ALLIANCE FOUNDATION TRIALS (AFT)

PROTOCOL NUMBER
AFT – 31

Nivolumab with or without nab-Paclitaxel in previously treated, advanced stage, non-small cell lung cancer: a randomized Phase II study

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PROTOCOL SIGNATURE PAGE

Protocol Title:

Protocol Number:

Sponsor Name: Alliance Foundation Trials (AFT), LLC

Declaration of Investigator

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described trial in compliance with all stipulations of the protocol, all applicable regulations, ICH Good Clinical Practice (GCP) and Declaration of Helsinki.

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First Name, Last Name Date, Signature

Study Resources

Adverse Event Reporting **via Medidata Rave® iMedidata Portal** accessible via the AFT website, https://alliancefoundationtrials.org/
IRT – Randomization System accessible via the AFT website, https://alliancefoundationtrials.org/
Site Zone https://sitezone.mywingspan.com/sitezone/trials accessible via the AFT website, https://alliancefoundationtrials.org/ For Site Zone Help: [redacted]
BiOMS AFT Resource Site https://cbmiapps.wustl.edu/confluence/x/TaETAO

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I. Synopsis and Study Schema

Study Title	Nivolumab with or without nab-paclitaxel in previously treated, advanced stage, non-small cell lung cancer: a randomized phase II Alliance Study
Study Number	AFT-31
Study Type/Phase	Interventional Randomized Phase II
Clinical Indication	Previously treated advanced stage non-small cell lung cancer (NSCLC)
ClinicalTrials.gov Identifier	NCT02967133
IND Number	132051
Number of Trial Patients	200
Estimated Duration of Trial	48 months
Rationale	Patients with advanced stage non-small cell lung cancer who have progression of cancer after receiving platinum doublet chemotherapy have known benefit from nivolumab immune therapy. We hypothesize that the addition of nab-paclitaxel to nivolumab in this setting will provide additional clinical benefit compared to nivolumab alone. We will retrospectively study blood based immune biomarkers, and tumor biomarkers to better understand biomarkers associated with benefit and immune related side effects of the study therapy.
Primary Objective	The primary endpoint will be to determine if the addition of nab-paclitaxel to nivolumab improves progression free survival compared to nivolumab alone.
Secondary Objectives	1) To evaluate the difference of response rates between treatment with nab-paclitaxel and nivolumab and treatment with nivolumab alone 2) To evaluate the difference of overall survival between the two treatment regimens 3) To characterize treatment related adverse events. 4) To characterize progression-free for PDL1 positive ($\geq$ 1% tumors positive) and PDL1 negative tumors. 5) To study blood based immune biomarkers 6) To study tumor based immune biomarkers

Translational Science Objectives	Principal: Retrospectively analyze tumor immune biomarkers associated with lung cancer sensitivity and resistance to immune therapy. Additional: Retrospectively analyze blood immune biomarkers associated with lung cancer sensitivity and resistance to immune therapy. To compare clinical outcomes for PDL1 positive and PDL1 negative tumors. To compare rate of deaths in the first 3 months between the two treatments. To compare characteristics of tumors for deaths in the first 3 months compared to those living more than 3 months.
Other Correlative Sciences Objectives	N/A
Trial Design	Patients with previously treated advanced stage non-small cell lung cancer will be eligible. Patients who give written informed consent will be **randomized** to receive: • nivolumab every 14 days OR • nivolumab every 21 days with nab-paclitaxel on Days 1 and 8 Patients without progression who tolerate may receive therapy for up to one year. If patients with disease control at the end of therapy relapse, they will be eligible to reinitiate therapy. Tumor assessment for response will be done every 6 weeks for 12 months. Both treatment arms will receive a maximum of 12 months of study therapy.
Inclusion Criteria	1. Histologically or cytologically documented non-small cell lung cancer 2. Stage 4 or recurrent incurable advanced non-small cell lung cancer 3. Platinum doublet chemotherapy for current diagnosis of lung cancer. EGFR, ALK and ROS biomarker positive tumors are eligible as long as the patient has received one or more courses of standard oral, molecular inhibitor therapy in addition to standard platinum doublet chemotherapy 4. All patients must have measurable disease by CT or MRI per RECIST 1.1 criteria (see section 11.2.2). 5. ECOG Performance Status: 0-1

	6. Second malignancy: no "currently active" second malignancy other than non-melanoma skin cancers. 7. Brain metastases: brain metastases must have been treated at least 2 weeks prior to enrollment, be asymptomatic from brain metastases, stable on brain imaging, and not be receiving a supra-physiologic dose of steroids. 8. Non-pregnant and non-nursing. The effect of nab-paclitaxel and nivolumab on the fetus and infant is unknown. 9. Age ≥ 18 years. 10. Normal organ function See Section 3.1.
Exclusion Criteria	1. No prior nab-paclitaxel therapy. 2. No prior immune therapy. 3. No active auto-immune disease. See Section 3.2.

SCHEMA

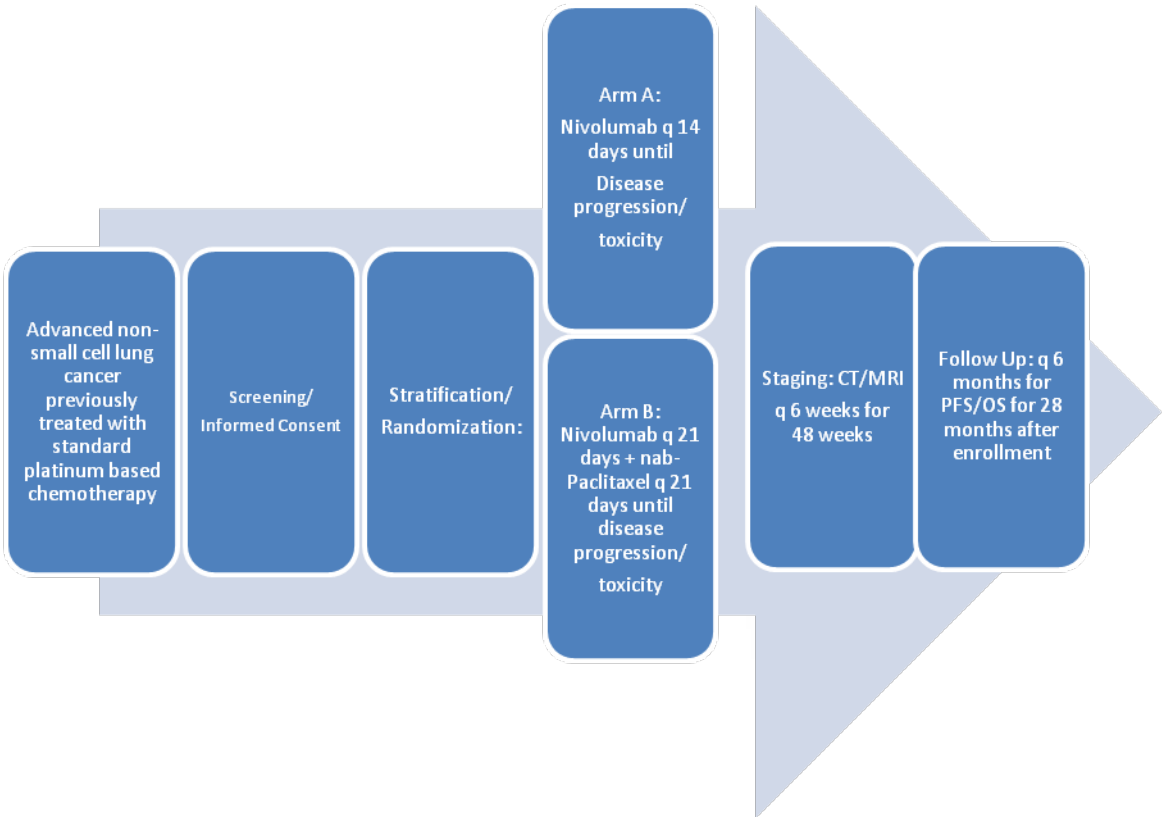
Advanced non-small cell lung cancer previously treated with standard platinum based chemotherapy
Screening/ Informed Consent
Stratification/ Randomization:
Arm A: Nivolumab q 14 days until Disease progression/ toxicity
Arm B: Nivolumab q 21 days + nab-Paclitaxel q 21 days until disease progression/ toxicity
Staging: CT/MRI q 6 weeks for 48 weeks
Follow Up: q 6 months for PFS/OS for 28 months after enrollment

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Table of Contents

1. Background Information

1.1. Overview of Disease and Patient Population and Study Rationale

1.1.1 Overview of Disease

Advanced non-small cell lung cancer (NSCLC) is the most common cause of cancer related mortality. Treatment with chemotherapy, molecular therapy, or immunotherapy can prolong survival and improve quality of life. Standard first-line treatment for patients with good performance status and normal organ function is platinum doublet chemotherapy. On progression after first-line therapy, standard options would include single agent chemotherapy or a program death receptor 1 (PD1) masking antibody such as nivolumab.

Nivolumab is a programmed death receptor (PD-1) masking anti-body that has shown single agent activity in previously treated and untreated advanced stage non-small cell lung cancer. Nivolumab has received FDA approval as therapy for previously treated squamous cell lung cancer and non-squamous cell lung cancer (1, 2).

1.1.2 Study Rationale

The optimal prioritization of second-line chemotherapy and immune therapy based on demographic or biomarker data is an area of ongoing investigation. The hypothesis of this study is that there may be an additive or synergistic antitumor effect of combined chemotherapy and nivolumab in the second-line treatment of NSCLC as an important concept to test in a clinical trial. Previously treated NSCLC remains a setting of unmet clinical need despite recent clinical research progress. Early progression for a subset of NSCLC patients receiving nivolumab is a specific area of clinical need.

1.2. Study Design

We propose adding nab-paclitaxel to standard nivolumab therapy in previously treated advanced stage non-small cell lung cancer to help prevent early progression and to improve progression free survival. The primary endpoint will be to determine if the addition of nab-paclitaxel to nivolumab improves progression free survival compared to nivolumab alone. We will retrospectively study blood based immune biomarkers, and tumor biomarkers to better understand the effect that nivolumab combined with chemotherapy has on the immune system in NSCLC. Patients with advanced stage non-small cell lung cancer who have progression of cancer after receiving platinum doublet chemotherapy will be randomized to receive nivolumab with or without nab-paclitaxel. Patients on both arms will receive a maximum of one year of therapy with the option to retreat at progression.

1.3. Study Design Rationale

Two large randomized phase 3 trials have compared nivolumab single agent immune therapy to standard dose docetaxel in advanced non-small cell lung cancer after progression on platinum based chemotherapy. In both trials, total all grade side effects and total grade 3-5 side effects were less with nivolumab compared to docetaxel. In both trials, overall survival was improved in favor of nivolumab at clinically and statistically significant levels. Nivolumab has recently been established as one standard of care for previously treated NSCLC of either squamous or non-

squamous histology. This will be one of the first trials to test whether the addition of a well-tolerated single chemotherapy agent improves therapeutic efficacy when added to the PD1 masking antibody nivolumab for patients with previously treated NSCLC.

Data suggest that there may be an additive benefit of combining chemotherapy and nivolumab in advanced stage non-small cell lung cancer. Our hypothesis is that the addition of nab-paclitaxel to nivolumab for previously treated non-small cell lung cancer may be beneficial.

The optimal duration of immune therapy is unknown for patients tolerating treatment and with disease control. After discussion with the Alliance and sponsor teams it was felt that one year of therapy with the option of retreating at progression was an appropriate duration of therapy.

1.4. Study Agents

1.4.1 Nab-Paclitaxel (Abraxane)

1.4.1.1 Clinical Pharmacokinetics and Immunogenicity

Nab-Paclitaxel (ABRAXANE®) for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) is paclitaxel formulated as albumin-bound nanoparticles with a mean particle size of approximately 130 nanometers. Paclitaxel exists in the particles in a non-crystalline, amorphous state. Nab-Paclitaxel is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion.

The pharmacokinetics of total paclitaxel following 30 and 180-minute infusions of nab-paclitaxel at dose levels of 80 to 375 mg/m2 were determined in clinical studies. Dose levels of mg/m2 refer to mg of paclitaxel in nab-paclitaxel. Following intravenous administration of nab-paclitaxel, paclitaxel plasma concentrations declined in a biphasic manner, the initial rapid decline representing distribution to the peripheral compartment and the slower second phase representing drug elimination.

The drug exposure (AUCs) was dose proportional over 80 to 300 mg/m2 and the pharmacokinetics of paclitaxel for nab-paclitaxel were independent of the duration of intravenous administration. The pharmacokinetic data of 260 mg/m2 nab-paclitaxel administered over a 30-minute infusion was compared to the pharmacokinetics of 175 mg/m2 paclitaxel injection over a 3-hour infusion. Clearance was larger (43%) and the volume of distribution was higher (53%) for nab-paclitaxel than for paclitaxel injection. There were no differences in terminal half-lives.

Following nab-paclitaxel administration to patients with solid tumors, paclitaxel is evenly distributed into blood cells and plasma and is highly bound to plasma proteins (94%). In a within-patient comparison study, the fraction of unbound paclitaxel in plasma was significantly higher with nab-paclitaxel (6.2%) than with solvent-based paclitaxel (2.3%). This contributes to significantly higher exposure to unbound paclitaxel with nab-paclitaxel compared with solvent-based paclitaxel, when the total exposure is comparable. *In vitro* studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 µg/mL, indicated that the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein

binding of paclitaxel. The total volume of distribution is approximately 1741 L; the large volume of distribution indicates extensive extravascular distribution and/or tissue binding of paclitaxel.

1.4.1.2 Preclinical Data

In vitro studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6α-hydroxypaclitaxel by CYP2C8; and to two minor metabolites, 3'-*p*-hydroxypaclitaxel and 6α, 3'-*p*-dihydroxypaclitaxel, by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6α-hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found *in vivo* following normal therapeutic doses. Testosterone, 17α-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-hydroxypaclitaxel *in vitro*. The pharmacokinetics of paclitaxel may also be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4.

At the clinical dose range of Nab-Paclitaxel 80 to 300 mg/m2, the mean total clearance of paclitaxel ranges from 13 to 30 L/h/m2, and the mean terminal half-life ranges from 13 to 27 hours. After a 30-minute infusion of 260 mg/m2 doses of nab-paclitaxel, the mean values for cumulative urinary recovery of unchanged drug (4%) indicated extensive non-renal clearance. Less than 1% of the total administered dose was excreted in urine as the metabolites 6α-hydroxypaclitaxel and 3'-*p*-hydroxypaclitaxel. Fecal excretion was approximately 20% of the total dose administered.

1.4.1.3 Pharmacokinetics in Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of paclitaxel following nab-paclitaxel administration was studied in patients with advanced solid tumors. The results showed that mild hepatic impairment (total bilirubin >1 to ≤1.5 x ULN, AST ≤10 x ULN, n=8) had no clinically important effect on pharmacokinetics of paclitaxel. Patients with moderate (total bilirubin >1.5 to ≤ 3 x ULN, AST ≤10 x ULN, n=7) or severe (total bilirubin >3 to ≤5 x ULN, n=5) hepatic impairment had a 22% to 26% decrease in the maximum elimination rate of paclitaxel and approximately 20% increase in mean paclitaxel AUC compared with patients with normal hepatic function (total bilirubin ≤ULN, AST ≤ULN, n=130).

Elimination of paclitaxel shows an inverse correlation with total bilirubin and a positive correlation with serum albumin. Pharmacokinetic/pharmacodynamic modeling indicates that there is no correlation between hepatic function (as indicated by the baseline albumin or total bilirubin level) and neutropenia after adjusting for nab-paclitaxel exposure. Pharmacokinetic data are not available for patients with total bilirubin >5 x ULN or for patients with metastatic adenocarcinoma of the pancreas.

1.4.1.4 Pharmacokinetics in Renal Impairment

The effect of pre-existing mild (creatinine clearance ≥60 to <90 mL/min, n=61) or moderate (creatinine clearance ≥30 to <60 mL/min, n=23) renal impairment on the pharmacokinetics of paclitaxel following nab-paclitaxel administration was studied in patients with advanced solid tumors. Mild to moderate renal impairment had no clinically important effect on the maximum elimination rate and systemic exposure (AUC and Cmax) of paclitaxel.

1.4.1.5 Other Intrinsic Factors

Population pharmacokinetic analyses for nab-paclitaxel show that body weight (40 to 143 kg), body surface area (1.3 to 2.4 m2), gender, race (Asian vs. White), age (24 to 85 years) and type of solid tumors do not have a clinically important effect on the maximum elimination rate and systemic exposure (AUC and Cmax) of paclitaxel.

1.4.1.6 Nab-Paclitaxel and Carboplatin for First-Line NSCLC

Socinski et al. conducted a Phase 3 randomized trial investigating the efficacy and safety of albumin-bound paclitaxel (nab-paclitaxel; Abraxane) and carboplatin compared with solvent-based paclitaxel and carboplatin in untreated advanced stage NSCLC patients (3). The primary endpoint of this trial was objective response rate with secondary endpoints of progression-free survival and overall survival. Patients treated with nab-paclitaxel and carboplatin demonstrated a significantly improved ORR compared with patients treated with paclitaxel and carboplatin (33% vs. 25%; response rate ratio [RRR] 1.31; $p<0.005$), with patients with squamous histology experiencing the greatest improvement (41% vs. 24%; RR 1.68; $p < 0.001$). Nab-paclitaxel and carboplatin achieved a similar ORR as paclitaxel and carboplatin (26% vs. 25%, respectively) in tumors with non-squamous histology. There was a comparable improvement in PFS (6.3 months vs. 5.8 months; HR 0.902, 95% CI: 0.767−1.060) and OS (12.1 months vs. 11.2 months; HR 0.922, 95% CI: 0.797−1.066) in patients treated with nab-paclitaxel and carboplatin compared with paclitaxel and carboplatin. Progression free survival was similar in both arms (6.9 months [nab-paclitaxel and carboplatin] vs. 6.5 months [paclitaxel and carboplatin]; HR 0.933) in the non-squamous subgroup. Overall survival was similar in both arms (13.1 months [nab-paclitaxel and carboplatin] vs. 13.0 months [paclitaxel and carboplatin]; HR 0.950) in the non-squamous subgroup. A statistically non-significant improvement in OS was seen in patients with squamous histology (10.7 months [nab-paclitaxel and carboplatin] vs. 9.5 months [paclitaxel and carboplatin]; HR 0.890, 95% CI 0.719−1.101). Nab-paclitaxel and carboplatin was approved for the treatment of NSCLC in the first-line setting in all histologies.

1.4.1.7 Nab-Paclitaxel for Second-Line NSCLC

A randomized phase 2 trial studied second-line therapy of nab-paclitaxel versus pemetrexed in NSCLC (4). Patients with advanced stage NSCLC and progression on first-line platinum-based chemotherapy were eligible. One arm received pemetrexed 500 mg/m^2 on day 1 of 3-week cycle. The second arm received nab-paclitaxel 150 mg/m^2 on days 1 and 8 of 3-week cycle. The primary endpoint was overall survival. One hundred and eleven patients were randomly assigned to receive pemetrexed (n = 56) and nab-paclitaxel (n = 55). Median overall survival was similar between the arms, 9.4 months (95% CI 7.1-12.5 months) for pemetrexed and 9.9 months (95% CI 8.2-11.9 months) for nab-paclitaxel. Median progression free survival was also similar between the study arms, 4.6 months (95% CI 2.7-6.1 months) for pemetrexed and 5.1 months (95% CI 3.9-7.4 months) for nab-paclitaxel. Similar disease control rates were observed between both arms; PRs and SDs were seen in 32/56 (57.1%) patients in pemetrexed arm and 36/55 (65.5%) patients in nab-paclitaxel arm. Grade 3 and grade 4 adverse events were similar between the two treatment arms. In this phase 2 trial, single-agent nab-paclitaxel showed similar efficacy and toxicity as pemetrexed in previously treated NSCLC.

1.4.1.8 Nab-Paclitaxel and PD1 Checkpoint Therapy

Results from a phase 1B trial combining atezolizumab with various platinum doublet chemotherapy regimens were presented at the World Lung Cancer Meeting in September 2015(5). Overall the study concluded that there were no unexpected toxicities for atezolizumab in combination with standard first-line chemotherapy regimens for advanced NSCLC. The combination of atezolizumab 15 mg/kg every 3 weeks combined with carboplatin AUC 6 every 3 weeks and nab-paclitaxel 100 mg/m^2 weekly showed no difference in serious adverse events compared to the other combinations, and there were no treatment related deaths for the nab-paclitaxel arm. The nab-paclitaxel arm (n=16 evaluable) had 4 CR, 5 PR, and 4 SD for an ORR of 56% and disease control rate of 81%. Many of the responses were durable beyond 6 months. Clinical trials to study the combination of nab-paclitaxel and PD1 checkpoint masking antibodies are justified.

A large phase 1 study studied the combination of atezolizumab and nab-paclitaxel in a cohort of triple negative breast cancer and the initial clinical data has been presented (6). The safety data from that trial showed that the combination of nab-paclitaxel with the PD1 checkpoint antibody was tolerable both in previously treated and untreated patients with triple negative metastatic breast cancer. The overall response rate was 70% with many of the responses being durable and ongoing. Based on the efficacy and tolerability seen in this phase 1 trial, the combination of atezolizumab and nab-paclitaxel is being evaluated in a Phase III study of patients with previously untreated metastatic triple negative breast cancer.

1.4.2 Nivolumab

1.4.2.1 General Information

Nivolumab is a fully human, IgG4 (kappa) isotype mAb that binds PD-1 on activated immune cells and disrupts inhibitory signals by masking the receptor and preventing binding of the ligands PD-L1 and PD-L2. Nivolumab has activity in several tumor types, including NSCLC. (1) In previously treated NSCLC objective response rates approached 20%, with no clear differences between squamous and non-squamous NSCLC (1). Many responses have been durable in contrast to the responses seen with cytotoxic therapy. (2) In the United States, nivolumab has been approved for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. It has also been approved for use in patients with advanced (metastatic) squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy.

1.4.2.2 Clinical Data

The safety profile of nivolumab monotherapy as well as combination therapy is manageable with no MTD reached at any dose tested up to 10 mg/kg. (1, 2) There was no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. Most AEs were grade 1 to 2 with relatively few related grade 3 to 4 AEs. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in the management algorithms provided in nivolumab investigator brochure.(3) In CA209003 (n=306, including 129 subjects with NSCLC), as of the 05-Mar-2013 data base lock, drug related AEs of any grade occurred in 75% of subjects. The most frequent drug-related AEs occurring in > 5% of subjects included fatigue (28%), rash (15%), diarrhea (13%), pruritis (11%), nausea (9%),

decreased appetite (9%), hemoglobin decreased (6%) and pyrexia (6%). The majority of events were low grade, with grade 3/4 drug-related AEs observed in 17% of patients. The most common Grade 3/4 drug-related AEs occurring in > 1% of subjects were fatigue (2%), pneumonitis (1%), diarrhea (1%), abdominal pain (1%), hypophosphatemia (1%), and lymphopenia (1%).

1.4.2.3 Nivolumab Flat Dosing

Nivolumab monotherapy has been extensively studied in a number of tumor types including NSCLC, MEL, RCC, and CRC with body weight normalized dosing (mg/kg). Nivolumab pharmacokinetics (PK) and exposures of subjects in these studies have been characterized by population pharmacokinetic (PPK) analysis of data collected these studies, together with PK data from several phase 1, 2, and 3 clinical studies of nivolumab monotherapy in solid tumors. Population PK (PPK) analyses have shown that the PK of nivolumab are linear, with dose proportional exposures over a dose range of 0.1 mg/kg to 10 mg/kg, and are similar across tumor types. Nivolumab clearance and volume of distribution were found to increase with increasing body weight, but the increase was less than proportional, indicating that an mg/kg dose represents an over-adjustment for the effect of body weight on nivolumab PK. Given the relationship between nivolumab PK and body weight, a flat dose is expected to lead to lower exposures in heavier patients, relative to the exposures in lighter patients.

Using the PPK model, nivolumab steady-state trough, peak and time-averaged concentration (Cminss, Cmaxss, and Cavgss, respectively) were predicted for a flat nivolumab dose of 240 mg Q2W and compared to those following administration of 3 mg/kg Q2W in NSCLC subjects. A dose of 240 mg nivolumab is identical to a dose of 3 mg/kg for subjects weighing 80 kg, which is the approximate median body weight of NSCLC subjects in the 3 Phase 2 and 3 BMS clinical studies of nivolumab monotherapy. The geometric mean values of Cminss, Cmaxss, and Cavgss with flat dosing are slightly (< 15%) higher than that produced by a 3 mg/kg dose, and the coefficient of variation (cv%) in these measures of exposure are only slightly (< 10%) greater than that of 3 mg/kg dosing.

Across the various tumor types in the BMS clinical program, nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy has been found to be relatively flat. Taken together, the PK, safety, and efficacy data indicate that the safety and efficacy profile of 240 mg nivolumab will be similar to that of 3 mg/kg nivolumab.

Thus a flat dose of 240 mg every 2 weeks is recommended for investigation in this study. Additional studies have indicated that the safety and efficacy of a flat dose of 360 mg every 3 weeks will be similar to 3 mg/kg every 2 weeks, and the 360 mg flat dose every 3 weeks will also be used for investigation in this study.

1.4.2.4 Nivolumab Second-Line NSCLC

Nivolumab was compared to docetaxel as second-line therapy in advanced stage NSCLC in two randomized phase 3 trials, one trial for squamous histology and the other trial for non-squamous histology (1, 2). In the BMS017 trial for second-line squamous cell lung cancer, overall survival was 9.2 months with nivolumab and 6.0 months with docetaxel, HR 0.59 and $p < 0.001$(1). In the BMS057 trial for second-line non-squamous lung cancer, overall survival was 12.2 months for nivolumab and 9.4 months for docetaxel, HR 0.73 and $p = 0.0015$ (2). In both trials, total all

grade and total high grade toxicities were less with nivolumab compared with docetaxel. Nivolumab has been FDA approved for previously treated squamous and non-squamous lung cancer.

1.4.2.5 Nivolumab plus Chemotherapy

In study CA209012, patients with treatment naïve advanced stage NSCLC received nivolumab combined with platinum based chemotherapy doublets: gemcitabine, pemetrexed, or paclitaxel (7). Nivolumab 10 mg/kg or 5mg/kg was given every 21 days with 4 cycles of standard dose chemotherapy followed by nivolumab maintenance. In general, the 4 cycles of combined therapy were safe and feasible with the majority of treatment related adverse events leading to therapy discontinuation occurring during the nivolumab single agent maintenance phase. There was evidence of possible additive therapeutic benefit for the combination compared to what would be expected for chemotherapy or nivolumab alone with overall response rates of 40%, promising 1 year survival, and a number of durable responses.

1.5. Risks and Benefits

In this randomized phase 2 trial, the control arm will be nivolumab single agent immune therapy for previously treated, advanced stage non-small cell lung cancer for which it is FDA approved. . Immune therapy for previously treated, non-small cell lung cancer has produced durable responses and improved overall survival compared to standard docetaxel chemotherapy but disappointingly short progression free survival. The experimental arm combines nab-paclitaxel to nivolumab therapy in an attempt to avoid early cancer progression on nivolumab alone, and enhance tumor antigen presentation to the immune system through chemotherapy induced tumor cell apoptosis. There is the possibility of additive typical chemotherapy toxicity and immune therapy toxicity with the combination of therapy. However nivolumab has been combined with platinum based doublets chemotherapy in untreated, advanced stage non-small cell lung cancer without excess toxicity. Similarly nab-paclitaxel chemotherapy combinations have been successfully combined with PD1 checkpoint antibody therapy, and nab-paclitaxel chemotherapy is the backbone of several large randomized, phase 3 clinical trials studying PD1 checkpoint therapy in previously untreated, advanced stage non-small cell lung cancer. Based on the empiric safety data from several clinical trials, it seems likely that the nab-paclitaxel and nivolumab combination will be generally safe and feasible in previously treated non-small cell lung cancer. This will be one of the first trials to test whether the addition of a well-tolerated single chemotherapy agent improves therapeutic efficacy when added to the PD1 masking antibody nivolumab for patients with previously treated NSCLC.

2. Objectives and Endpoints

2.1. Primary Objectives

The primary objective of this study is to determine whether progression-free survival of patients with advanced stage non-small cell lung cancer whose cancer has progressed after standard first-line platinum based doublet chemotherapy is improved with nivolumab plus nab-paclitaxel compared to nivolumab alone.

2.2. Secondary Objectives

The secondary objectives of this study are:

1. To evaluate the difference of response rates between two treatments.

2. To evaluate the difference of overall survivals between two treatments.

3. To characterize treatment related adverse events.

4. To characterize progression-free for PDL1 positive ($\geq$ 1% tumors positive) and PDL1 negative tumors.

2.3. Exploratory Objectives

1. To study immunologic biomarkers in the blood before and after nab-paclitaxel plus nivolumab.

2. To study immunologic biomarkers in the tumor at baseline before nab-paclitaxel plus nivolumab.

3. To evaluate the difference of response rates in squamous cell lung cancer between the two treatments.

4. To evaluate the difference in progression free survival in squamous cell lung cancer between the two treatments.

5. To evaluate the difference in overall survival.

6. To compare clinical outcomes for PDL1 positive and PDL1 negative tumors.

7. To compare rate of deaths in the first 3 months between the two treatments.

8. To compare characteristics of tumors for deaths in the first 3 months compared to those living more than 3 months.

2.4. Endpoints

The primary endpoint for this trial is improvement of progression free survival.

Secondary endpoints are:
1. Evaluation of response rate
2. Overall survival
3. Adverse events

2.5. Rationale for Endpoints

2.5.1 Primary and Secondary Endpoints

Progression of NSCLC is often accompanied by morbidity. Evaluating for an improvement in progression free survival is a feasible and clinically significant primary endpoint. Secondary endpoints of evaluation of response rate, overall survival, and adverse events are other standard clinical endpoints.

2.5.2 Correlative Science Endpoints

Program death receptor ligand 1 (PDL1) Dako IHC 28-8 assay is an FDA approved complementary diagnostic for nivolumab. PDL1 will be assessed retrospectively to determine whether PDL1 status is associated with benefit for the nivolumab and nab-paclitaxel study combination. Blood immune biomarkers will be evaluated in a secondary exploratory analysis. Archival tissue will be collected at baseline for all participants, and from patients who agree to an optional biopsy at progression.

Markers of inflammation will be analyzed in the Duke Phase I Biomarker Lab, which serves as a core lab for these analyses for the NCI's NCTN Alliance Trials Group. Analyses will be performed on pre-treatment and on-treatment plasma samples and on samples at disease progression as described in Section 12.

2.6. Future Biomedical Research

Tumor tissue, blood and plasma specimens will be collected at baseline as part of this study. Additional tissue, blood and plasma specimens will be collected during the study (See Protocol Section11). In addition to analysis of PDL1 expression, collected biospecimens may also be used to evaluate nucleic acid, proteomic, and/or metabolic biomarkers of response and outcome.

All collected biospecimens will be stored in the Alliance Foundation Biorepository (AFB), until biospecimen accrual and clinical follow up is sufficiently complete to allow for the design and execution of specific correlative analyses.

All collected biospecimens will be stored in the Alliance Foundation Biorepository (AFB), a CAP-accredited biorepository at Washington University in St. Louis, until biospecimen accrual and clinical follow-up is sufficiently complete to allow for the design and execution of specific correlative analyses using 'state-of-the-art' analytical platforms that will be available at that time.

Such biomarker research will address emergent questions not described elsewhere in this protocol and will only be conducted on specimens from appropriately consented patients. The objective of collecting specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of disease and/or their therapeutic treatments in the context of this trial. Proposals for future correlative research will undergo rigorous scientific, programmatic, and statistical review by AFT, and biospecimens will only be released to those investigators who have obtained appropriate regulatory approval and demonstrate adequate funding to successful complete proposed research aims. AFT will ensure that all collected specimens are used only for approved research protocols.

Anonymized (de-identified) data generated from biospecimens used for future correlative research, including somatic and constitutional (germline) genomic data, may be shared with other researchers or deposited in a publicly accessible or controlled-access data repositories. Correlative study results and data will never be returned to individual patients.

3. Patient Selection/Population

3.1. Inclusion Criteria

1. Histologically or cytologically confirmed, Stage IV non-small cell lung cancer (per the Union Internationale contre le Cancer/American Join Committee on Cancer staging system, 7th edition) or recurrent incurable non-small cell lung cancer that has progressed after first-line chemotherapy.
2. Prior Therapy: Platinum doublet chemotherapy for current diagnosis of advanced lung cancer. Only one prior line of chemotherapy for advanced lung cancer allowed. Adjuvant chemotherapy, neoadjuvant chemotherapy, or chemoradiotherapy given for early stage lung cancer at least 6 months prior to diagnosis of recurrent/metastatic disease is not counted as a line of therapy for advanced lung cancer. Patients who received platinum doublet therapy with or without radiotherapy as part of treatment for early stage non-small cell lung cancer less than 6 months after developing stage 4 or recurrent incurable disease will be considered study eligible by the criterion of having received one line of chemotherapy for non-small cell lung cancer.
3. EGFR, ALK and ROS biomarker positive tumors are eligible as long as the patient has received at least one standard oral, molecular inhibitor therapy in addition to standard platinum doublet chemotherapy. More than one molecular inhibitor is allowed such as a first generation EGFR inhibitor followed by a next generation EGFR inhibitor when T790 mutation develops. Prior molecular therapy for biomarker positive tumors such as (but not limited to) MET, RET and BRAF allowed but not required.
4. Prior chemotherapy must have been completed 21 days prior to initiation of protocol therapy and all toxicities must $\leq$ grade 2.
5. Patients must have < Grade 2 or pre-existing neuropathy (per CTCAE).
6. Palliative radiation must have been completed 2 weeks prior to the initiation of study therapy.
7. All patients must have measurable disease.
   Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$ 20mm with conventional techniques or as $\geq$10mm with spiral CT scan.
8. ECOG Performance Status: 0-1
9. Second malignancy: No “currently active” second malignancy other than non-melanoma skin cancers.
10. Brain metastases: brain metastases must have been treated at least 2 weeks prior to enrollment, be asymptomatic from brain metastases, stable on brain imaging, and not be receiving a supra-physiologic dose of steroids (> 10 mg prednisone daily or equivalent).

11. Non-pregnant and non-nursing. The effect of nab-paclitaxel and nivolumab on the fetus is unknown.
12. Women of childbearing potential (WOCBP) must be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 6 months after the last dose of study medication. Patients of childbearing potential are those who have not been surgically sterilized or have not been free of menses > 1 year.
13. Male patients must agree to use an adequate method of contraception starting with the first dose of study therapy through 7 months after the last dose of study therapy.
14. Age ≥18 years.
15. Required Initial Laboratory Values:

Leukocytes	≥2000/ µl
Hemoglobin	>9.0 g/dL
Platelets	≥100,000/ µl
ANC	≥1,500/mcL

- Serum creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥ 40 mL/min (if using the Cockcroft-Gault formula below):

$$\textit{Female}\ \text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

$$\textit{Male}\ \text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$$

Total Bilirubin	≤1.5 mg/dl (except for subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dl)
SGOT (AST)	<2.5 x ULN
ALP	<2.5 x ULN in absence of liver metastases (<5 x ULN if liver metastases present
PTT	≤1.5 x ULN

16. An archival tumor sample from either a prior core needle biopsy or surgical specimen must be available to be submitted for correlative studies as an eligibility requirement prior to registration. The sample must be shipped within 6 weeks of enrollment. Participants without an available archival tumor sample are considered ineligible.

3.2. Exclusion Criteria

1. Prior nab-paclitaxel chemotherapy excluded.
2. Prior immune therapy for NSCLC excluded. Patients should be excluded if they have had prior treatment with an anti-PD-1, anti-PD-L1, anti PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways.

3. