protocol therapy 4. Prior chemotherapy, adjuvant therapy, or radiotherapy for lung cancer other than standard concurrent chemoradiation or up to 2 cycles of consolidation as described above 5. Prior therapy with a PD-1, PD-L1, PD-L2 or CTLA-4 inhibitor or a lung cancer-specific vaccine therapy 6. Previously received a solid organ transplant or allogeneic progenitor/stem cell transplant. 7. Presence of metastatic disease (stage IV NSCLC) is not allowed. Subjects must be evaluated with a CT or PET scan prior to registration for protocol therapy to exclude metastatic disease. 8. Active second cancers. 9. Active autoimmune disease requiring systemic treatment within the past 90 days or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjogren's syndrome will not be excluded from the study 10. Presence of interstitial lung disease or history of pneumonitis requiring treatment with corticosteroids 11. Diagnosis of immunodeficiency or receiving chronic systemic corticosteroid therapy or other immunosuppressive therapy (excludes inhaled corticosteroids) within 7 days of first dose of study drug 12. History of psychiatric illness or social situations that would limit compliance with study requirements. 13. Clinically significant acute infection requiring systemic antibacterial, antifungal, or antiviral therapy including: tuberculosis, hepatitis B,

	hepatitis C or human immunodeficiency virus (see protocol for exceptions). 14. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the site investigator. 15. Has a known history of active TB (Bacillus Tuberculosis). 16. Hypersensitivity to nivolumab, ipilimumab, or any of their excipients. 17. Has received a live vaccine within 30 days prior to planned start of study therapy. **NOTE:** Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.
STATISTICAL CONSIDERATIONS	This is a non-comparative two-arm trial with each arm being analyzed separately. For Arm 1, when the sample size is 51, a non-parametric test (single-group and based on a non-parametric estimate of the cumulative hazard function) with a one-sided 0.10 significance level will have 80% power to detect an 18 month PFS rate of 44% relative to a historical control rate of 30% (similar to the PACIFIC trial) assuming an accrual period of approximately 24 months and maximum follow-up of 48 months (i.e. would allow for up to 24 months of follow-up after accrual ends). For Arm 2, when the sample size is 48, a non-parametric test (as above) with a one-sided 0.10 significance level will have 80% power to detect an 18 month PFS of 59% relative to a historical control rate of 44% (similar to the PACIFIC trial in the checkpoint inhibitor arm and a 15% increase in absolute magnitude) assuming an accrual period of approximately 24 months and maximum follow-up of 48 months. To account for non-evaluable subjects (5%), 54 subjects will be enrolled in Arm 1 and 51 subjects in Arm 2. Time to metastatic disease and Overall survival will be estimated with Kaplan-Meier curves and medians described with 95% confidence intervals. 18 month PFS will also be described with 80% confidence intervals. Toxicity and tolerability will be tabulated. Tumor and blood biomarkers will be correlated with clinical outcomes using logistic and Cox regression methods.
TOTAL NUMBER OF SUBJECTS	N = 105 (54 subjects in Arm 1 and 51 in Arm 2)
ESTIMATED ENROLLMENT PERIOD	24 months
ESTIMATED STUDY DURATION	48 months

TABLE OF CONTENTS

SCHEMA


Concurrent Chemoradiation
Platinum Doublet Chemotherapy
PLUS
Radiation (Dose 59.4-66.6 Gy)
Subjects that have completed chemotherapy/radiation will have radiology scans within 56 days of completing treatment
OR
Subjects that have completed up to 2 cycles of consolidation therapy will have radiology scans within 56 days of completing treatment
Stable Disease or Response (PR, CR)
Progressive Disease
Completion of eligibility requirements and study registration
Not Eligible
Randomization 1:1
Subjects will be stratified by:
• stage (IIIA vs. IIIB) and
• histology (SqCC vs. non-SqCC vs. NOS)
Arm 1
Nivolumab 480mg IV every 4 weeks for up to 6 cycles
Arm 2
Nivolumab 240mg IV every 2 weeks
PLUS
Ipilimumab 1mg/kg IV every 6 weeks
for up to 4 cycles (12 doses Nivolumab and 4 doses of Ipilimumab)
Subjects that have completed chemotherapy and radiation will begin immunotherapy within 56 days of completing treatment OR Subjects that have completed up to 2 cycles of consolidation therapy will begin immunotherapy within 56 days of completing of treatment

1. BACKGROUND AND RATIONALE

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on nivolumab and ipilimumab.

1.1 Lung Cancer Background

Lung cancer is the leading cause of cancer-related mortality in the United States and in the world with an estimated 224,390 new cases and 158,080 deaths in the U.S. in 2016 (1). This accounts for approximately 26.5% of all cancer deaths, more than breast, prostate, and colorectal cancer combined (1, 2). Non-small cell lung cancer (NSCLC) represents about 85% of all primary lung malignancies. Outcomes for this disease are poor, with the five-year overall survival (OS) rate for NSCLC being only 17.7% (2). While improvements have been made including molecularly targeted drugs and immunotherapy, new approaches are clearly needed to improve outcomes in this disease.

1.2 Current Standard of Care

One particular area with a specific need for new therapeutic options is stage III NSCLC, especially for patients with unresectable or inoperable tumors. The five-year OS for patients with stage IIIA and IIIB NSCLC are 14% and 5% respectively (3). Previous efforts to improve outcomes in this population have not changed the landscape of treatment significantly in the last few decades. Until the 1980s, radiotherapy alone was the standard of care for patients with locally or regionally advanced NSCLC. Five-year survival rates for radiotherapy alone were only 3-10% (4). Because of these poor outcomes, trials looking at sequential chemoradiation were completed showing an advantage in OS for the addition of chemotherapy (4, 5). Following this, sequential chemoradiation was compared to concurrent chemoradiation showing a subsequent improvement in OS for concurrent therapy (6, 7). This finding was confirmed in a meta-analysis showing an absolute benefit of 4.5% at five years favoring concurrent chemoradiation over sequential (8). Since that time, a number of subsequent trials evaluating induction (9, 10) and consolidation (10-14) chemotherapy have failed to demonstrate an improvement in OS in this population. Recently, a trial was completed which gave patients with unresectable stage III NSCLC concurrent chemoradiation followed by either 12 months of consolidation Durvalumab (PD-L1 inhibitor) or placebo. This trial showed an improved median PFS of 17.2 months with durvalumab vs. 5.6 months with placebo (HR 0.51). Overall survival also favored the Durvalumab arm with a 24-month OS of 66.3% vs. 55.6% in the placebo arm (HR 0.68, p=0.0025) (15). Based on this data, consolidation Durvalumab should be considered a potential new standard of care following chemoradiation for patients with unresectable stage III NSCLC.

1.3 Investigational Treatment

1.3.1 Nivolumab

1.3.1.1 Introduction

Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes (16). Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster

ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration. OPDIVO™ (nivolumab) is approved for use in multiple countries including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014). (17).

1.3.1.2 Non-clinical Studies

Nivolumab has been shown to bind specifically to the human PD-1 receptor and not to related members of the CD28 family (17). 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 (17, 18). Nivolumab binds with high affinity to activated human T-cells expressing cell surface PD-1 and to cynomolgus monkey PD-1 (17). In a mixed lymphocyte reaction (MLR), nivolumab promoted a reproducible concentration-dependent enhancement of IFN-γ release (19).

1.3.1.3 Effects in Humans

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy and in combination with ipilimumab in several tumor types, including NSCLC, melanoma, renal cell carcinoma (RCC), classical Hodgkin Lymphoma (cHL), small cell lung cancer (SCLC), gastric cancer, urothelial cancer, hepatocellular carcinoma (HCC), and colorectal cancer (CRC). In confirmatory trials, nivolumab as monotherapy demonstrated a statistically significant improvement in OS as compared with the current standard of care in subjects with advanced or metastatic NSCLC, unresectable or metastatic melanoma, advanced RCC, or squamous cell carcinoma of the head and neck (SCCHN). Nivolumab in combination with ipilimumab improved PFS and ORR over ipilimumab alone in subjects with unresectable or metastatic melanoma (see Section 5.4 of IB) (17).

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 16,900 subjects treated to date. For monotherapy, the safety profile is similar across tumor types. There is no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. In Phase 3 controlled studies, the safety profile of nivolumab monotherapy is acceptable in the context of the observed clinical efficacy, and manageable using established safety guidelines. Clinically relevant AEs typical of stimulation of the immune system were infrequent and manageable by delaying or stopping nivolumab treatment and timely immunosuppressive therapy or other supportive care.

Based on preliminary data from an ongoing Phase 1 study, there have been no unexpected safety findings to date in patients with sepsis who received a single dose of nivolumab monotherapy.

In several ongoing clinical trials, the safety of nivolumab in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies is being explored. Most studies are ongoing and, as such, the safety profile of nivolumab combinations continues to evolve. The most advanced combination under development is nivolumab + ipilimumab, which is approved in subjects with unresectable or metastatic melanoma (see Appendix 1 and Appendix 2 of IB), and being studied in multiple tumor types. Results to date suggest that the safety profile of nivolumab+ipilimumab combination therapy is consistent with the mechanisms of action of nivolumab and ipilimumab. The nature of the AEs is similar to that observed with either agent used as monotherapy; however, both frequency and severity of most AEs are increased with the combination (17).

1.3.1.4 Pharmacokinetics

The pharmacokinetics (PK) of nivolumab was studied in subjects over a dose range of 0.1 to 10 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. Nivolumab clearance (CL) decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of approximately 24.5% (47.6%) resulting in a geometric mean steady state clearance (CLss) (CV%) of 8.2 mL/h (53.9%); the decrease in CLss is not considered clinically relevant. The geometric mean volume of distribution at steady state (Vss) was 6.8 L (27.3%), and geometric mean elimination half-life (t1/2) was 25 days (77.5%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was approximately 3.7-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. Additionally, nivolumab has a low potential for drug-drug interactions (see Section 5.2.4 of IB). The clearance of nivolumab increased with increasing body weight. The PPK analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1, solid tumor type, baseline tumor size, and hepatic impairment.

Although ECOG status, baseline glomerular filtration rate (GFR), albumin, and body weight had an effect on nivolumab CL, the effect was not clinically meaningful. PPK analysis suggest that nivolumab CL in subjects with cHL was approximately 32% lower relative to subjects with NSCLC; however, the lower CL in cHL subjects was not considered to be clinically relevant as nivolumab exposure was not a significant predictor for safety risks for these patients. When nivolumab is administered in combination with ipilimumab, the CL of nivolumab was increased by 29%, whereas there was no effect on the clearance of ipilimumab.

PPK and exposure response analyses have been performed to support use of nivolumab 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W dosing regimens in subjects with cancer in addition to the 3 mg/kg Q2W regimen. A flat dose of nivolumab 240 mg Q2W was selected since it is identical to a dose of 3 mg/kg for subjects weighing 80 kg, the observed median body weight in nivolumab-treated cancer patients, while the nivolumab 360 mg Q3W and 480 mg Q4W regimens allow flexibility of dosing with less frequent visits and in combination with other agents using alternative dosing schedules to Q2W. 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 Q2W. Following nivolumab 360 mg Q3W and 480 mg Q4W, Cavgss are expected to be similar to those following nivolumab 3 mg/kg or 240 mg Q2W, while Cminss are predicted to be 6% and ~16% lower, respectively, and are not considered to be clinically relevant. Following nivolumab 360 mg Q3W and 480 mg Q4W, Cmaxss are predicted to be approximately ~23% and ~43% greater, respectively, relative to that following nivolumab 3 mg/kg Q2W dosing. However, the range of nivolumab exposures (median and 90% prediction intervals) following administration of 240 mg flat Q2W, 360 mg Q3W, and 480 mg Q4W regimens across the 35 to 160 kg weight range are predicted to be maintained well below the corresponding exposures observed with the well tolerated 10 mg/kg nivolumab Q2W regimen (see Section 5.3 of IB) (17).

The PK of nivolumab is linear and in study CA209-003, nivolumab was adequately tolerated up to 10 mg/kg, no maximum tolerated dose was identified, and the E-R relationship for safety was flat.

Population pharmacokinetic modeling results have predicted that the exposure, safety, and efficacy of nivolumab administered at 480 mg Q4W will be similar to those with nivolumab 3 mg/kg Q2W.

1.3.2 Ipilimumab

1.3.2.1 Introduction

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) has been approved for use in over 47 countries including the United States (US, Mar-2011), the European Union (EU, Jul-2011), and Australia (Jul-2011) (20).

1.3.2.2 Non-clinical Studies

Ipilimumab has specificity and a high affinity for human CTLA-4. The calculated dissociation constant value from an average of several studies was 5.25 nM. Binding of ipilimumab to purified, recombinant human CTLA-4 antigen was also demonstrated by enzyme-linked immunosorbent assay with half-maximal binding at 15 ng/mL, whereas saturation was observed at approximately 0.1 µg/mL. No cross-reactivity was observed against human CD28. Ipilimumab completely blocked binding of B7.1 and B7.2 to human CTLA-4 at concentrations higher than 6 and 1 µg/mL, respectively (20).

1.3.2.3 Effects in Humans

Bristol-Myers Squibb (BMS) and Medarex, Inc. (MDX, acquired by BMS in Sep-2009) have co-sponsored an extensive clinical development program for ipilimumab, encompassing more than 19,500 subjects (total number of subjects enrolled in ipilimumab studies) in several cancer types in completed and ongoing studies, as well as a compassionate use program. The focus of the clinical program is in melanoma, prostate cancer, and lung cancer, with advanced melanoma being the most comprehensively studied indication. Ipilimumab is being investigated both as monotherapy and in combination with other modalities such as chemotherapy, radiation therapy, and other immunotherapies. Phase 3 programs are ongoing in melanoma, prostate cancer, and lung cancer. In melanoma, 2 completed Phase 3 studies (MDX010-20 and CA184024) have demonstrated a clinically meaningful and statistically significant survival benefit in pretreated advanced melanoma and previously untreated advanced melanoma, respectively. Refer to Appendix 1 (Yervoy® United States Package Insert [USPI]) and Appendix 2 (Yervoy Summary of Product Characteristics [SmPC]) for further details. The safety profile of ipilimumab is generally consistent across these trials with a) the majority adverse events (AEs) being inflammatory in nature, which is consistent with the proposed mechanism of action of ipilimumab; b) the same types of such immune-mediated events in the gastrointestinal (GI) tract, skin, liver, and endocrine system being reported; and c) most of these events being manageable with immune suppressive therapies.

In melanoma, 2 BMS-sponsored Phase 3 studies are ongoing in subjects with high-risk Stage III melanoma (CA184029, with adjuvant immunotherapy) and pretreated and treatment-naïve advanced melanoma (CA184169, 3 mg/kg versus 10 mg/kg ipilimumab). The completed Phase 3 study

(CA184043) evaluated ipilimumab in subjects with metastatic castration-resistant prostate cancer (mCRPC) who had progressed during or following treatment with docetaxel. Eligible subjects were randomized to a single dose of bone-directed radiotherapy (RT), followed by either ipilimumab 10 mg/kg or placebo (799 randomized: 399 ipilimumab, 400 placebo). This study did not meet its primary endpoint of overall survival (OS). The hazard ratio (HR) of 0.85 (95% confidence interval [CI]: 0.72, 1.00) for survival favored ipilimumab but did not reach statistical significance with a P value of 0.053. Planned sensitivity analyses favored ipilimumab, where the greatest benefit appeared to be in subgroups defined by good prognostic features and low burden of disease. Additional evidence of ipilimumab activity observed in the study included a reduced risk of disease progression relative to placebo (HR = 0.70), superior clinical outcomes compared to placebo in tumor regression, and declines in prostate specific antigen (PSA). The safety profile in this study was consistent with the previously defined AE profile at the same dose (see Section 5.4.3 and Section 5.5.3 of the Ipilimumab IB) (20).

A second Phase 3 study (CA184095) evaluated ipilimumab 10 mg/kg versus placebo in men with asymptomatic or minimally symptomatic, chemotherapy-naïve mCRPC with no visceral metastases. A total of 602 subjects were randomized in a 2:1 ratio (400 subjects to 10 mg/kg ipilimumab and 202 subjects to placebo). Preliminary data indicate the study did not meet its primary endpoint based on intent-to-treat analysis. The HR of 1.11 (95.87% CI: 0.88, 1.39; P value = 0.3667) for OS did not favor ipilimumab. A longer median progression-free survival (PFS) interval was observed for the ipilimumab group than for the placebo group, which may be indicative of activity of ipilimumab in delaying disease progression. The safety profile in this study was generally consistent with the previously defined AE profile at the same dose (see Section 5.4.3 and Section 5.5.3.1 of Ipilimumab IB).

In addition, a completed, large Phase 2 study (CA184041) has investigated the addition of ipilimumab to carboplatin and paclitaxel using 2 different schedules (concurrent and phased) in subjects with non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC, a secondary endpoint) [Section 5.4.4 of Ipilimumab IB]. Ipilimumab, given in combination with paclitaxel/carboplatin in a phased schedule improved immune-related progression-free survival (irPFS) compared to the control treatment, but no improvement was seen when ipilimumab was given in a concurrent schedule. Phased ipilimumab also improved PFS according to modified World Health Organization (mWHO) criteria and showed a trend for improved OS.

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

Ipilimumab is also in clinical development in combination with nivolumab. The combination is approved in the US for the treatment of advanced melanoma. Information regarding safety and efficacy can be found in the nivolumab Investigator Brochure (17, 21).

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

In metastatic diseases, stabilization is more common than response, and in some instances is associated with a slow, steady decline in tumor burden over many months, sometimes improving to partial and/or complete responses (CRs). Thus, the immune-based mechanism of action of ipilimumab results in durable disease control, sometimes with novel patterns of response, which contribute to its unique improvement in OS.

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

The early diagnosis of inflammatory events is important to initiate therapy and minimize complications. Inflammatory events are generally manageable using symptomatic or immuno-suppressive therapy as recommended through detailed diagnosis and management guidelines. The management guidelines for general irAEs and ipilimumab-related GI toxicities, hepatitis, endocrinopathy, and neuropathy are described in Section 7 and Appendix 3 of the Ipilimumab IB.

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

In summary, ipilimumab offers clinically meaningful and statistically significant survival benefit to patients with pretreated advanced melanoma (as 3 mg/kg monotherapy compared to the melanoma peptide vaccine gp100) and previously untreated advanced melanoma (at 10 mg/kg in combination with dacarbazine [DTIC] compared to DTIC alone) and evidence of clinical activity in randomized studies in other tumor types. These findings, together with evidence of a safety profile that is manageable with careful monitoring and appropriate intervention for treatment of immune-related toxicities, suggest an acceptable benefit to risk ratio (20).

1.3.2.4 Pharmacokinetics

The PK of ipilimumab has been extensively studied in subjects with melanoma, at the 3 and 10-mg/kg doses administered as a 1.5-hour IV infusion. The PK of ipilimumab was characterized by population PK (PPK) analysis and determined to be linear and time invariant in the dose range of 0.3 to 10 mg/kg. The summary of PK parameters after single and multiple doses of ipilimumab in subjects with advanced melanoma from Studies MDX010-15, CA184007, and CA184008 (with intensive PK samples available) are listed in Table 5.2.1-1 of Ipilimumab IB.

The PPK of ipilimumab was studied in 785 subjects (3200 serum concentrations) with advanced melanoma in 4 Phase 2 studies (CA184004, CA184007, CA184008, and CA184022),601 Phase 3 study (CA184024), and 1 Phase 1 study (CA184078). The PPK analysis demonstrated that the PK of ipilimumab is linear, the exposures are dose proportional across the tested dose range of 0.3 to 10 mg/kg, and the model parameters are time-invariant, similar to that determined by noncompartmental analyses.

Upon repeated dosing of ipilimumab, administered q3w, minimal systemic accumulation was observed by an accumulation index of 1.5-fold or less, and ipilimumab steady-state concentrations were achieved by the third dose. The ipilimumab CL of 16.8 mL/h from PPK analysis is consistent with that determined by noncompartmental PK analysis and shown in Table 5.2.1-1. The terminal T-HALF and Vss of ipilimumab calculated from the model were 15.4 days and 7.47 L, respectively, which are consistent with that determined by noncompartmental analysis. Volume of central compartment (Vc) and peripheral compartment were found to be 4.35 and 3.28 L, respectively, suggesting that ipilimumab first distributes into plasma volume and, subsequently, into extracellular fluid space. CL of ipilimumab and Vc were found to increase with increase in BW. However, there was no significant increase in exposure with increase in BW when dosed on a milligram/kilogram basis, supporting dosing of ipilimumab based on a weight normalized regimen. The PK of ipilimumab is not affected by age, gender, race, and immunogenicity (anti-drug antibody [ADA] status); concomitant use of chemotherapy; prior therapy; BW; performance status; or tumor type. Other covariates had effects that were either not statistically significant or were of minimal clinical relevance (20).

1.4 Rationale for Study

Ipilimumab, a CTLA-4 inhibitor, was one of the first therapies developed to target regulatory T-cell function, and it has demonstrated improved PFS in a phase II trial of advanced NSCLC (22). More recently, trials involving another negative regulatory pathway of T-cell function, PD-1/PD-L1, have demonstrated encouraging results in metastatic NSCLC (23-27), and currently, there are three Food and Drug Administration (FDA)-approved PD-1 or PD-L1 inhibitors for metastatic NSCLC. The combination of CTLA-4 and PD-1 blockade has been shown to be more effective than monotherapy in

melanoma (21), and thus there is interest in expanding combination immunotherapy to NSCLC. The Checkmate 012 trial was a phase I, multi-cohort trial looking at the combination of nivolumab and ipilimumab in varying doses in metastatic NSCLC. The combination of ipilimumab and nivolumab appeared tolerable with encouraging clinical activity, particularly in the cohorts with nivolumab 3mg/kg every 2 weeks and ipilimumab 1mg/kg every 6 or 12 weeks. Objective response rates for these two cohorts were 38% and 47% respectively and were numerically higher for patients with PD-L1 expression of 1% or greater. The median duration of response was not yet reached in either cohort (28). Based on experience in other tumor types suggesting that greater ipilimumab exposure is associated with greater activity (29, 30), Bristol-Myers Squibb has elected to move forward with development of the nivolumab 3mg/kg every 2 weeks plus ipilimumab 1mg/kg every 6 weeks regimen. Another phase 1b trial of the PD-L1 inhibitor, Durvalumab, in combination with a CTLA-4 inhibitor, Tremelimumab, has also shown a manageable safety profile with evidence of clinical activity in patients with NSCLC (31). Based on these encouraging results, further investigation into combination immunotherapy is warranted, and phase III trials are already ongoing looking at different regimens in the metastatic setting.

There is pre-clinical rationale for the use of immunotherapeutic strategies following the use of ionizing radiation. Radiation has been shown to be associated with an abscopal effect which is felt to be immune-mediated, though this phenomenon is rarely seen with radiation alone (32). In animal models, the addition of checkpoint inhibitors to radiation has demonstrated an additive effect both to the radiated tumor and to sites of distant disease (32, 33). Furthermore, radiation alters the immune and tumor microenvironments in a number of ways including: 1) release of neoantigens, 2) promotion of cross-priming of tumor specific cytotoxic T-lymphocytes (CTL), 3) stimulation of the immune effector function of CTLs, and 4) neutralization of the immunosuppressive effects of the tumor microenvironment (34).

Based on this rationale, two trials have been conducted evaluating the benefit of adding PD-1 or PD-L1 blockade as consolidation therapy following standard of care chemoradiation for unresectable stage III NSCLC. The first trial, PACIFIC, evaluated the role of consolidation Durvalumab versus no therapy following chemoradiation. Consolidation Durvalumab demonstrated imporoved median, 12-month, and 18-month PFS with only a very modest increase in overall toxicity, and it is now FDA-approved for use in this setting. The second trial, completed by the Hoosier Cancer Research Network (HCRN), assessed the safety and efficacy of pembrolizumab in this setting. That trial also confirmed the safety and feasibility of giving consolidation checkpoint blockade following concurrent chemoradiation, and the efficacy data from that trial will be presented at ASCO 2018.

In summary, unresectable stage III NSCLC represents an area with a need for improved treatment strategies as current survival outcomes are poor. The current standard of care is concurrent chemoradiation followed by consideration of consolidation Durvalumab. This trial looks to establish the safety and efficacy of consolidation Nivolumab alone and to evaluate whether combination immunotherapy with Nivolumab and Ipilimumab may improve upon outcomes with single-agent checkpoint blockade Previous trials in the metastatic setting, both in NSCLC and other tumor types, have suggested that combination immunotherapy may be more effective than monotherapy. This finding, in combination with the PACIFIC data, preclinical rationale for immunotherapy after radiation, and the safety and efficacy data from Checkmate 012, suggests that combination immunotherapy with nivolumab plus ipilimumab or nivolumab alone is worth investigating in unresectable stage III NSCLC. In this trial, the Nivolumab only arm will be compared to the historical control which was validated by

the placebo arm of PACIFIC (18-month PFS of 27%), and the combination immunotherapy arm will be compared to the Durvalumab arm of PACIFIC (18-month PFS of 44%) (15).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objectives

- Arm 1- To determine if consolidation therapy with nivolumab alone following concurrent chemoradiation improves 18-month progression free survival (PFS) relative to a historical control of chemoradiation alone, in subjects with inoperable or unresectable stage IIIA or IIIB NSCLC
- Arm 2- To determine if consolidation therapy with nivolumab and ipilimumab following concurrent chemoradiation improves 18-month PFS relative to a historical control of chemoradiation followed by single agent checkpoint inhibitor, in subjects with inoperable or unresectable stage IIIA or IIIB NSCLC

2.1.2 Secondary Objectives

- To determine if consolidation therapy with nivolumab alone following concurrent chemoradiation improves time to metastatic disease and overall survival (OS) relative to a historical control of chemoradiation alone in subjects with inoperable or unresectable stage IIIA or IIIB NSCLC (Arm 1).
- To determine if consolidation therapy with nivolumab and ipilimumab following concurrent chemoradiation improves time to metastatic disease and overall survival (OS) relative to a historical control of chemoradiation followed by single agent checkpoint inhibitor in subjects with inoperable or unresectable stage IIIA or IIIB NSCLC (Arm 2).
- To assess toxicity and tolerability of consolidation therapy with nivolumab plus ipilimumab or nivolumab alone following concurrent chemoradiation in subjects with inoperable or unresectable stage IIIA or IIIB NSCLC.

2.1.3 Correlative/Exploratory Objectives

- To assess PD-L1, CD4, CD8, expression levels in the tumor samples of subjects with inoperable or unresectable stage IIIA or IIIB NSCLC and correlate with PFS, OS, time to metastatic disease, and treatment toxicity.
- To assess associations between DNA, RNA, microRNA, DNA methylation, protein expression, lipidomic profiling, immune markers, protein biomarker panels, and other markers and efficacy and toxicity of treatment.
- To explore whether clinical characteristics may be associated with the development of pneumonitis and correlate with PFS, OS, time to metastatic disease, and treatment toxicity.
- To explore whether radiation treatment plan deviation or lung dosimetric factors may be associated with the development of pneumonitis and correlate with PFS, OS, time to metastatic disease, and treatment toxicity.
- To examine characteristics of BAL samples (e.g cytokines and chemockines) in patients who develop pneumonitis.

2.2 Endpoints

2.2.1 Primary Endpoints

- PFS at 18 months. PFS is defined as the time from randomization until the criteria for disease progression is met as defined by RECIST 1.1 or death as a result of any cause.
  - Arm 1- We hypothesize that consolidation with nivolumab alone will improve 18-month PFS from 30% with observation alone to 44%.
  - Arm 2- We hypothesize that consolidation with nivolumab plus ipilimumab will improve 18-month PFS from 44% with single agent PD-1/PD-L1 inhibition to 59% with combination immunotherapy.

2.2.2 Secondary Endpoints

- Overall survival will be defined as the time from randomization until death from any cause.
- Time to metastatic disease will be defined as the time from randomization until evidence of disease outside of the radiated field.
- Toxicities will be defined by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.

3. ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

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

1. Written informed consent and HIPAA authorization for release of personal health information.
   NOTE: HIPAA authorization may be included in the informed consent or obtained separately.

2. Age ≥ 18 years at the time of consent.

3. ECOG Performance Status of 0 or 1 within 14 days prior to registration.

4. Histological or cytological confirmation of NSCLC. A pathology report confirming the diagnosis of NSCLC must be obtained and reviewed by the treating physician prior to registration to study.

5. Must have unresectable or inoperable stage IIIA or IIIB disease according to the 7th edition IASLC stage classification for lung cancer. Subjects must be considered unresectable or inoperable based on the judgment of the treating physician.

6. Subjects must have completed concurrent chemoradiation with a platinum doublet and a dose of radiation ranging from 59.4-66.6 Gy. Subjects must have stable disease or disease response as evidenced on CT or PET scan evaluation. For those eligible, protocol therapy should begin within 56 days of completing chemoradiation
   OR
   Subjects must have completed up to 2 cycles of consolidation therapy started within 56 days of completion of radiation. After completion of consolidation chemotherapy, subjects must have stable disease or disease response as evidenced by CT or PET scan evaluation. For those eligible, protocol therapy should begin within 56 days after the last cycle of chemotherapy.

7. Prior cancer treatment must be completed between 1-56 days prior to registration and the subject must have recovered from all reversible acute toxic effects of the regimen (other than alopecia) to ≤Grade 1 or baseline.

8. Demonstrate adequate organ function as defined in the table below; all screening labs to be obtained within 14 days prior to registration.

System	Laboratory Value
Hematological	
Absolute Neutrophil Count (ANC)	≥ 1.5 K/mm^3
Hemoglobin (Hgb)	≥ 9 g/dL. Transfusion is allowed.
Platelets	≥100,000/mcl
Renal	
Serum creatinine **OR** Measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤ 1.5 x upper limit of normal (ULN) **OR** ≥ 60 mL/min for subjects with creatinine levels >1.5 x institutional ULN
Hepatic	
Bilirubin	≤ 1.5 × ULN **OR** Direct bilirubin of ≤ ULN for subjects with total bilirubin levels of >1.5x ULN
Aspartate aminotransferase (AST)	≤ 2.5 × ULN
Alanine aminotransferase (ALT)	≤ 2.5 × ULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT/INR/PTT is within therapeutic range of intended use of anticoagulants

9. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 7 days prior to registration. **NOTE:** Women are considered of childbearing potential unless they are surgically sterile (have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or are post-menopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. In addition, women under the age of 62 must have a documented serum follicle stimulating hormone (FSH) level greater than 40 mIU/mL to be considered post-menopausal.

10. Women of childbearing potential must be willing to abstain from heterosexual activity or use an effective method of contraception from the time of informed consent until 23 weeks after treatment discontinuation. See Section 5.5.2 for adequate methods of contraception.

11. Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men receiving study drug and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product. See Section 5.5.2 for methods of contraception.

12. As determined by the enrolling physician or protocol designee, ability of the subject to understand and comply with study procedures for the entire length of the study

3.2 Exclusion Criteria

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

1. Pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 23 weeks (female) or 31 weeks (male) after the last dose of trial treatment.
2. Active central nervous system (CNS) metastases. If symptomatic or without prior brain imaging, subjects must undergo a head computed tomography (CT) scan or brain MRI within 28 days prior to registration for protocol therapy to exclude brain metastases.
3. Treatment with any investigational agent within 28 days prior to registration for protocol therapy.
4. Prior chemotherapy, adjuvant therapy, or radiotherapy for lung cancer other than standard concurrent chemoradiation or up to 2 cycles of consolidation as described above.
5. Prior therapy with a PD-1, PD-L1, PD-L2 or CTLA-4 inhibitor or a lung cancer-specific vaccine therapy
6. Previously received a solid organ transplant or allogeneic progenitor/stem cell transplant.
7. Presence of metastatic disease (stage IV NSCLC) is not allowed. Subjects must be evaluated with a CT or PET scan prior to registration for protocol therapy to exclude metastatic disease.
8. Active second cancers.
9. Evidence of active autoimmune disease requiring systemic treatment within the past 90 days or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjogren's syndrome will not be excluded from the study
10. Interstitial lung disease or history of pneumonitis requiring treatment with corticosteroids
11. Diagnosis of immunodeficiency or is receiving chronic systemic corticosteroid therapy or other immunosuppressive therapy (excludes inhaled corticosteroids) within 7 days of first dose of study drug
12. History of psychiatric illness or social situations that would limit compliance with study requirements
13. Clinically significant acute infection requiring systemic antibacterial, antifungal, or antiviral therapy including:
    a. **tuberculosis** (clinical evaluation that includes clinical history, physical examination, and radiographic findings, and TB testing in line with local practice),

b. **hepatitis B** (known positive HBV surface antigen (HBsAg) result),
c. **hepatitis C**, or
d. **human immunodeficiency virus** (positive HIV 1/2 antibodies).
NOTES: Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA. Subjects with HIV/AIDS with adequate antiviral therapy to control viral load would be allowed if they are stable and have been on treatment for ≥ 4 weeks prior to first dose of study drug(s). Subjects with viral hepatitis with controlled viral load would be allowed while on suppressive antiviral therapy. Testing not required.

14. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the site investigator.

15. Hypersensitivity to nivolumab, ipilimumab, or any of their excipients.

16. Has received a live vaccine within 30 days prior to planned start of study therapy.
Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

4. SUBJECT REGISTRATION

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

Subjects must be registered and randomized prior to starting protocol therapy. Subjects must be randomized within **1 business day** of registration and begin therapy within **5 business days** of randomization/registration.

5. TREATMENT PLAN

This study is an open label, multicenter, randomized phase II trial of consolidation immunotherapy with either nivolumab alone or the combination of nivolumab and ipilimumab following concurrent chemoradiation in patients with unresectable stage III NSCLC.

Patients with unresectable stage IIIA or IIIB NSCLC (unresectable as defined by treating physician) will be treated outside this study with concurrent chemoradiation with a platinum doublet in addition to standard dose radiation (dosing can range from 59.4 Gy to 66.6 Gy). If repeat imaging within 56 days following completion of chemoradiation or consolidation shows no progressive or metastatic disease, the patients will be eligible for enrollment on the study.

5.1 Randomization and Stratification

At the time of enrollment, patients will be randomized in a 1:1 fashion to receive either nivolumab 480mg IV every 4 weeks or the combination of nivolumab 240mg IV every 2 weeks with ipilimumab

1mg/kg IV every 6 weeks. We chose a 1:1 randomization because the sample sizes in the two arms are approximately the same. Due to the slightly different sample sizes in the two arms, enrollment will be monitored closely and stopped when each arm reaches it goal. Consolidation immunotherapy will be continued until progression or unacceptable toxicity for up to a total of 24 weeks (see schema).

Subjects will be stratified by stage (IIIA vs. IIIB) and histology (squamous vs. non-squamous vs. NOS).

5.2 Study Drug Administration and Treatment Schedule

5.2.1 Dose Calculations

Arm 1: The dose of nivolumab will be a fixed dose (not based on subject's weight) at 480mg.

Arm 2: The dose of nivolumab will be a fixed dose at 240mg. The dose of ipilimumab will be weight-based at 1mg/kg. Weight should be based on a recording taken within 3 days of each study drug administration. Dosing only needs to be re-calculated if the current weight differs from the baseline weight by ≥10%.

5.2.2 Pre-medications

Subjects may receive Ondansetron 8mg IVPB in 50ml of normal saline infused over 10 minutes prior to immunotherapy on each day of treatment (or per institutional standards).

For subjects who experience a grade 1 or grade 2 infusion reaction, prior to subsequent infusions it is recommended that diphenhydramine 50 mg (or equivalent) and/or paracetamol (acetaminophen) 325 to 1000 mg should be administered at least 30 minutes before additional nivolumab or ipilimumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

5.2.3 Arm 1- Nivolumab Alone

Drug	Dose	Route	Schedule[1]	Cycle Length	Total Number of Cycles
Nivolumab	480mg	IV	Every 4 weeks	4 weeks	6
[1] A window of +/- 3 days may be applied to all study visits to accommodate observed holidays, inclement weather, scheduling conflicts etc. Date and time of each drug administration should be clearly documented in subject's chart and electronic case report forms (eCRFs).					

5.2.3.1 Arm 1: Nivolumab Administration

Nivolumab 480 mg will be administered as a 30 minute IV infusion on Day 1 of each 28 day cycle. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of +/-10 minutes is permitted (i.e., infusion time is 30 minutes: +/-10 min). Treatment will continue for up to 6 cycles, in the absence of prohibitive toxicities or disease progression.

5.2.4 Arm 2- Nivolumab Plus Ipilimumab

Drug	Dose	Route	Schedule	Cycle Length	Total Number of Cycles
Nivolumab (1st)	240mg	IV	Every 2 weeks[1]	6 weeks (42 days)	4
Ipilimumab (2nd)	1mg/kg	IV	Every 6 weeks[2]		

[1] A window of ±3 days may be applied to all nivolumab treatments to accommodate observed holidays, inclement weather, scheduling conflicts etc as long as nivolumab is not given any earlier than 12 days from the previous dose.
[2] A window of ±5 days may be applied to all ipilimumab treatments to accommodate observed holidays, inclement weather, scheduling conflicts, etc.
Date and time of each drug administration should be clearly documented in subject's chart and electronic case report forms (eCRFs).

5.2.4.1 Arm 2: Nivolumab Administration

Nivolumab 240mg will be administered as a 30 minute IV infusion on Day 1, 15, and 29 of each 42 day cycle. Nivolumab should not be given any earlier than 12 days from the previous dose. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of +/-10 minutes is permitted (i.e., infusion time is 30 minutes: +/-10 min). Treatment will continue for up to 4 cycles, in the absence of prohibitive toxicities or disease progression.

5.2.4.2 Arm 2: Ipilimumab Administration

Ipilimumab 1mg/kg will be administered as a 30 minute IV infusion on Day 1 of each 42 day cycle. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of +/-10 minutes is permitted (i.e., infusion time is 30 minutes: +/-10 min). Treatment will continue for up to 4 cycles, in the absence of prohibitive toxicities or disease progression.

On day 1 of cycle 1, nivolumab will be given first, followed by 30 minutes of monitoring, and then ipilimumab given second, followed by 30 minutes of monitoring. If the subject does not have an infusion reaction during the first cycle, the post-ipilimumab monitoring may be discontinued for subsequent cycles at the discretion of the treating physician. Day 1 monitoring between the nivolumab/ ipilimumab infusions will continue throughout all 4 cycles. Post nivolumab monitoring on days 15 and 29 is not mandatory and should follow the guidelines of the local infusion center.

5.3 Concomitant Medications

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered more than 30 days after the last dose of trial treatment should be recorded for serious adverse events (SAE) as defined in Section 11.1.2.

5.3.1 Allowed Concomitant Medications

All treatments that the site investigator considers necessary for a subject's welfare may be administered at the discretion of the site investigator in keeping with the community standards of medical care. All

concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

5.3.2 Prohibited Concomitant Medications

Medications or vaccinations 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 site investigator should discuss any questions regarding this with BTCRC AHQ who will then communicate with the sponsor-investigator and Bristol-Myers Squibb Clinical team regarding the situation. The final decision on any supportive therapy or vaccination rests with the site investigator and/or the subject's primary physician. There are no prohibited therapies during the Post-Treatment Follow-up Phase.

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than nivolumab or ipilimumab
- Radiation therapy
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.

- Systemic glucocorticoids (>10 mg prednisone equivalent) for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. Brief, limited use of systemic corticosteroids (≤7 days) are permitted where such use is considered standard of care (e.g. as premedication for contrast allergy or for COPD exacerbation). Inhaled or topical steroids, and adrenal replacement doses of steroids (for example prednisone 10mg daily) are permitted while on study.

Subjects who, in the assessment by the site investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.4 Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the site investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology 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. The treatment guidelines are intended to be applied when the investigator determines the events to be related to nivolumab or ipilimumab.

5.4.1 Suggested supportive care measures for the management of adverse events that are related to nivolumab or ipilimumab

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab and ipilimumab are considered immuno-oncology agents in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of AEs: Gastrointestinal, Renal, Pulmonary, Hepatic, Endocrinopathies, Skin, Neurological.

For subjects expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage an AE, consider recommendations provided in the algorithms. These algorithms are found in Appendix 1. The guidance provided in these algorithms should not replace the Investigator's medical judgment but should complement it.

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.

Patients who are started on steroids for management of an immune-related event should not resume immunotherapy until steroids have been tapered to ≤ prednisone 10mg daily or an equivalent dose of an alternative corticosteroid.

- **Management of Infusion Reactions:** Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs.

The table below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of nivolumab.

Management of Infusion Related Reaction (IRR), Allergic Reaction, Hypersensitivity reaction or Bronchospasm from Nivolumab or Ipilimumab

Description	Action
CTCAE Grade 1 IRR, allergic reaction or bronchospasm[1]	Remain at bedside and monitor subject until recovery from symptoms.
CTCAE Grade 2 IRR, allergic reaction or bronchospasm[1]	Stop the 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 nivolumab 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).
CTCAE Grade 3 or 4 IRR, allergic reaction, bronchospasm or hypersensitivity reaction[2]	Immediately discontinue infusion of nivolumab. 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. ***Nivolumab or ipilimumab 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 (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).
[1]For any ≤Grade 2 IRR, allergic reaction or bronchospasm, see Section 5.1.2 for recommended premedication for subsequent infusions. [2]Hypersensitivity reactions included in CTCAEv4 include anaphylaxis, Stevens-Johnson syndrome and toxic epidermal necrolysis; 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).	

5.5 Diet/Activity/Other Considerations

5.5.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

5.5.2 Contraception

Women of childbearing potential are defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes. In addition, women under the age of 62 must have a documented serum follicle stimulating hormone (FSH) level greater than 40 mIU/mL to be considered post-menopausal.

Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year Men receiving study drug and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product.

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

5.5.2.1 Highly Effective Methods of Contraception

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

5.5.2.2 Less Effective Methods of Contraception

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

5.5.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with nivolumab or ipilimumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Big Ten Research Consortium (BTCRC) **within 24 hours** of discovery of event and BTCRC will notify the sponsor-investigator and Bristol-Myers Squibb **within 24 hours** if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The site investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to BTCRC who will report to Bristol-Myers Squibb. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the BTCRC who will report the event to Bristol-Myers Squibb and followed as described above.

6. TOXICITIES AND DOSE DELAYS/DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v4 will be used to grade adverse events.

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

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

Subjects discontinued from the treatment phase of the study for any reason will be evaluated 30 days (± 7) after the last dose of protocol therapy.

6.1 Dose Delays/Dose Modifications

Nivolumab and/or ipilimumab will be withheld for drug-related: Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 3 including laboratory abnormalities, and severe or life-threatening AEs as per the table below. Protocol therapy will also be held for some persistent grade 2 toxicities (please see table below).

There are no dose reductions for either nivolumab or ipilimumab. For toxicity as outlined in this protocol, study therapy should be delayed until the adverse event improves to the stated level or should be discontinued permanently depending on severity (see table below and section 5.4).

Dose modification guidelines for drug-related adverse events

Toxicity	Hold Treatment For	Timing for Restarting Treatment	Discontinue Subject
Diarrhea/Colitis	Grade 2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose unless delay beyond 6 weeks allows for prolonged steroid taper to manage toxicity. In such cases, the Sponsor Investigator must be consulted prior to re-initiating treatment.
	Grade 4	Permanently discontinue	Permanently discontinue
Pneumonitis	Grade 2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose unless delay beyond 6 weeks allows for prolonged steroid taper to manage toxicity. In such cases, the Sponsor Investigator must be consulted prior to re-initiating treatment.
	Grade 3-4	Permanently discontinue	Permanently discontinue
Hepatitis	≥ Grade 2 if subject has baseline AST, ALT or total bilirubin that is within	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose unless delay beyond 6 weeks

Toxicity	Hold Treatment For	Timing for Restarting Treatment	Discontinue Subject
	normal limits; ≥ Grade 3 if subject has baseline AST, ALT or total bilirubin within the Grade 1 toxicity range		allows for prolonged steroid taper to manage toxicity. In such cases, the Sponsor Investigator must be consulted prior to re-initiating treatment.
	AST or ALT > 8 x ULN **OR** total bilirubin >5 x ULN **OR** concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN	Permanently discontinue	Permanently discontinue
Type I diabetes mellitus [TIDM] (if new onset) or Hyperglycemia	New onset T1DM or Grade 3 hyperglycemia	Toxicity resolves to Grade 0-1 even if requires physiologic hormone replacement	Resume nivolumab or ipilimumab when subjects are clinically and metabolically stable.
	Grade 4	May need to permanently discontinue; see footnote #4	May need to permanently discontinue; see footnote #4
Hypophysitis	Grade 2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose unless delay beyond 6 weeks allows for prolonged steroid taper to manage toxicity. In such cases, the Sponsor Investigator must be consulted prior to re-initiating treatment.
	Grade 4	Permanently discontinue	Permanently discontinue
Nephritis and Renal Dysfunction	Serum creatinine more than 1.5 and up to 6 times the upper limit of normal	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose unless delay beyond 6 weeks allows for prolonged steroid taper to manage toxicity. In such cases, the Sponsor Investigator must be consulted prior to re-initiating treatment.
	Serum creatinine more than 6 times the upper limit of normal	Permanently discontinue	Permanently discontinue
Skin	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose unless delay beyond 6 weeks allows for prolonged steroid taper to manage toxicity. In such cases, the Sponsor Investigator must be consulted prior to re-initiating treatment.
	Grade 4 or confirmed SJS or TEN	Permanently discontinue	Permanently discontinue

Toxicity	Hold Treatment For	Timing for Restarting Treatment	Discontinue Subject
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose unless delay beyond 6 weeks allows for prolonged steroid taper to manage toxicity. In such cases, the Sponsor Investigator must be consulted prior to re-initiating treatment.
	Immune-mediated encephalitis	Permanently discontinue	Permanently discontinue
Adrenal Insufficiency	Grade 2	Toxicity resolves to Grade 0-1 even if requires physiologic hormone replacement	Toxicity does not resolve within 12 weeks of last dose.
	Grade 3-4	May need to permanently discontinue; see footnote #4	May need to permanently discontinue; see footnote #4
Uveitis[1]	≥Grade 2	Permanently discontinue	Permanently discontinue
Thrombocytopenia	Grade 3 >7 days or associated with bleeding or Grade 4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity	Grade 2[2]	Toxicity resolves to Grade 0-1 even if requires physiologic hormone replacement for drug related endocrinopathy	Toxicity does not resolve within 6 weeks of last dose unless delay beyond 6 weeks allows for prolonged steroid taper to manage toxicity. In such cases, the Sponsor Investigator must be consulted prior to re-initiating treatment.
	Grade 3 or severe[3]	Toxicity resolves to Grade 0-1 even if requires physiologic hormone replacement for drug related endocrinopathy	Toxicity does not resolve within 6 weeks of last dose unless delay beyond 6 weeks allows for prolonged steroid taper to manage toxicity. In such cases, the Sponsor Investigator must be consulted prior to re-initiating treatment.
	Grade 4[4]	Permanently discontinue	Permanently discontinue

[1] Uveitis or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment

[2] Exceptions include grade 2 drug-related fatigue or laboratory abnormalities; do not delay for these events.

[3] Exceptions include grade 3 lymphopenia or leukopenia; do not delay for these events. In addition, any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay. The Investigator should be consulted for such Grade ≥ 3 amylase or lipase abnormalities.

[4] The following events do not require discontinuation:

- Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to ≤ Grade 1 within 6 weeks of onset. If recovery occurs,

Toxicity	Hold Treatment For	Timing for Restarting Treatment	Discontinue Subject
drug(s) may be restarted at the discretion of the treating physician. If asymptomatic grade 2 or greater amylase or lipase abnormalities still exists after 6 weeks, the sponsor investigator should be notified and patients may be given up to 12 weeks to recover to ≤ Grade 1. Permanently discontinue for any grade 4 amylase or lipase abnormalities that are associated with symptoms or clinical manifestations of pancreatitis that do not decrease to ≤ Grade 3 within 1 week of onset. • Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset • Grade 4 lymphopenia or leucopenia • Grade 4 drug-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Investigator. **Note:** Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event. Subjects with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.			

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, trial treatment should be discontinued after consultation with BTCRC and the sponsor-investigator. With site investigator and sponsor-investigator agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled. For information on the management of adverse events, see Section 5.3. If a subject has a delay of more than 12 weeks or more than 3 delays in study drug dosing due to toxicities they will be discontinued from the trial treatment.

Subjects who experience a recurrence of the same severe or life-threatening event at the same grade or greater with re-challenge of nivolumab or ipilimumab should be discontinued from trial treatment.

For subjects on Arm 2 with immune-related adverse events, the assessment for discontinuation of ipilimumab should be made separately from the assessment for discontinuation of nivolumab. Although there is overlap among the discontinuation criteria, if criteria are met for ipilimumab but not for nivolumab, treatment with nivolumab may continue if ipilimumab is discontinued. If a subject meets criteria for discontinuation and treating physician is unable to determine whether the event is related to nivolumab or ipilimumab, the subject should discontinue both nivolumab and ipilimumab.

6.2 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be withdrawn from the trial at the discretion of the site investigator should any untoward effect occur. In addition, a subject may be withdrawn by the sponsor-investigator or BTCRC if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided below.

A subject must be discontinued from the trial treatment for any of the following reasons:

- Confirmed radiographic disease progression by RECIST 1.1 criteria
- Unacceptable adverse experiences as described in Section 5.3 and 11.1

- Intercurrent illness that prevents further administration of treatment
- Site investigator's decision to withdraw the subject
- A female subject has a confirmed positive serum/urine pregnancy test
- Noncompliance with trial treatment or procedure requirements
- Completed 6 months of treatment with protocol therapy
- Subject refuses further treatment
- If a subject has a treatment delay of more than 12 weeks from last infusion. See section 6.1.

A subject must be discontinued from the trial for any of the following reasons:

- Administrative reasons
- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- The subject is lost to follow-up

The End of Treatment and Follow-up visit procedures are listed in Section 7 (Study Schedule of Events and Visit Requirements). After the end of treatment, each subject will be followed for 100 days for adverse event monitoring (serious adverse events will be collected for 100 days after the end of treatment as described in Section 12.2.2). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed for survival for up to 2 years, withdrawal of consent, or the end of the study, whichever occurs first.

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 12.2.1 – AE Reporting).

6.3 Protocol Discontinuation

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

7. ARM 1 (NIVOLUMAB): STUDY CALENDAR & EVALUATIONS

Cycle Length: Arm 1= 28 days	Screening		On Treatment Cycle 1+	Safety Follow up	Long Term Follow up[11]
	-28 d	-14 d	Day 1 (±3)	30 days (±7)	(±14 days)
REQUIRED ASSESSMENTS					
Informed Consent	X				
Medical history (inc. NGS results, if done) and Height[1]		X			
Physical examination including vital signs (BP, weight)		X	X	X	
ECOG performance status		X	X	X	
AEs & concomitant medications[2]		X	X	+30, +100	X
Radiation Treatment Plan Data[3]	X				
LABORATORY TESTING					
CBC with differential and platelet count		X	X[4]	X	
Complete Metabolic Profile		X	X[4]	X	
Direct bilirubin, Mg, Phos		X	X[4]	X	
Creatinine clearance[5]		X			
PT/INR and aPTT		X			
Thyroid function (TSH, T3, T4)[6]		X	C1[4], Every odd cycle[6]		
ESR, CRP, vWF Ag and ferritin[5]			Pre C1, Pre C2	X[5]	
WOCBP: Serum or Urine pregnancy test, FSH (as needed)[7]		-7d[7]			
DISEASE ASSESSMENT					
Pathology Report of diagnosis	X[8]				
CT of chest through adrenals or PET CT[9]	X[10]		Q 12 weeks during Tx[10]		X[11]
CT or MRI Brain[12]	X				
TREATMENT EXPOSURE (Arm1)- treatment window +/- 3 days					
Nivolumab 480mg Q4W			X[13]		
CORRELATIVE STUDIES					
Mandatory Unstained Slides for Analyses, if available[14]	X				
Mandatory Whole Blood for Somatic Baseline			Pre C1		
Mandatory Blood, Serum, and Plasma for Analyses[15]			Pre C1, Pre C2	X	
Optional Bronchoalveolar Lavage[16]			X[16]		
BANKING SAMPLES					
Optional Whole Blood[17]			Pre C1, Pre C2	X	
Optional Unstained Slides[18]		X			
Optional Serum and Plasma[19]			Pre C1, Pre C2	X	
FOLLOW-UP					
Progression and survival[11]					X

Arm 1- Key to Footnotes

1. Medical history to include demographics, trial awareness question, smoking history, prior treatments, radiation and surgical history. Smoking history to include: amount, frequency, start and stop dates of cigarette, cigar and pipe usage. If subject has prior genetic sequencing analyses results available, those results should be submitted by end of Cycle 1.
2. Treatment-related adverse events will be followed until resolution, return to baseline, or deemed clinically insignificant. Adverse events (from time of consent) and concomitant medications (28 days prior to start of protocol treatment) should be assessed and recorded until 100 days after last dose of study drug. SAE's and the conmeds used to treat them will be collected up to 100 days post treatment.
3. Collection of radiation treatment plan data can take place any time during the study. Data such as total lung volume, V20, and additional radiation parameters will be collected. See Documents/Info tab of the EDC. This data will be recorded in the database for future analysis, but it will not affect treatment while on study and is not required to be collected prior to enrollment or initiation of treatment.
4. C1D1 testing does not need to be repeated if performed within 7 days of starting protocol therapy.
5. Measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl). Erythrocyte Sedimentation Rate (ESR); C-Reactive Protein (CRP); von Willebrand Factor antigen (vWF Ag). Collect ESR, CRP, vWF and ferritin pre-treatment on C1D1, C2D1 and either at the End of Treatment or if the subject develops any grade 3-4 pneumonitis.
6. Thyroid function testing: Perform TSH, T3, T4 at baseline and at odd cycles starting at cycle 3 (i.e. Q 8 wks). T3, T4: free/ total as per local standards.
7. For women of childbearing potential. Must have negative pregnancy test within 7 days of registration. Women < 62 yrs old must have FSH > 40 mIU/mL to be considered post-menopausal.
8. A pathology report confirming the diagnosis of NSCLC must be obtained and reviewed by the treating physician prior to registration to study.
9. All patients require Chest CT through adrenals or PET-CT at the time of screening and at subsequent imaging time points. Abdomen or pelvic CTs or bone scans can be included at the discretion of the treating physician should it be clinically indicated, but these are not mandatory.
10. Screening scan including at least CT portion of the chest and abdomen must be performed within 56 days after the completion of chemoradiation or consolidation. PET CT may be done in place of regular CT scans at the discretion of the site investigator. Baseline scans should be done within 28 days prior to treatment initiation. Radiographic disease assessment will be done every 12 weeks ± 4 weeks during study treatment. The scan interval may be reset if scans were done early for clinical reasons. See also 8.3.
11. After completion of protocol therapy, subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. Post treatment radiographic disease assessment should be performed every 3 months until progression. After documented disease progression each subject will be followed for survival every 3 months for up to 2 years, withdrawal of consent, or the end of the study (whichever occurs first).
12. A head MRI or CT should be done prior to study treatment for subjects that are symptomatic or have not had prior brain imaging.
13. For subjects who meet all eligibility criteria and have recovered sufficiently from treatment with chemoradiation, initial consolidation therapy with nivolumab will be started within 56 days after chemoradiation is complete. For subjects who meet all eligibility criteria after completion of up to two consolidation chemotherapy treatments, therapy with nivolumab will be started within 56 days after last cycle of chemotherapy.
14. Mandatory submission of unstained slides from an archived tumor block (if available) for PD-L1, CD4, CD8 by IHC. In addition, whole exome sequencing, RNA sequencing, methylation analysis will be performed. See Correlative Laboratory Manual (CLM) for collection, labeling and shipping instructions.
15. Mandatory blood samples for correlative testing should be drawn pre-treatment on C1D1, C2D1 and either at the End of Treatment Visit or if the subject develops any grade 3-4 pneumonitis. See CLM for collection, labeling, and shipping instructions.
16. If subject has a bronchoscopy with BAL for clinical reasons, please collect a portion of the of BAL fluid for correlative analysis (optional).
17. Optional submission of whole blood for banking is to be collected at Pre-Treatment C1D1, C2D1, and End of Treatment Visit. See CLM for collection, processing, labeling and shipping instructions.
18. Optional submission of unstained slides for banking from an archived FFPE tumor block is requested. See CLM for collection, labeling, and shipping instructions.
19. Optional submission of serum and plasma for banking are to be collected at Pre-Treatment C1D1, C2D1, and End of Treatment Visit. See CLM for collection, labeling, processing, and shipping instructions.

8. ARM 2 (NIVOLUMAB + IPILIMUMAB): STUDY CALENDAR & EVALUATIONS

Cycle Length: Arm 2= 42 days	Screening		On Treatment Cycle 1+ (±3)			Safety Follow up	Long Term Follow up[11]
	-28 d	-14 d	Day 1	Day 15[11]	Day 29[11]	30 days (±7)	(±14 days)
REQUIRED ASSESSMENTS							
Informed Consent	X						
Medical history (inc. NGS results, if done) and Height[1]		X					
Physical examination including vital signs (BP, weight)		X	X	X	X	X	
ECOG performance status		X	X	X	X	X	
AEs & concomitant medications[2]		X	X	X	X	+30, +100	X
Radiation Treatment Plan Data[3]			X				
LABORATORY TESTING							
CBC with differential and platelet count		X	X[4]	X	X	X	
Complete Metabolic Profile		X	X[4]	X	X	X	
Direct bilirubin, Mg, Phos		X	X[4]			X	
Creatinine clearance[5]		X					
PT/INR and aPTT		X					
Thyroid function (TSH, T3, T4)[6]		X	X[4]				
ESR, CRP, vWF Ag and ferritin[5]			preC1,C2			X[5]	
WOCBP: Serum or Urine pregnancy test, FSH (as needed)[7]		-7d[7]					
DISEASE ASSESSMENT							
Pathology Report of diagnosis	X[8]						
CT of chest through adrenals or PET CT[9]	X[10]		Q 12 weeks during treatment[10]				X[11]
CT or MRI Brain[12]	X						
TREATMENT EXPOSURE (Arm2)- treatment window +/- 3 days							
Nivolumab 240mg Q2W			X[13]	X	X		
Ipilimumab 1mg/kg Q6W			X[13]				
CORRELATIVE STUDIES							
Mandatory Unstained Slides for Analyses, if available[14]	X						
Mandatory Whole Blood for Somatic Baseline			Pre C1				
Mandatory Blood, Serum, and Plasma for Analyses[15]			preC1,C2			X	
Optional Bronchoalveolar Lavage[16]			X			X[14]	
BANKING SAMPLES							
Optional Whole Blood[17]			preC1,C2			X	
Optional Unstained Slides[18]		X					
Optional Serum and Plasma[19]			preC1,C2			X	
FOLLOW-UP							
Progression and survival[11]							X

Arm 2- Key to Footnotes

1. Medical history to include include demographics, trial awareness question, smoking history, prior treatments, radiation and surgical history. Smoking history to include: amount, frequency, start and stop dates of cigarette, cigar and pipe usage. If subject has prior genetic sequencing analyses results available, those results should be submitted by end of Cycle 1.
2. Treatment-related adverse events will be followed until resolution, return to baseline, or deemed clinically insignificant. Adverse events (from time of consent) and concomitant medications (28 days prior to start of protocol treatment) should be assessed and recorded until 100 days after last dose of study drug. SAE's and the conmeds used to treat them will be collected up to 100 days post treatment. See Section 8.5.
3. Collection of radiation treatment plan data can take place any time during the study. Data such as total lung volume, V20, and additional radiation parameters will be collected. See Documents/Info tab of the EDC. This data will be recorded in the database for future analysis, but it will not affect treatment while on study and is not required to be collected prior to enrollment or initiation of treatment.
4. C1D1 testing does not need to be repeated if performed within 7 days of starting protocol therapy.
5. Measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl). Erythrocyte Sedimentation Rate (ESR); C-Reactive Protein (CRP); von Willebrand Factor antigen (vWF Ag). Collect ESR, CRP, vWF and ferritin pre-treatment on C1D1, C2D1 and either at the End of Treatment or if the subject develops any grade 3-4 pneumonitis.
6. Thyroid function testing: Perform TSH, T3, T4 at baseline and on Day 1 of each cycle (i.e. every 6 weeks). T3, T4: free/ total as per local standards.
7. For women of childbearing potential. Must have negative pregnancy test within 7 days of registration. Women < 62 yrs old must have FSH > 40 mIU/mL to be considered post-menopausal.
8. A pathology report confirming the diagnosis of NSCLC must be obtained and reviewed by the treating physician prior to registration to study.
9. All patients require Chest CT through adrenals or PET-CT at the time of screening and at subsequent imaging time points. Abdomen or pelvic CTs or bone scans can be included at the discretion of the treating physician should it be clinically indicated, but these are not mandatory.
10. Screening scan including at least CT portion of the chest and abdomen must be performed within 56 days after the completion of chemoradiation. PET CT may be done in place of regular CT scans at the discretion of the site investigator. Baseline scans should be done within 28 days prior to treatment initiation. Radiographic disease assessment will be done every 12 weeks ±4 weeks during study treatment. The scan interval may be reset if scans were done early for clinical reasons. See also 8.3.
11. After completion of protocol therapy, subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. Post treatment radiographic disease assessment should be performed every 3 months until progression. After documented disease progression each subject will be followed for survival every 3 months for up to 2 years, withdrawal of consent, or the end of the study (whichever occurs first).
12. A head MRI or CT should be done prior to study treatment for subjects that are symptomatic or have not had prior brain imaging.
13. For subjects who meet all eligibility criteria and have recovered sufficiently from treatment with chemoradiation, initial consolidation therapy with nivolumab and ipilimumab will be started within 56 days after chemoradiation is complete. For subjects who meet all eligibility criteria after completion of up to two consolidation chemotherapy treatments, therapy with nivolumab and ipilimumab will be started within 56 days after last cycle of chemotherapy.
14. Mandatory submission of unstained slides from an archived tumor block (if available) for PD-L1, CD4, CD8 by IHC. In addition, whole exome sequencing, RNA sequencing, methylation analysis will be performed. See CLM for collection, labeling and shipping instructions.
15. Mandatory blood samples for correlative testing should be drawn pre-treatment on C1D1, C2D1, and either at the End of Treatment Visit or if the subject develops any grade 3-4 pneumonitis. See CLM for collection, labeling, and shipping instructions.
16. If subject has a bronchoscopy with BAL for clinical reasons, please collect a portion of BAL fluid for correlative analysis (optional).
17. Optional submission of whole blood for banking is to be collected at Pre-Treatment C1D1, C2D1, and End of Treatment Visit. See CLM for collection, processing, labeling and shipping instructions.
18. Optional submission of unstained slides for banking from an archived FFPE tumor block is requested. See CLM for collection, labeling, and shipping instructions.
19. Optional submission of serum and plasma for banking are to be collected at Pre-Treatment C1D1, C2D1, and End of Treatment Visit. See CLM for collection, labeling, processing, and shipping instructions.

8.1 Screening Evaluations

8.1.1 Within 28 days prior to registration for protocol therapy

- Informed consent
- Pathology Report Confirmation. A pathology report confirming the diagnosis of NSCLC must be obtained and reviewed by the treating physician prior to registration to the study.
- Radiology Imaging: A CT of the chest and abdomen will be done within 56 days after chemoradiation. This imaging will be done within 28 days of treatment initiation on study. A PET CT may be done instead of regular CT scans. A head MRI or CT should be done for subjects that are symptomatic or have not had prior brain imaging of study treatment.
- Mandatory submission of unstained slides from an archived tumor block for correlative analysis, if available. New biopsy is not required if archival tissue is not available. Tissue should be identified and requested before registration; submission to BTCRC AHQ will occur after subject is successfully registered. Analysis will include PD-L1 and other IHC, and genetic analyses.
- Optional submission of unstained slides from an archived tumor block for banking, with consent. Tissue should be identified and requested before registration; submission to BTCRC AHQ will occur after subject is successfully registered.
- Collection of radiation treatment plan data can take place any time during the study. Data such as total lung volume, V20, and additional radiation parameters will be collected. See Documents/Info tab of the EDC. This data will be recorded in the database for future analysis, but it will not affect treatment while on study and is not required prior to enrollment or initiation of treatment.

8.1.2 Within 14 days prior to registration for protocol therapy

- Medical History. Medical history to include demographics, trial awareness question, smoking history, prior treatments, radiation and surgical history. Smoking history to include: amount, frequency, start and stop dates of cigarette, cigar and pipe usage. If subject has prior genetic sequencing analyses results available, those results should be submitted by end of Cycle 1.
- Height
- Physical examination including vital signs (blood pressure, weight)
- ECOG performance status
- Complete Metabolic Profile to include Na, K, Cl, CO_2, total bilirubin, total protein, albumin, alk phos, AST, ALT, serum creatinine, BUN, calcium, and glucose. Direct bilirubin, Mg and Phos will also be drawn. Please see Section 3.1.8 for additional information regarding serum creatinine, calculated creatinine clearance and GFR values.
- Complete Blood Count with differential to include absolute neutrophil count (ANC), platelets and hemoglobin
- PT/INR and aPTT
- Thyroid function (TSH, T3, T4); T3, T4: free/ total as per local standards.
- **Within 7 days**: Serum or urine pregnancy test for women of childbearing potential. Women < 62 yrs old must have FSH > 40 mIU/mL to be considered post-menopausal.
- Adverse events and concomitant medications.

8.2 On Treatment Evaluations

8.2.1 Treatment Arm 1 (cycle length = 28 days)

8.2.1.1 Day 1 of each cycle

- Physical examination including vital signs (blood pressure, weight)
- ECOG performance status
- Complete Metabolic Profile to include Na, K, Cl, CO_2, total bilirubin, total protein, albumin, alk phos, AST, ALT, creatinine, BUN, calcium, and glucose. Direct bilirubin, Mg and Phos will also be drawn. (For C1D1 do not repeat if screening CMP is within 7 days of starting protocol therapy)
- Complete Blood Count with differential to include absolute neutrophil count (ANC), platelet and hemoglobin (For C1D1 do not repeat if screening CBC is within 7 days of starting protocol therapy).
- Thyroid function (TSH, T3, T4) (For C1D1 do not repeat if screening testing is within 7 days of starting protocol therapy). T3, T4: free/ total as per local standards.
- ESR, CRP, vWF Ag and ferritin: pre-treatment C1D1 and C2D1
- Adverse events and concomitant medications.
- Nivolumab 480 mg IV
- Blood samples for correlative testing will be drawn at pre-treatment C1D1 and C2D1.

8.2.1.2 Odd numbered cycles starting at Cycle 3

- Thyroid function (TSH, T3, T4) (For C1D1 do not repeat if screening testing is within 7 days of starting protocol therapy). T3, T4: free/ total as per local standards.

8.2.2 Treatment Arm 2 (cycle length = 42 days)

8.2.2.1 Day 1 of each cycle

- Physical examination including vital signs (blood pressure, weight)
- ECOG performance status
- Complete Metabolic Profile to include Na, K, Cl, CO_2, total bilirubin, total protein, albumin, alk phos, AST, ALT, creatinine, BUN, calcium and glucose. Direct bilirubin, Mg and Phos will also be drawn. (For C1D1 do not repeat if screening CMP is within 7 days of starting protocol therapy)
- Complete Blood Count with differential to include absolute neutrophil count (ANC), platelet and hemoglobin (For C1D1 do not repeat if screening CBC is within 7 days of starting protocol therapy).
- Thyroid function (TSH, T3, T4) (For C1D1 do not repeat if screening testing is within 7 days of starting protocol therapy). T3, T4: free/ total as per local standards.
- ESR, CRP, vWF Ag and ferritin: pre-treatment C1D1 and C2D1
- Adverse events and concomitant medications.
- Nivolumab 240mg IV
- Ipilimumab 1mg/kg IV
- Blood samples for correlative testing will be drawn at pre-treatment C1D1 and C2D1.

8.2.2.2 Day 15 and 29 of each cycle

- Physical examination including vital signs (blood pressure, weight)
- ECOG performance status
- Complete Metabolic Profile
- Complete Blood Count with differential
- Adverse events and concomitant medications.
- Nivolumab 240mg IV

8.3 Imaging while on treatment

All patients are required to have either chest and abdomen CTs or PET/CT as part of their initial screening imaging. Following initiation of treatment, patients should undergo repeat imaging every 12 weeks while on treatment. However, the scan interval may be reset if scans were done sooner for clinical reasons. This imaging should include at least chest CT or PET/CT (per discretion of treating physician) and should include abdomen CT if clinically indicated. If not clinically indicated, abdomen CT does not have to be done at each imaging time point. Imaging may be done locally. The window for imaging while on treatment is ±4 weeks.

8.4 Safety Follow-up Evaluations

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

- Physical examination including vital signs (blood pressure, weight)
- ECOG performance status
- Complete Metabolic Profile
- Complete Blood Count with differential
- ESR, CRP, vWF Ag and ferritin
- Adverse events, and concomitant medications must be assessed. Treatment-related adverse events will be followed until resolution, return to baseline, or deemed clinically insignificant. Adverse events (from time of consent) and concomitant medications (28 days prior to start of protocol treatment) should be assessed and recorded until 100 days after last dose of study drug. SAE's and the conmeds used to treat them will be collected up to 100 days post treatment. See Section 8.5 below.
- Mandatory blood samples for correlative testing and optional samples for banking will be drawn

8.5 Long Term Follow-up Evaluations

After completion of protocol therapy, subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed for survival every 3 months (± 4 weeks) for up to 2 years, withdrawal of consent, or the end of the study (whichever occurs first).

- Treatment-related adverse events will be followed until resolution, return to baseline, or deemed clinically insignificant. Adverse events (from time of consent) and concomitant medications (28 days prior to start of protocol treatment) should be assessed and recorded until 100 days after last

dose of study drug or until a new anti-cancer treatment starts, whichever is earlier. SAE's and the conmeds used to treat them will be collected up to 100 days post treatment.

- For subjects who discontinue for reasons other than progressive disease, radiographic disease assessment should be performed every 3 months for up to 2 years until progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. The scan interval may be reset if scans were done sooner for clinical reasons. PET CT may be done in place of regular CT scans at the discretion of the site investigator. This imaging may be done locally. Once patients are off treatment and on follow-up, the window for imaging is ±4 weeks.

9. BIOSPECIMEN STUDIES AND PROCEDURES

For tumor specimens or blood collected in the protocol, please see the Correlative Laboratory Manual (CLM) for additional information regarding collection, labeling and shipping.

9.1 Mandatory Unstained Slides for Analysis[1]

Mandatory submission of formalin-fixed, paraffin-embedded archival tumor tissue block for biomarker evaluation are requested if available. A new biopsy is not required if archival tissue is not available. Tissue should be identified and requested before registration; submission to BTCRC AHQ will occur after subject is successfully registered.These biopsy samples should be from current diagnosis and should be excisional, incisional, punch or core needle. Fine needle aspirate samples should be collected via a needle of 18 gauges or larger or be collected per institutional guidelines. Samples should be evaluated for tumor cell quantity (i.e. >100 tumor cells) to allow for adequate PD-L1 immunohistochemistry analyses. Sample requirement is FFPE block or unstained slides. Please see CLM for sample specifications.

Specimens will be submitted for immune marker analyses, including PD-L1.

- If subject has prior PD-L1 results, the results will be sent at the time of other tissue submission. PD-L1 testing will not be repeated if one of the following testing platforms were used: Merck (Dako 22C3), BMS (Dako 28-8) or AstraZeneca (Ventana SP263). Submitted tissue will then be re-prioritized for use in other biomarker analyses.[1]
- If prior PD-L1 testing was not performed or an acceptable platform was not used, PD-L1 immunohistochemistry (IHC) will be assessed centrally using the PD-L1 28-8 FDA (OPDIVO) kit. PD-L1 stained tissue sections will be assessed by a pathologist at Neogenomics and scored as PD-L1 positive if membrane staining is observed, with a minimum requirement of 100 evaluable tumor cells.

Additional IHC such as (but not limited to) CD4, CD8 to be performed by Neogenomics.

In addition, tissue will be dissected and nucleic acids extracted for genetic analyses. Genetic analyses to be performed may include CAPP-Seq, Whole Exome Sequencing, RNA-seq, and DNA methylation analyses.

[1]: Tissue prioritization: PD-L1 is first priority. If sufficient tissue remains then CD8, followed by CD4. If sufficient tissue is still available then genetic sequencing, and finally methylome analyses.

9.2 Mandatory Whole Blood Collection for Somatic Baseline

Whole blood samples will be collected prior to C1D1 treatment.

9.3 Mandatory Serum Collection for Proteomic Profiling, Cytokine Analyses, and Signature Protein Analyses

Serum specimens will be submitted prior to C1D1 treatment, prior to C2D1 treatment, and at time of pneumonitis or at End of Treatment Visit.

9.3.1 Proteomic Profiling

This initial proteomics study by the Purdue Proteomics Facility will focus on profiling experiments to identify proteins that are differentially expressed (up- or down-regulation and newly synthesized) under each treatment condition. At the end of this discovery phase proteomics, we expect to discover a number of proteins as putative biomarkers.

Samples will be initially depleted for high abundant albumin and immunoglobulin using Pierce Top 2 Abundant Protein Depletion Spin Columns (Thermo Fisher Scientific) and evaluated via 1D SDS-PAGE gels. Proteins in the depleted samples will be denatured and quantified by BCA assay. After reduction and alkylation, urea concentration will be adjusted with ammonium bicarbonate buffer. Proteins will be digested with trypsin/LysC mix and the resulting peptides will be cleaned using Pierce C18 spin columns (Pierce Biotechnology, Rockford, IL) and peptide concentration will be determined by BCA assay again.

Data will be collected in a new Q-Exactive Orbitrap HF mass spectrometer coupled with UltiMate 3000 nano LC system at the Purdue Proteomics Facility using 2h LC gradient. LC-MS/MS data will be searched using a MaxQuant search tool for protein identification and relative quantitation. Search results will be filtered at 1% false discovery rate (FDR) both at the peptide and protein levels. Identified peptides and proteins will be quantified using precursor ion (MS1) intensity-based label free quantitation. The MS1 results will be validated by comparing with the spectral counts results.

The results will be further analyzed using bioinformatic and computational pipeline of the Purdue core facility to identify proteins that are significantly different. Proteins will be subjected to pathway and network analyses to determine if any specific metabolic pathway is activated or inhibited due to the disease and the treatment conditions. The proteomics results will be complemented with other physiological, biochemical, molecular, and treatment data for correlative analysis.

Protein functions are controlled by post-translational modifications (PTMs) and protein-protein interactions. Future study will focus on characterizing the changes in the modifications of the identified marker proteins, and also focus on how the disease and the treatments affects the oligomerization state of these proteins. In addition, future work would include targeted proteomic analysis using Multiple Reaction Monitoring (MRM) assays for absolute quantitation of the marker proteins. These studies are critical for developing these proteins as therapeutic targets. Purdue Proteomics Facility has the resources and capability to carry out these studies, and will lead these efforts.

9.3.2 Lipidomic Profiling

The Metabolite Profiling Facility at Bindley Bioscience Center (Purdue University) will apply a recently developed mass spectrometry approach for accelerated biomarker discovery named multiple reaction monitoring (MRM)-profiling, which is based on the direct injection (no chromatographic separation) of

diluted lipid and metabolite extracts. By this method, molecules are first detected for each experimental group base on chemical functional groups. In a second step, individual samples are screened for all the molecules detected using a scan mode (MRM) that is very fast and sensitive, resulting in few minutes (15min) of data acquisition for each sample. Statistical analysis will be used to isolate a panel of molecules related to patient response to the treatment. Additional experiments may be necessary to confirm the molecular structure of the informative molecules. Researchers expect that the analysis of these two relevant samples sets by MRM-profiling will be a valuable proof-of-concept for this method as a biomarker-enrichment approach to be added to clinical trials for identifying cohorts of patients who have best changes of benefiting from specific therapies, supporting medical decisions and improving therapeutic success.

MRM-profiling is a two-step strategy for small molecule biomarker identification developed from R. Graham Cooks and Christina Ferreira (35) (**Figure 1**).

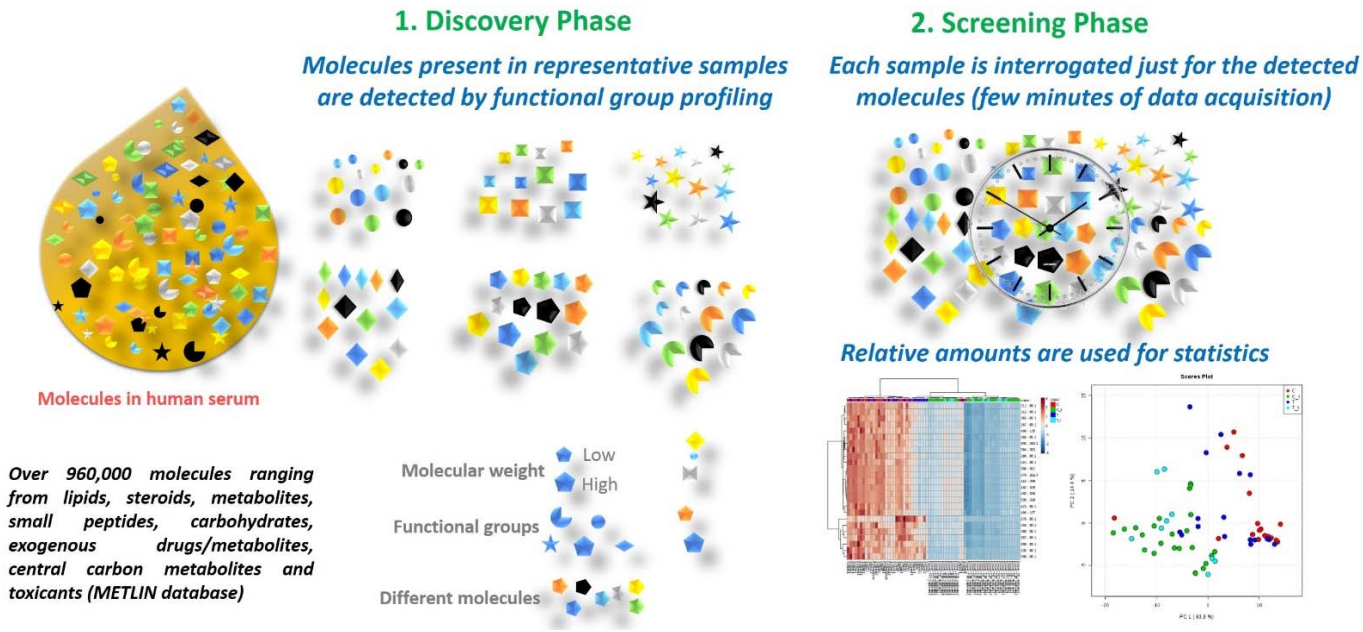


Figure 1. MRM-profiling a 2-Step Method. In the first step (discovery) only one representative sample of each experimental group, such as a pooled sample, is interrogated. In the second screening step of MRM-profiling, the entire sample set is interrogated but only for ion pairs (MRMs) detected in the discovery step. MRM measurements are extremely fast and their profiles are used for statistical differentiation of the sample types. In other words, the samples are individually interrogated only for the ion pairs that the representative samples have shown to be characteristic of each class.

Treatment outcome will be initially accessed by multivariate (principle component analyses) statistics using MetaboAnalyst 3.0. The performance of the identified metabolites in discriminating treatment outcome will also be evaluated by constructing receiver operating characteristic curves (ROCs) on the dataset, and estimating the area under the curve (AUC).

9.3.3 Cytokine Analysis

Serum samples will be analyzed for cytokines.

Analyses will include assessment of pre- and post-treatment serum cytokine markers of interest, such as (but not limited to) Interferon gamma, Interleukin-10, Interleukin-18, Interleukin-2, Interleukin-4,

Interleukin-6, Interleukin-8, Macrophage Inflammatory Protein-1 beta, Tumor Necrosis Factor alpha, Tumor Necrosis Factor beta.

9.3.4 Signature Protein Analyses

Serum samples will be analyzed for signature diagnostic detection for NSCLC by Dr. Cong Yan at Indiana University Simon Cancer Center.

Clinically, it is difficult to use only one biomarker for lung cancer detection. First, lung cancers are heterogeneous diseases and caused by multiple factors, a particular biomarker may or may not be up-regulated in a given patient. Second, different inflammation-associated diseases may produce overlapping biomarkers. In either case, a panel of multiple biomarkers should be used for more accurate lung cancer detection and classification. Thirteen distinctive serum biomarkers identified in the laboratories at Indiana University Simon Cancer Center represent a solution and signature for lung cancer diagnosis and prognosis.

The expression level of signal transducer and activator of transcription 3 (Stat3) is up-regulated in human lung cancers. In Dr. Cong Yan's lab, persistent activation of Stat3 in lung epithelial cells induced inflammation and lung adenocarcinoma sequentially in lung cancer CCSP-rtTA/(tetO)7Stat3C mouse model. Multiple Stat3 downstream genes (>800, 2 fold change, $p<0.05$) have been identified by Affymetrix GeneChip microarray analysis using this lung cancer model. From this gene list, they have successfully identified more than 13 secretory proteins that serve as biomarkers for NSCLC screen in the human serum without biopsy. The expression levels of 13 secretory proteins can be measured by ELISA (or multiplex assay system) with specific antibodies. It is easy and accurate for NSCLC detection.

9.4 Mandatory Plasma Collection for microRNA Analyses

Plasma specimens will be submitted prior to C1D1 treatment and prior to C2D1 treatment for microRNA analyses.

Dr. Lautenschlaeger's laboratory at Indiana University School of Medicine or an outside vendor will perform the microRNA analyses. miRNA will be isolated from plasma samples and reverse transcribed prior to quantitative PCR analyses using Exiqon's Serum/Plasma focus panel.

9.5 Mandatory Whole Blood Collection for Flow Cytometry

Whole blood specimens will be submitted prior to C1D1 treatment, prior to C2D1 treatment, and at time of pneumonitis or at End of Treatment Visit.

Flow cytometry will be performed at the Purdue Flow Cytometry Core Facility under the direction of Dr. Timothy Ratliff. Analyses will be performed on a 5 laser, 18 color Becton Dickinson Fortessa flow cytometry analyzer suitable for analyzing expression on human peripheral blood cells stained with fluorochrome tagged antibodies such as, but not limited to, CTLA-4 and CD28.

9.6 Optional Bronchoalveolar Lavage

For subjects undergoing bronchoalveolar lavage (BAL) for clinical reasons, the primary fluid collection will be used for routine clinical analysis per the treating physician. If feasible, please collect a portion of the BAL fluid for correlative analysis.

Dr. Homer Twigg's laboratory at Indiana University School of Medicine will perform the BAL analysis. The BAL correlative analysis will include the following such as:

- cellular count and differential
- lymphocyte phenotyping (CD3, CD4, CD8)
- activation markers (CD38, HLA DR)
- Th1 cytokines (IFNgamma, TNF, IL-6)
- Th2 cytokines (IL-4, IL-10)
- chemokine panel assessment of recruitment cells (MCP-1, IP-10, MIG, RANTES, IL-8).

If available, leftover sample will be saved as cells and acellular fluid for future studies.

9.7 Storage of Biospecimens

Any remaining correlative specimens will be stored for future research after protocol described biospecimen-based studies are completed.

9.8 Optional Banking Samples for future studies

Subject consent will be obtained for additional samples collected for future Big Ten Cancer Research Consortium studies. Hoosier Cancer Research Network, as Administrative Headquarters for the BTCRC, will manage the banked samples. Samples will be banked indefinitely in the Hoosier Cancer Research Network Biorepository.

This includes:

- Pre- and Post-treatment whole blood: Whole blood will be collected prior to treatment on Cycle 1 Day 1, Cycle 2 Day 1, and at the 30-day Safety Follow-up visit.
- Pre- and Post-treatment plasma: Whole blood for plasma will be collected prior to treatment on Cycle 1 Day 1, Cycle 2 Day 1, and at the 30-day Safety Follow-up visit.
- Pre- and Post-treatment serum: Whole blood for serum will be collected prior to treatment on Cycle 1 Day 1, Cycle 2 Day 1, and at the 30-day Safety Follow-up visit.
- Unstained slides: Unstained slides will be obtained from the subject's archived formalin fixed paraffin embedded tumor sample.

Please refer to the CLM for all sample collection, processing, labeling, and shipping instructions.

9.9 Confidentiality of Biospecimens

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

10. CRITERIA FOR DISEASE EVALUATION

10.1 Measurable Disease

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

10.1.1 Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

10.2 Non-measurable Lesions

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

NOTE: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

10.3 Target Lesions

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

10.4 Non-target Lesions

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

10.5 Evaluation of Target Lesions

NOTE: In addition to the information below, also see section 4.3.2 in the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for special notes on the assessment of target lesions.

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

Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

10.6 Evaluation of Non-target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
Non-CR/ Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the site investigator should prevail in such circumstances, and the progression status should be confirmed at a later time by the sponsor investigator.

10.7 Evaluation of Best Overall Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
CR	Not evaluated	No	PR

PR	Non-PD/ or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Non-evaluable
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD
*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.			

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

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

10.8 Definitions for Response Evaluation – RECIST 1.1

10.8.1 First Documentation of Response

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

10.8.2 Confirmation of Response

To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

10.8.3 Duration of Overall Complete Response

The period measured from the time that measurement criteria are met for complete response until the first date that recurrent disease is objectively documented.

10.8.4 Objective Response Rate

The objective response rate is the proportion of all subjects with confirmed PR or CR according to RECIST 1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

10.8.5 Time to Progression

A measurement from the date of randomization until the criteria for disease progression is met as defined by RECIST 1.1. Subjects who have not progressed or have died due to any cause will be right-censored at the date of the last disease evaluation.

10.8.6 Progression Free Survival
A measurement from the date of randomization until the criteria for disease progression is met as defined by RECIST 1.1 or death occurs. Subjects who have not progressed will be right-censored at the date of the last disease evaluation.

10.8.7 Time to Metastatic Disease
From date of randomization until the date of metastatic disease outside of the radiated field. Subjects who have not metastasized will be right censored

10.8.8 Overall Survival
Overall survival is defined by the date of randomization to date of death from any cause.

11. DRUG INFORMATION

11.1 Nivolumab (Opdivo®)

11.1.1 Other names and properties
ONO-4538, MDX-1106, BMS-936558-01 or BMS-936558, anti-PD-1, anti-programmed cell death-1 monoclonal antibody

11.1.2 Supplier/How Supplied
Bristol-Meyers Squibb will supply nivolumab at no charge to subjects participating in this clinical trial.

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

11.1.3 Product Description and Dosage Form

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

11.1.4 Storage and Stability
Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Store nivolumab under refrigeration at 2°C to 8°C (36°F to 46°F). Protect nivolumab from light by storing in the original package until time of use. Do not freeze or shake. For additional details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the BMS-936558 (nivolumab) Investigator Brochure section for “Recommended Storage and Use Conditions.”

Undiluted Nivolumab Injection and Diluted Nivolumab Injection in the IV Container.
The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2° to 8°C, 36° 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° to 25°C, 68° to 77°F) and room light. The maximum 8-hour period under room temperature and room light conditions includes the product administration period.

11.1.5 Handling and Disposal

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

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

11.1.6 Dispensing

Nivolumab must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Clinical supplies may not be used for any purpose other than that stated in the protocol. The site investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

11.1.7 Administration

Nivolumab 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. When the dose is fixed (eg, 240mg, 360mg, or 480mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 160 mL. During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. No incompatibilities between nivolumab and polyvinyl chloride (PVC) and non-PVC/non-DEHP (di(2-ethylhexyl)phthalate) containers/IV components or glass bottles have been observed. Please refer to the current Investigator Brochure for a comprehensive description of nivolumab preparation.

11.1.8 Adverse Events

Please refer to the nivolumab Investigator's Brochure for a complete list of adverse events.

Potential safety concerns and recommended management guidelines regarding pulmonary toxicities, GI toxicities, hepatotoxicities, endocrinopathies, dermatologic toxicities, and other toxicities of concern are summarized below. Management algorithms are found in Appendix 1.

The overall safety experience with nivolumab is based on experience in approximately 17,700 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. 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.

Pulmonary Adverse Events

Pulmonary AEs have been observed following treatment with nivolumab. The frequency of pulmonary AEs may be greater with nivolumab combination therapies than with nivolumab monotherapy. The majority of cases reported were Grade 1 or 2, and subjects presented with either asymptomatic radiographic changes (e.g., focal ground glass opacities and patchy infiltrates) or with symptoms of dyspnea, cough, or fever. Subjects with reported Grade 3 or 4 pulmonary AEs were noted to have more severe symptoms, more extensive radiographic findings, and hypoxia. Pulmonary AEs have been reported in subjects with a variety of tumor types; however, there have been numerically more cases in subjects with NSCLC. It is not clear whether the underlying NSCLC is a distinct risk factor, or if subjects with NSCLC are more likely to develop radiographic changes and symptoms for which it is difficult to distinguish between nivolumab-related and unrelated causes. At this time, no other underlying risk factor, including prior radiotherapy, presence of lung metastases, or underlying pulmonary medical history, has yet to be identified.

Gastrointestinal Adverse Events

Gastrointestinal AEs have been observed following treatment with nivolumab. Most cases of diarrhea were of low grade (Grade 1-2). Colitis occurred less frequently than diarrhea. High-grade cases of diarrhea and colitis were managed with corticosteroids and, in all cases, the events resolved.

Diverticular Perforation

The prevalence of diverticulosis in the general population is common and increases with age from 10% under 40 years of age to approximately 50% over 60 years of age. Approximately 10% to 25% of subjects with diverticulosis develop diverticulitis. Perforation occurs in 50% to 70% of instances of complicated diverticulitis [36, 37]. Corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and opioid analgesics are known risk factors for diverticular perforation [38]. Given the high prevalence of diverticulosis and diverticulitis in the general population, it is expected that some nivolumab-treated subjects will have these conditions concurrently with their malignancy. Cases of diverticular perforation while on concomitant corticosteroids (6 cases) or NSAID (1 case) were observed in nivolumab program. While there is insufficient evidence to suggest that diverticulosis or diverticulitis is a predisposing factor for GI perforation following nivolumab administration, clinical caution should be exercised, as appropriate, for subjects on concomitant medications of corticosteroids, NSAID, or opioid analgesics. In addition, be vigilant for signs and symptoms of potential perforation, especially in subjects with known diverticular disease.

Hepatic Adverse Events
Hepatic AEs, including elevated liver function tests (LFTs) and, infrequently, drug-induced liver injury (DILI) have been observed following treatment with nivolumab and nivolumab in combination with ipilimumab. Most cases were of low or moderate grade. Higher-grade hepatic AEs, including DILI, were managed with corticosteroids (with or without mycophenolate mofetil) and, in almost all cases, the events resolved.

Endocrinopathies
Endocrinopathies have been observed following treatment with nivolumab. Most cases were of low or moderate grade. The events have typically been identified through either routine periodic monitoring of specific laboratories (e.g., TSH) or as part of a work-up for associated symptoms (e.g., fatigue). Events may occur within weeks of beginning treatment, but also have been noted to occur after many months (while still on treatment). More than 1 endocrine organ may be involved (e.g., hypophysitis [pituitary inflammation] may need to be evaluated at the time adrenal insufficiency or thyroid disorder is suspected). Moderate- to high-grade cases were managed with hormone replacement therapy and, in some cases, with the addition of corticosteroids. In some cases, nivolumab treatment was held until adequate hormone replacement was provided.

Skin Adverse Events
Rash and pruritus were the most common skin AEs observed following treatment with nivolumab. The rash was typically focal with a maculopapular appearance occurring on the trunk, back, or extremities. Most cases have been of low or moderate grade. In some cases, rash and pruritus resolved without intervention. Topical corticosteroids have been used for some cases of rash. Anti-histamines have been used for some cases of pruritus. More severe cases responded to systemic corticosteroids.

Renal Adverse Events
Elevated creatinine and biopsy-confirmed tubulointerstitial nephritis and allergic nephritis have been infrequently observed following treatment with nivolumab. The frequency of renal AEs may be greater with nivolumab combination therapies than with nivolumab monotherapy. Most cases were Grade 2 or 3 and based on creatinine elevation. Subjects with a history of renal cell carcinoma or prior nephrectomy did not appear to be at higher risk. Events were managed with corticosteroids and, in all cases, renal function partially or fully improved.

Neurologic Adverse Events
Neurologic AEs have been uncommonly observed following treatment with nivolumab. The frequency of neurologic AEs may be greater with nivolumab + ipilimumab combination therapies than with nivolumab monotherapy or other nivolumab combinations. Neurologic AEs can manifest as central abnormalities (e.g., aseptic meningitis, encephalopathy, or encephalitis) or peripheral sensory/motor neuropathies (e.g., Guillain-Barre Syndrome, myasthenia gravis complicated with sepsis and fatality). The onset has been observed as early as after a single treatment with the nivolumab + ipilimumab combination.

Infusion Reactions
Infusion reactions, including high-grade hypersensitivity reactions, following administration of nivolumab are uncommon. Investigators are advised to monitor for fever, chills, shakes, itching, rash,

hypertension or hypotension, or difficulty in breathing during and immediately after administration of nivolumab.

Lipase/Amylase Elevations
Asymptomatic elevations in lipase and amylase have been reported. In monotherapy studies, lipase and amylase levels were not systematically monitored, so an estimate of the frequency of asymptomatic lipase/amylase elevations is unknown. In studies evaluating the safety of the nivolumab + ipilimumab combination in multiple tumor types, lipase and amylase levels were systematically monitored, and elevations in any grade of lipase/amylase were consistently noted in approximately 10% to 30% of subjects. Very few subjects reported associated symptoms (e.g., abdominal pain) or radiographic findings (e.g., stranding) consistent with pancreatitis. Thus, there does not seem to be clinical significance to the elevated laboratory values.

Uveitis and Visual Complaints
Immune therapies have been uncommonly associated with visual complaints. Inflammation of components within the eye (e.g., uveitis) is an uncommon, but clinically important, event. Uveitis may occur more frequently with nivolumab + ipilimumab combination therapy than with nivolumab monotherapy or nivolumab in combination with other therapies. An ophthalmologist should evaluate visual complaints with examination of the conjunctiva, anterior and posterior chambers, and retina. Topical corticosteroids may be used to manage low-grade events. Low-grade events that do not resolve and high-grade events should be managed with systemic corticosteroids. Consultation with a BMS medical monitor should be sought for all cases of ocular inflammatory events. Complaints of double vision should also prompt medical evaluation. In addition to ocular inflammatory events, a work-up should also consider pituitary inflammation as a cause.

Other Immune-mediated Adverse Events
For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, nivolumab or nivolumab in combination with ipilimumab should be withheld or discontinued, and corticosteroids administered accordingly. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper. If there is recurrence of any Grade 3 or 4 immune-mediated adverse reactions or life-threatening immune-related adverse reactions, nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued.

Rare cases of myotoxicity (myositis, myocarditis, and rhabdomyolysis), some with fatal outcome, have been reported with nivolumab or nivolumab in combination with ipilimumab. If a patient develops signs and symptoms of myotoxicity, close monitoring should be implemented, and the patient referred to a specialist for assessment and treatment without delay. Based on the severity of myotoxicity, nivolumab or nivolumab in combination with ipilimumab should be withheld or discontinued, and appropriate treatment instituted. For Grade 3 myocarditis, nivolumab or nivolumab in combination with ipilimumab should be permanently discontinued.

The following events have been identified during post approval use of nivolumab or nivolumab in combination with ipilimumab. Because reports are voluntary from a population of unknown size, an estimate of frequency cannot be made.

- Solid organ and tissue transplant rejection has been reported in patients who have previously undergone transplantation and who were subsequently treated with programmed cell death 1/programmed cell death ligand 1 (PD-1/PD-L1) inhibitors, including nivolumab. Treatment with nivolumab may increase the risk of rejection in solid organ or tissue transplant recipients.
- Rapid-onset and severe GVHD, some with fatal outcome, has been reported in patients who had undergone prior allogeneic HSCT and subsequently received PD-1/PD-L1 inhibitors. Subjects should be screened to determine whether they have undergone a prior allogeneic HSCT prior to participating in nivolumab clinical trials.
- Complications of allogeneic HSCT after treatment with PD-1/PD-L1 inhibitors including nivolumab, administered before allogeneic HSCT, may be associated with an increased risk of transplant-related complications, including GVHD. Fatal cases have been reported in clinical studies. Patients should be monitored closely for early evidence of transplant-related complications.

11.2 Ipilimumab (Yervoy™)

11.2.1 Other names and properties

Ipilimumab is a recombinant, human monoclonal antibody that binds to the CTLA-4. Ipilimumab is an IgG1 kappa immunoglobulin with an approximate molecular weight of 148 kDa. Ipilimumab is produced in mammalian (Chinese hamster ovary) cell culture.

11.2.2 Supplier/How Supplied

Bristol-Meyers Squibb will supply ipilimumab at no charge to subjects participating in this clinical trial.

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

11.2.3 Product Description and Dosage Form

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

11.2.4 Storage and Stability

Ipilimumab Injection, 200 mg/40 mL (5 mg/mL), must be stored refrigerated (2°C to 8°C) and protected from light. Ipilimumab injection must not be frozen. Partially used vials or empty vials of ipilimumab injection should be discarded at the site according to appropriate drug disposal procedures.

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

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

After opening:
Solution for infusion: From a microbiological point of view, once opened, the medicinal product should be infused or diluted and infused immediately. The chemical and physical in-use stability of the undiluted or diluted concentrate (between 1 and 4 mg/ml) has been demonstrated for 24 hrs at 25°C and 2 to 8°C. If not used immediately, the infusion solution (undiluted or diluted) may be stored for up to 24 hours in a refrigerator (2°C to 8°C) or at room temperature (20°C to 25°C).

11.2.5 Handling and Disposal

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

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

11.2.6 Dispensing

Ipilimumab must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Clinical supplies may not be used for any purpose other than that stated in the protocol. The site investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

11.2.7 Administration

Ipilimumab infusion must not be administered as an intravenous push or bolus injection. Administer the ipilimumab infusion intravenously over a period of 30 minutes. Ipilimumab infusion should not be infused at the same time in the same intravenous line with other agents. Use a separate infusion line for the infusion. Use an infusion set and an in-line, sterile, non-pyrogenic, low protein binding filter (pore size of 0.2 μm to 1.2 μm).

Ipilimumab infusion is compatible with:

- PVC infusion sets
- Polyethersulfone (0.2 μm to 1.2 μm) and nylon (0.2 μm) in-line filters

Flush the line with sodium chloride 9 mg/ml (0.9%) solution for injection or 50 mg/ml (5%) glucose solution for injection at the end of the infusion. Any unused medicinal product or waste material should be discarded in accordance with local requirements.

Ipilimumab can be used for intravenous administration either:

- without dilution, after transfer to an infusion container using an appropriate sterile syringe; or
- after diluting to up to 5 times the original volume of concentrate (up to 4 parts of diluent to 1 part of concentrate). The final concentration should range from 1 to 4 mg/ml. To dilute the ipilimumab concentrate, you can use either:
  - sodium chloride 9 mg/ml (0.9%) solution for injection; or
  - 50 mg/ml (5%) glucose solution for injection

11.2.8 Adverse Events

Please refer to the ipilimumab Investigator's Brochure for a complete list of adverse events.

Blockade of CTLA-4 by ipilimumab leads to T-cell activation, with the potential for clinical inflammatory AEs primarily involving the skin (dermatitis/pruritus), GI tract (diarrhea/colitis), liver (hepatitis), endocrine glands (eg, hypophysitis and adrenal or thyroid abnormalities), and other less frequent organs (eg, uveitis/episcleritis). The majority of these inflammatory AEs initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab. The majority of the inflammatory AEs is reversible with the guidance issued below and in Appendix 1. In rare cases, these inflammatory AEs may be fatal.

Gastrointestinal Toxicities
The most common site for ipilimumab-induced GI toxicity was the lower GI tract, and the most common presentation was mild to severe diarrhea or colitis with occasional bloody stools. In some cases, diarrhea began as mild and then worsened. Constipation was rarely associated with ipilimumab administration.

Liver Toxicities
Subjects receiving ipilimumab may develop elevations in LFTs in the absence of clinical symptoms. Occasionally, patients may present with symptoms, including right upper quadrant abdominal pain or unexplained vomiting.

Endocrine Toxicities
The most common inflammatory endocrine toxicities occurring in ipilimumab-treated subjects are hypophysitis and hypopituitarism. Secondary cortisol deficiency (hypoadrenalism), hypothyroidism or thyroiditis, and, less commonly, other endocrinopathies may occur concomitantly with hypophysitis; however, these may also present as the only or as primary endocrinopathy. Most patients with hypopituitarism presented with nonspecific complaints such as fatigue, visual field defects, confusion, or impotence. Some patients have had headache as the predominant presentation. The majority of subjects with hypopituitarism demonstrated enlarged pituitary glands based on brain magnetic resonance imaging (MRI). Low ACTH and cortisol were the most common biochemical abnormality; abnormal (mostly low) thyroid-stimulating hormone (TSH), free thyroxine (fT4), triiodothyronine (T3), testosterone, or prolactin have also been reported in some subjects.

Skin Toxicities
The most common inflammatory skin toxicities occurring in ipilimumab-treated subjects are rash and pruritus, mostly mild to moderate in severity. Two cases of fatal treatment-related toxic epidermal necrolysis have been reported in clinical trials. Postmarketing surveillance identified a fatal toxic epidermal necrolysis event in 1 subject who received ipilimumab after experiencing a severe or life-threatening skin adverse reaction on a prior cancer immune-stimulating therapy. Caution should be used when considering the use of ipilimumab in patients who have previously experienced a severe or life-threatening skin adverse reaction on a prior cancer immune-stimulating therapy.

Neurological Toxicities
Neurological manifestations in subjects treated with ipilimumab may include motor and/or sensory neuropathy. Given the difficulty in definitely establishing an inflammatory etiology, alternative

etiologies (eg, tumor progression) should be excluded. Fatal Guillain-Barre syndrome and cases of myasthenia gravis have been reported in clinical trials of ipilimumab. Unexplained motor neuropathy, muscle weakness, or sensory neuropathy should be evaluated, and noninflammatory causes such as disease progression, infections, metabolic disorders, and medications should be excluded.

Other Toxicities
Ocular inflammation, manifested as Grade 2 or 3 episcleritis or uveitis, was associated with concomitant diarrhea in a few subjects (< 1%) and occasionally occurred in the absence of clinically apparent GI symptoms.

Other presumed inflammatory events reported include, but were not limited to, the following (individually reported for < 1% of subjects unless noted otherwise): arthritis/arthralgias, pneumonitis, pancreatitis, autoimmune (aseptic) meningitis, autoimmune nephritis, pure red cell aplasia, noninfective myocarditis, polymyositis, eosinophilia, pericarditis, urticaria (2%), large intestinal ulcer, esophagitis, acute respiratory distress syndrome, renal failure, infusion reactions, and MG.

12. ADVERSE EVENTS

12.1 Definitions

12.1.1 Adverse Event (AE)

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

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

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

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

Disease progression should not be recorded as an AE, unless it is attributable to the study regimen by the site investigator.

12.1.2 Serious Adverse Event (SAE)

An SAE is an adverse event that:

- Results in death. NOTE: Death due to disease progression should not be reported as a SAE, unless it is attributable by the site investigator to the study drug(s)
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization for >24 hours or prolongation of existing hospitalization. **NOTE:** Hospitalization for anticipated or protocol specified procedures such as administration

of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

12.1.3 Unexpected Adverse Event

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

12.1.4 Relatedness

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

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

12.1.5 Pregnancy

If, following initiation of the study drugs, it is subsequently discovered that a subject is pregnant or may have been pregnant at the time of study drug exposure, including during at least 6 half-lives after study drug administration, the study drug will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety).

The site investigator must immediately notify BTCRC AHQ who will then notify Worldwide Safety @BMS of this event via the Pregnancy Form in accordance with SAE reporting procedures.

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

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

12.1.6 Overdose

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

12.2 Reporting

12.2.1 Adverse Events

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

12.2.2 Serious Adverse Events (SAEs)

12.2.2.1 Site Requirements for Reporting SAEs to BTCRC Administrative Headquarters

- SAEs will be reported from time of signed informed consent until 100 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever is earlier.
- SAEs will be reported on the SAE Submission Form and entered in the SAE tab in OnCore **within 1 business day** of discovery of the event.
- SAEs include events related and unrelated to the study drug(s).
- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form(s) within OnCore.
- All SAEs regardless of relation to study drug will be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant and/or until a new anti-cancer treatment starts, whichever occurs first.

The site will submit the completed SAE Submission Form (see Documents/Info tab of the EDC) to BTCRC AHQ within **1 business day** of discovery of the event**.** The form may be sent electronically to safety@hoosiercancer.org. The site investigator is responsible for informing the IRB and/or other local regulatory bodies of the SAE as per local requirements.

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

Once the SAE has resolved, sites must submit a follow up SAE Submission Form within a reasonable timeframe to BTCRC AHQ electronically at safety@hoosiercancer.org.

12.2.2.2 BTCRC AHQ Requirements for Reporting SAEs to BMS

BTCRC AHQ will report all SAEs to BMS within **1 business day** of receipt of the SAE Reporting Form from a site. Follow-up information will be provided to BMS as it is received from a site.

Contact information for sending SAE information to BMS:

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

12.2.2.3 Sponsor-Investigator Responsibilities

BTCRC AHQ will send a SAE summary to the sponsor-investigator **within 1 business day** of receipt of SAE Submission Form from a site. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

12.2.2.4 BTCRC AHQ Responsibilities for Reporting SAEs to FDA

BTCRC AHQ has been designated to manage the Investigational New Drug Application (IND) associated with this protocol on behalf of the sponsor-investigator. BTCRC AHQ will cross-reference this submission to BMS's parent IND at the time of submission. Additionally, BTCRC AHQ will submit a copy of these documents to BMS at the time of submission to FDA.

BTCRC AHQ will be responsible for all communication with the FDA in accordance with 21CFR312 which includes but is not limited to the 7 and 15 Day Reports, as well as an Annual Progress Report. Additionally, BTCRC AHQ will submit a copy of the 7 and 15 Day Reports and the Annual Progress reports to BMS at the time of submission to FDA.

12.2.2.5 IND Safety Reports Unrelated to this Trial

BMS will provide BTCRC AHQ with IND safety reports from external studies that involve the study drug(s) per their guidelines. BTCRC AHQ will forward the safety reports to the sponsor-investigator who will review these reports and determine if revisions are needed to the protocol or consent. BTCRC AHQ will forward these reports to participating sites **within 1 business day** of receiving the sponsor-investigator's review. Based on the sponsor-investigator's review, applicable changes will be made to the protocol and informed consent document (if required). All IND safety reports will also be made available to sites via OnCore.

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

13. STATISTICAL METHODS

Statistical analysis of this study will be the responsibility of the Department of Biostatistics at Indiana University School of Medicine. Parameter estimates and relevant summary statistics will be reported for both efficacy and safety outcomes. Continuous variables will be summarized by means, medians, minima, maxima, and standard deviations. Categorical variables will be summarized by frequencies and percentages. Missing data will not be imputed. Additional exploratory analysis will be conducted when appropriate. Changes from the analysis plan will not require an amendment to the protocol unless it changes a significant feature in the protocol; however all changes from the original analysis plan will be documented in the final study report. The statistical analysis methods are outline below.

13.1 Study Design

This is a two-arm 1:1 randomized non-comparative Phase II study of consolidation immunotherapy with nivolumab and ipilimumab or nivolumab alone following concurrent chemoradiotherapy for unresectable stage IIIA/IIIB NSCLC. Randomization will be stratified by stage (IIIA vs. IIIB) and histology (squamous vs. non-squamous vs. NOS). The two arms will not be compared statistically.

13.2 Endpoints

13.2.1 Definition of Primary Endpoint

- PFS is defined as the time from randomization until the criteria for disease progression is met as defined by RECIST 1.1 or death as a result of any cause.

13.2.2 Definition of Secondary Endpoints

- Overall survival will be defined as the time from randomization until death from any cause.
- Time to metastatic disease will be defined as the time from randomization until evidence of disease outside of the radiated field.
- Toxicities will be defined by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.

13.3 Sample Size and Accrual

This is a non-comparative two-arm trial with each arm being analyzed separately. For Arm 1, when the sample size is 51, a non-parametric test (single-group and based on a non-parametric estimate of the cumulative hazard function) with a one-sided 0.10 significance level will have 80% power to detect an 18 month PFS rate of 44% relative to a historical control rate of 30% (similar to the PACIFIC trial) assuming an accrual period of approximately 24 months and maximum follow-up of 48 months (i.e. would allow for up to 24 months of follow-up after accrual ends). For Arm 2, when the sample size is 48, a non-parametric test (as above) with a one-sided 0.10 significance level will have 80% power to detect an 18 month PFS of 59% relative to a historical control rate of 44% (similar to the PACIFIC trial in the checkpoint inhibitor arm and a 15% increase in absolute magnitude) assuming an accrual period of approximately 24 months and maximum follow-up of 48 months. To account for non-evaluable subjects (5%), 54 subjects will be enrolled in Arm 1 and 51 subjects in Arm 2.

13.4 Analysis Datasets

Population	Definition
Enrolled	This will comprise all subjects who meet the eligibility criteria and are registered onto the study.
Evaluable	This will comprise all subjects who receive at least one dose of trial drug and either undergo at least one post-baseline assessment or die before any evaluation.
Safety	This will comprise all subjects that take a least one dose of either drug.

13.5 Assessment of Safety

Toxicities will be defined by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.

13.6 Assessment of Efficacy

PFS, OS and Time to metastatic disease will be assessed with RECIST 1.1.

13.7 Data Analysis Plans

13.7.1 Analysis Plans for Primary Objective

For the primary endpoint, PFS at 18 months, each arm will be separately compared to the historical control rate of 30% for Arm 1 and 44% for Arm 2 using a one-sided Sign Test for censored data (36) in the randomized population. PFS overall will be estimated with a Kaplan-Meier curve and 80% confidence interval.

13.7.2 Analysis Plans for Secondary Objectives

OS will be estimated using a Kaplan-Meier curve and 95% confidence intervals for the OS medians in the randomized population. The cumulative incidence for time to metastatic disease will be calculated with those dying from causes other than metastatic disease as a competing risk, and right censoring for patients alive and without metastases. Safety will be assessed in the Safety population. Separate frequency tables will be generated for each arm.

13.7.3 Analysis Plans for Exploratory Objectives

PD-L1, CD4, and CD8 expression levels in tumor will be correlated with clinical outcomes using logistic and Cox regression methods. Changes over time in microRNA, signature protein expression, immune markers, inflammatory markers, and other markers (e.g. ESR, CRP, vWF, Ferritin, CTLA-4, CD28) will be analyzed with paired t-tests. For BAL samples in the subset of patients with pneunonitis, cytokine, chemokine, and other levels will be described using descriptive statistics and graphs.

A univariate analysis using logistic regression and odds ratio will be utilized to assess for an association between clinical characteristics of those developing grade 2-5 pneumonitis and those who did not. A univariate analysis using logistic regression and odds ratio will be utilized to assess for an association between radiation treatment parameters and pneumonitis.Similar logistic and Cox regression models will be used to correlate other correlative endpoints mentioned above and below with various clinical outcomes.

13.7.3.1 Whole exome sequencing

The whole exome sequencing data will be first examined for quality control by using the software FastQC (Babraham Bioinformatics, Cambridge, UK). Then all qualified sequence reads will be aligned to the human genome (hg19) using BWA MEM aligner. The PCR duplicates will be marked by PICARD MarkDuplicates. The tool PICARD CollectAlignmentSummaryMetrics and CollectHsMetrics will be adopted to assess the coverage across target regions. Analysis-ready BAM files will be generated after base quality recalibration by GATK BaseRecalibrator and PrintReads. Then we will perform variant call on each individual using GATK HaplotypeCaller in GVCF mode. The joint genotyping will be analyzed across all the individuals using GATK GenotypeGVCFs, followed by variant quality recalibration by GATK VariantRecalibrator and ApplyRecalibration on

SNPs and INDELs, respectively. Finally, ANNOVAR will be used to annotate variants including refGene, 1000 genome allele frequency, and dbNSFP.

13.7.3.2 RNA-seq

The RNA sequencing data will be mapped to the human genome (UCSC hg19) by the software STAR RNA-seq aligner, following the quality control by the software FastQC. The bamutils will assess the reads distribution across the whole genome. Then those uniquely mapped sequencing reads will be summarized as gene expression levels by assigned to hg19 refGene genes using featureCounts. Genes with low read count per million (CPM), e.g. CPM < 0.5 in more than 2/3 of the samples, will be defined as low/non-expressed genes and removed for further analysis. TMM (trimmed mean of M values) method will be used to normalize gene expression data. The software edgeR will be used for differential expression analysis to compare pre-post treatment samples. Differentially expressed genes (DEGs) will be selected by a specific cutoff of false discovery rate (FDR), e.g. FDR < 5%, which will be computed based on multiple test correction of p-values using the Benjamini-Hochberg procedure.

13.7.3.3 Proteomics

Similar to RNA-seq analysis, we will compare the gene expression difference at protein level between pre-post treatment samples.

13.7.3.4 Lipidomics

Treatment outcome will be initially accessed by multivariate (principle component analyses) statistics using MetaboAnalyst 3.0. The performance of the identified metabolites in discriminating treatment outcome will also be evaluated by constructing receiver operating characteristic curves (ROCs) on the dataset, and estimating the area under the curve (AUC).

13.7.3.5 Methylome

All methylation sequencing reads will be mapped to the human genome hg19 by using bowtie2. We then use a software package, bismark, to achieve the methylation information for all sites of CpG, CHG, and CHH, respectively. In this study, we may focus on only CpG methylation. Differentially methylated regions (DMRs) between groups of samples will be determined for false discovery rate (FDR) < 0.05 using methylKit package in R. Identified DMRs will be associated with genes based on their locations.

13.7.3.6 Data integration

Based on above individual analysis, we will integrate following sets of genes: (G1) genes with mutations, (G2) DEGs at mRNA level, (G3) DEGs at protein level, and (G4) genes with DMRs. Our aims are (1) to understand how mutations influence on the gene expression at mRNA level and protein level, respectively; (2) to uncover the correlation between mRNA and protein expression; (3) to study the association between mutation and DNA methylation; (4) to find the gene network involved in the mutation and epigenetic regulation.

13.7.3.7 Effect of the addition of ipilimumab to consolidation therapy plus nivolumab on PFS.

For exploratory purposes only, we will compare the two treatment arms via a stratified log-rank test to explore the potential effects of the addition of ipilimumab to consolidation therapy plus nivolumab on PFS. The study is not powered to test this exploratory hypothesis; however, as an illustration, a sample size of 51 per group would have 81% power to detect a difference in 18 month survival of .44 in one arm vs .70 in the other arm (hazard ratio of 2.3) using a one-sided log-rank test and alpha level of 0.10.

13.7.4 Subgroup Analyses

No subgroup analyses are planned.

13.7.5 Other Planned Analyses

We will generate descriptive statistics for demographic and clinical characteristics in the Enrolled Population.

13.8 Interim Analysis/Criteria for Stopping Study

After the 10th subject in each arm is treated with at least one dose of study drug and observed for a minimum of 3 months after first dose of study therapy, "unacceptable toxicities warranting early closure of the trial" will be evaluated, defined as a) any definitely related immunotherapy death; or b) any unexpected and previously unreported grade 4 toxicities definitely related to immunotherapy. If such events are observed in one subject, the DSMB will discuss and provide recommendations to the sponsor-investigator whether to terminate the appropriate arm. If such events are observed in two or more of the first 10 subjects, the arm will be terminated. Each arm will be analyzed separately and may result in different actions per arm.

After the 25th subject in each arm is treated with at least one dose of study drug and observed for a minimum of 3 months after first dose of study therapy, "unacceptable toxicities warranting early closure of the trial" will again be evaluated and defined as a) any definitely related immunotherapy death ; or b) any unexpected and previously unreported grade 4 toxicities definitely related to immunotherapy. If such events are observed in two subjects, the DSMB will discuss and provide recommendations to the sponsor-investigator whether to terminate the arm. If such events are observed in three or more of the first 25 subjects, the arm will be terminated. Each arm will be analyzed separately and may result in different actions per arm.

Pneumonitis of grade 3 and 4 will be continuously monitored. An overall rate of 20% or above would be considered unacceptable. If the probability of the grade 3/4 pneumonitis rate being less than 20% drops below 0.1, the arm will be terminated. A priori, the rate is assumed to follow $\theta \sim beta(1,1)$. Conditional on observing y events out of n subjects, the rate follows $\theta|y,n \sim beta(1+y, 1+n-y)$. The probability of $\theta < 20\%$ is $\int_0^{0.2} f(\theta|n,y)d\theta$. The threshold (k) is defined as the smallest y corresponding to the integral being smaller than 0.1, which will lead to termination of the arm.

Thresholds "k" for N=10 to N=54

N	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
k	4	4	4	5	5	5	6	6	6	6	7	7	7	7	8
N	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39
k	8	8	8	9	9	9	9	10	10	10	10	11	11	11	11
N	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54
k	12	12	12	12	12	13	13	13	13	14	14	14	14	15	15

14. TRIAL MANAGEMENT

14.1 Data and Safety Monitoring Plan (DSMP)

The study will be conducted in accordance with the Indiana University Melvin and Bren Simon Cancer Center's (IUSCC) DSMP for moderate risk trials.

BTCRC AHQ facilitated oversight activities include:

- Review and process all adverse events requiring expedited reporting as defined in the protocol
- Notify participating sites of adverse events requiring expedited reporting
- Provide trial accrual progress, safety information, and data summary reports to the sponsor-investigator
- Investigators will conduct continuous review of data and patient safety

14.2 Data Safety Monitoring Board

This study will have a Data and Safety Monitoring Board (DSMB). The DSMB is chaired by an independent medical oncologist external to this trial. The DSMB will provide a recommendation to the sponsor-investigator after all information is reviewed. This information will also be provided to BTCRC AHQ who will distribute to the site investigator/participating sites for submission to their respective IRB according to the local IRB's policies and procedures.

The DSMB will meet after the first 10 subjects are treated with at least one dose of study drug and observed for a minimum of 3 months after first dose of study therapy, in each arm respectively. Accrual will not be held while the DSMB review is pending. Each arm will be scrutinized separately and may result in different actions per arm.

The DSMB will also meet after the first 25 subjects are treated with at least one dose of study drug and observed for a minimum of 3 months after first dose of study therapy, in each arm respectively. Accrual will not be held while the DSMB review is pending. Each arm will be scrutinized separately and may result in different actions per arm.

From the time of first subject enrollment until the last subect completes study drug administration, the DSMB will conduct reviews at least twice a year.

The DSMB review will include but is not limited to:

- Study accrual patterns
- Treatment regimen information
- Adverse event summary report
- Summary of any deaths on study including cause of death
- Audit and/or monitoring results, if applicable
- Protocol deviations

14.3 Data Quality Oversight Activities

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

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

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

14.4 Compliance with Trial Registration and Results Posting Requirements

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

15. DATA HANDLING AND RECORD KEEPING

15.1 Data Management

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

15.2 Case Report Forms and Submission

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

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

15.3 Record Retention

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

15.4 Confidentiality

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

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

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

16. ETHICS

16.1 Institutional Review Board (IRB) Approval

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

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

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

16.2 Ethical Conduct of the Study

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

16.3 Informed Consent Process

The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free

to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

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

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18. APPENDIX 1: ADVERSE EVENT MANAGEMENT ALGORITHMS

These general guidelines constitute guidance to the site Investigator and may be supplemented through discussions with the Sponsor-Investigator by contacting the BTCRC project manager. The guidance applies to all immuno-oncology agents and regimens.

As general principle, differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

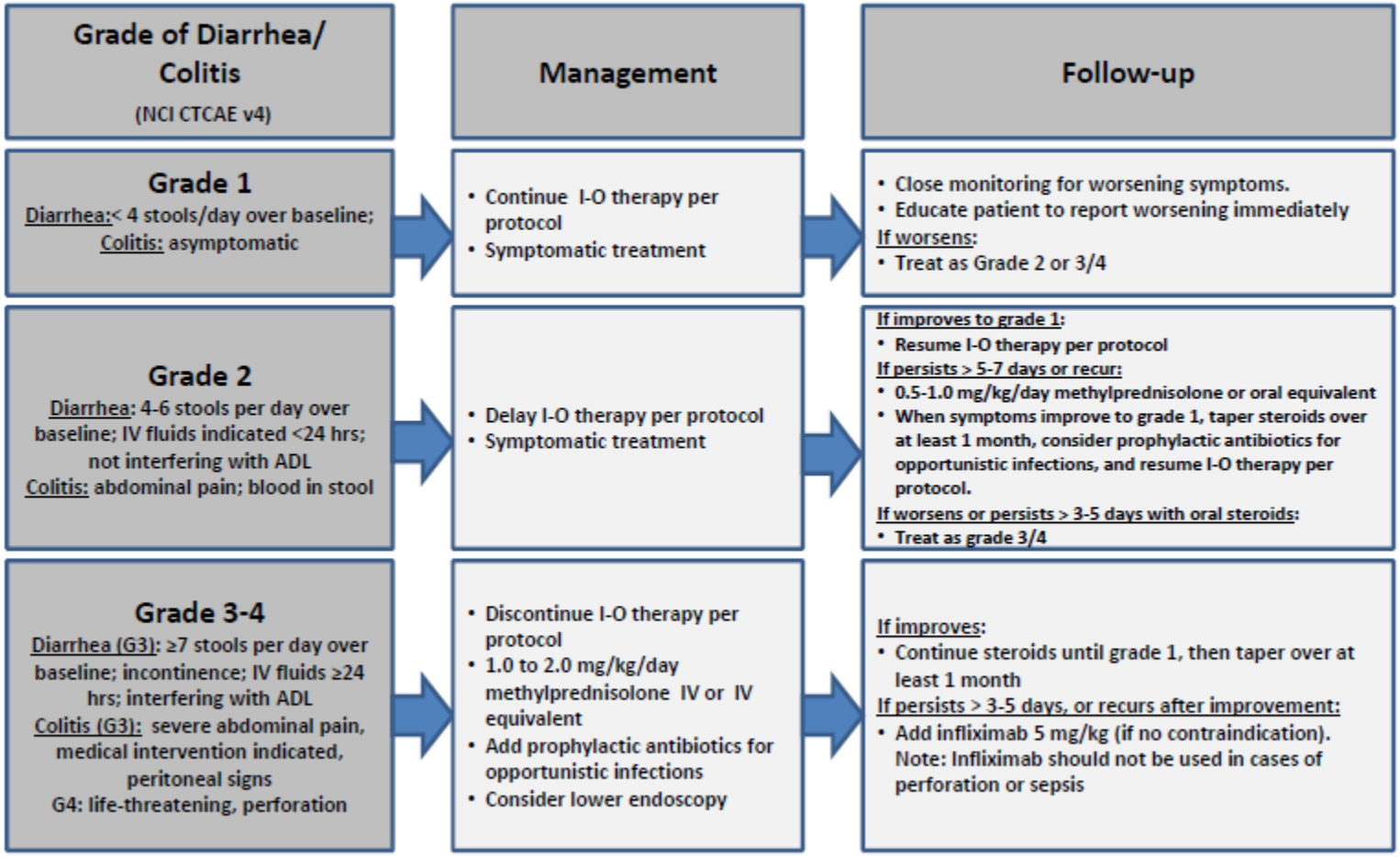
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

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

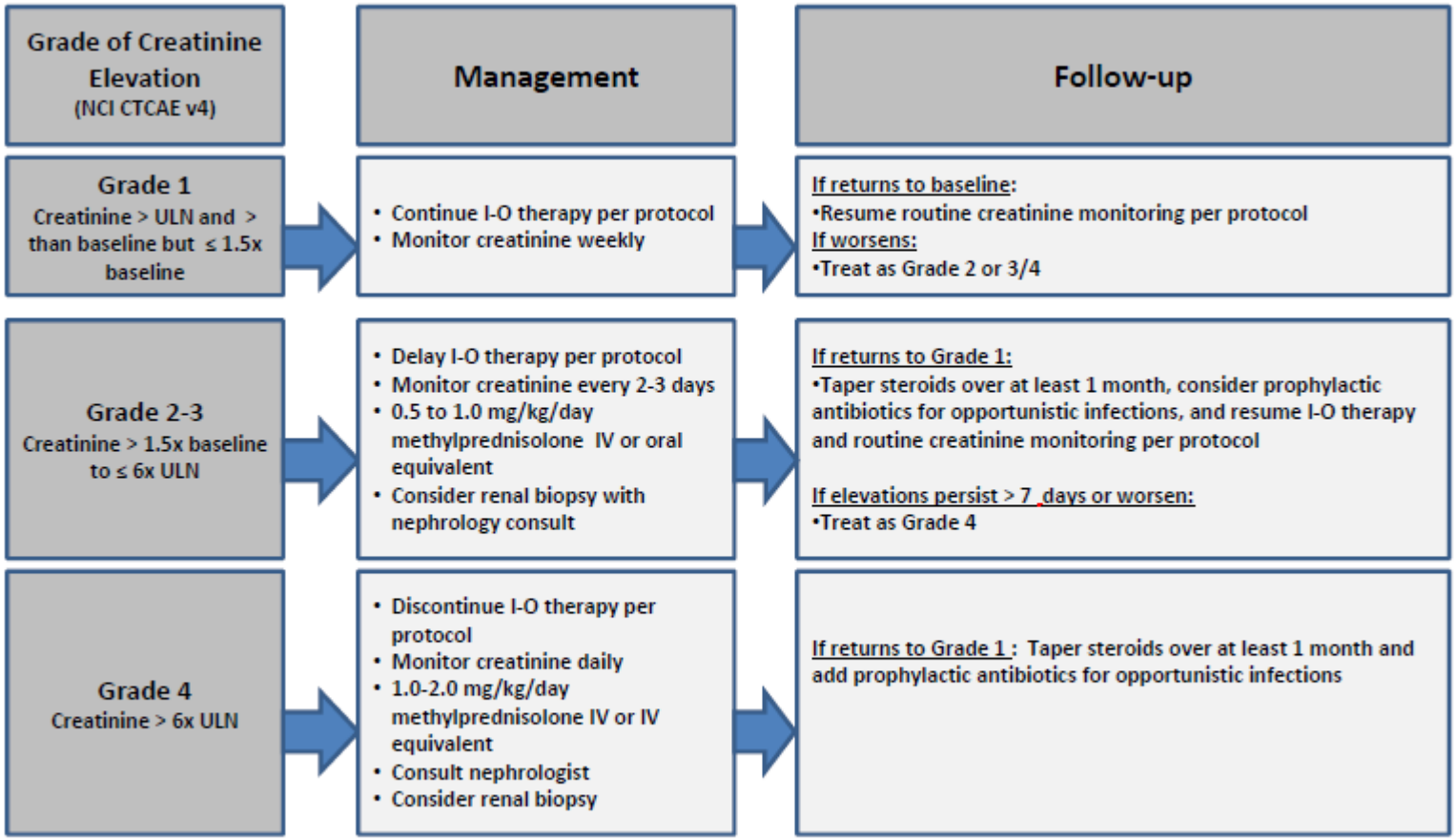


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Renal Adverse Event Management Algorithm

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



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

Updated 05-Jul-2016

Pulmonary Adverse Event Management Algorithm

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

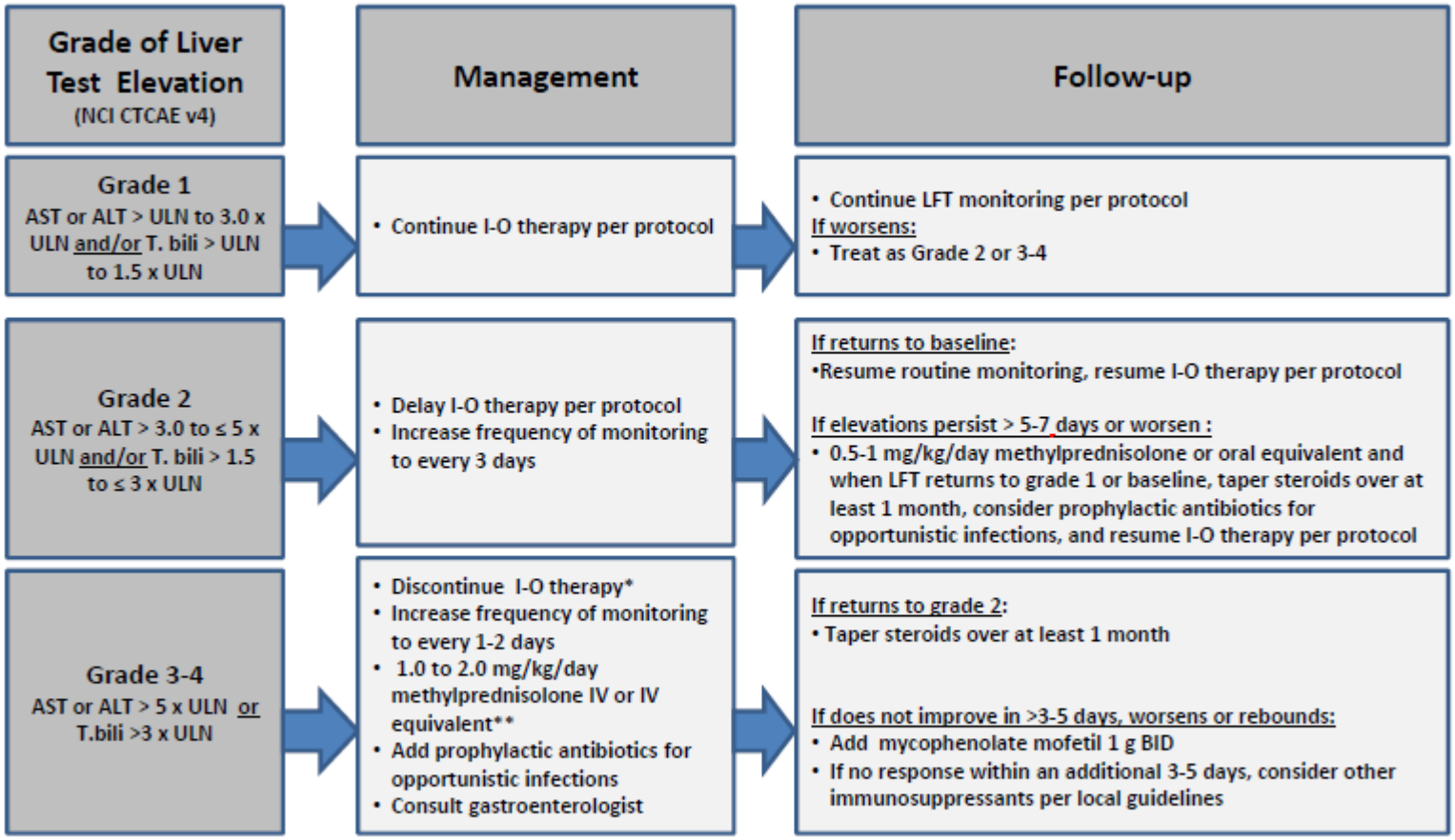
Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy , lung biopsy	• Re-image every 1-3 days If improves: • When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics If not improving after 2 weeks or worsening: • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves 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.

Updated 05-Jul-2016

Hepatic Adverse Event Management Algorithm

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



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

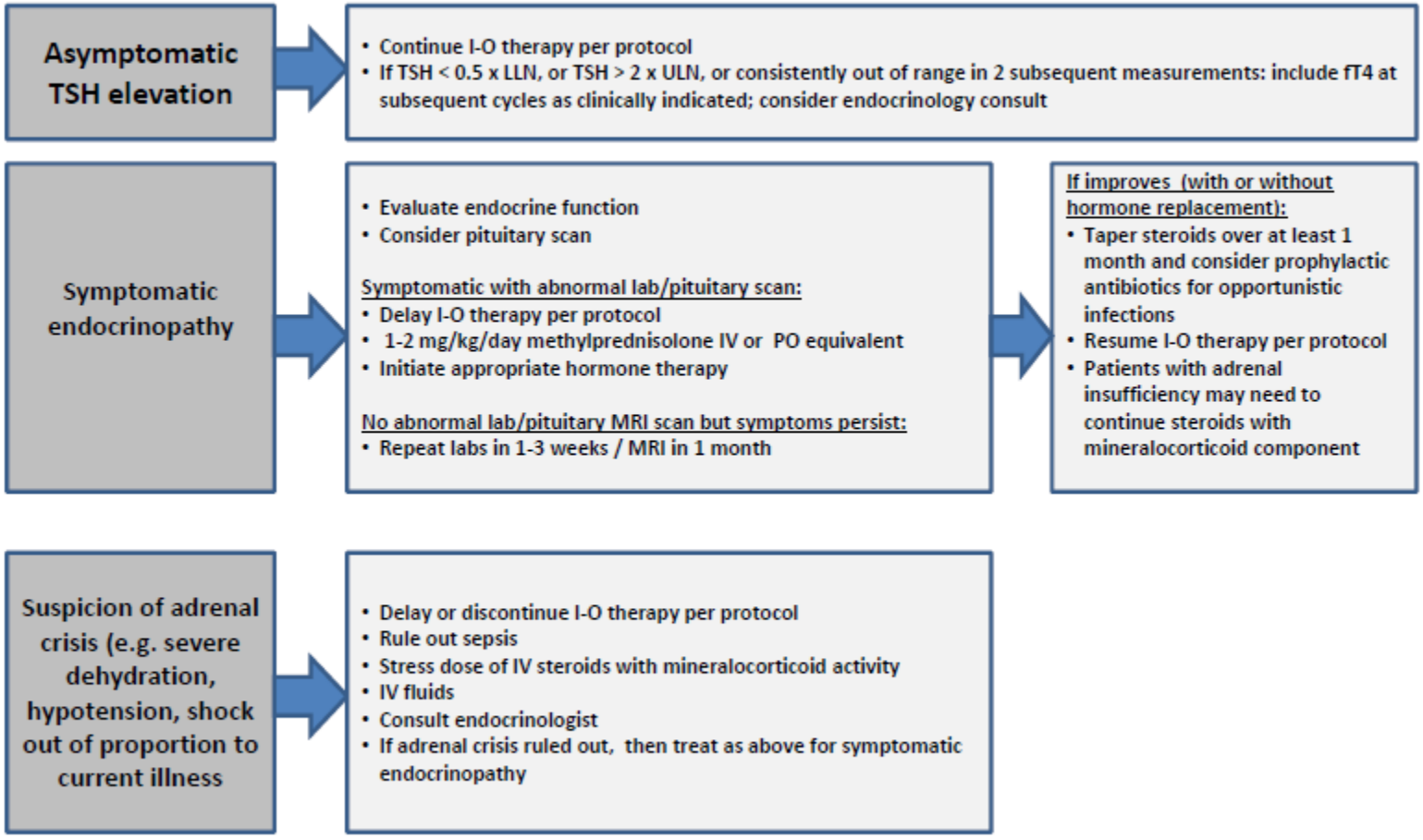
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

****The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.**

Updated 05-Jul-2016

Endocrinopathy Management Algorithm

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

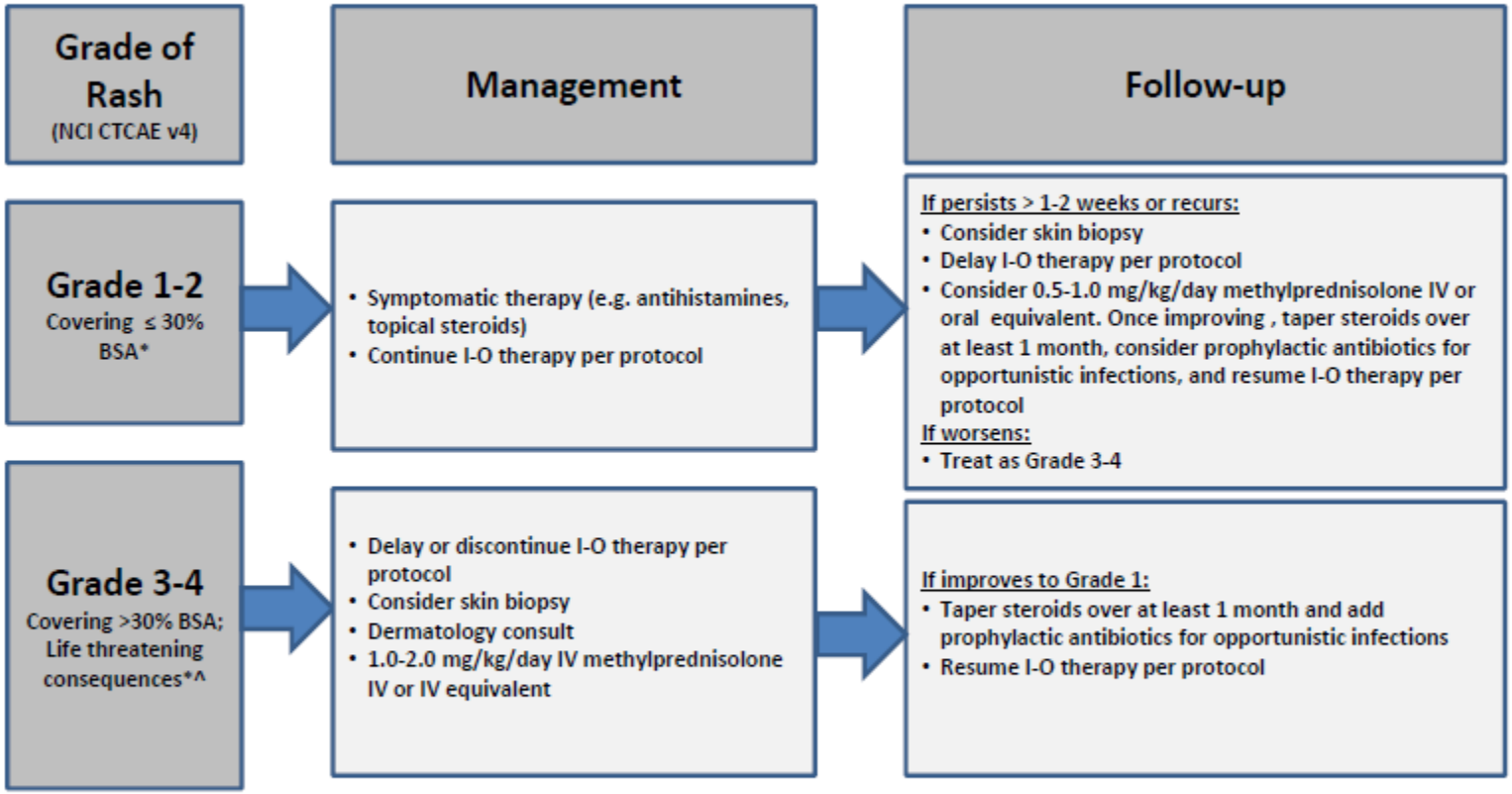


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Skin Adverse Event Management Algorithm

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

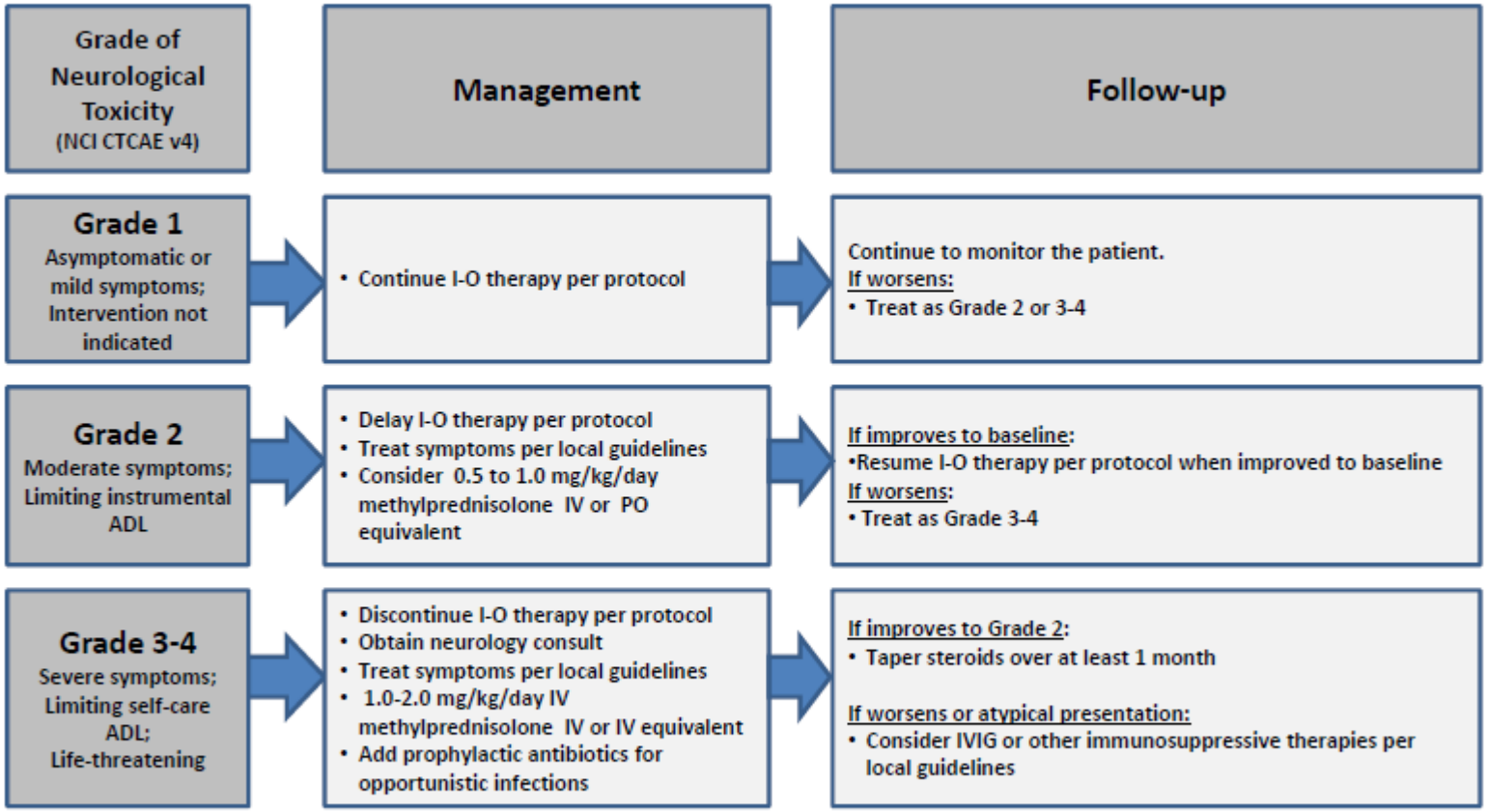


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Updated 05-Jul-2016

Neurological Adverse Event Management Algorithm

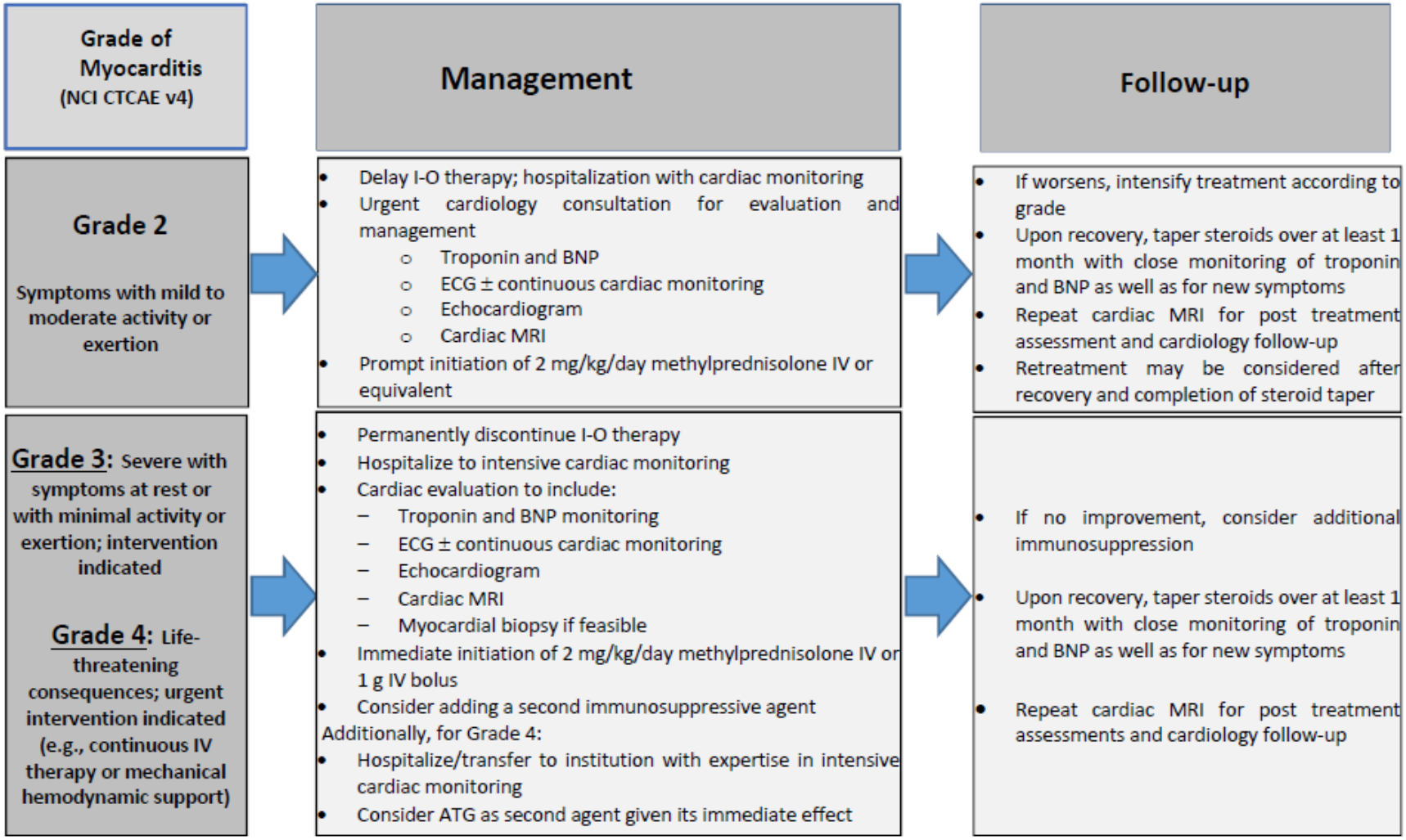
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

Updated 05-Jul-2016

Myocarditis Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, 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.
Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.
ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging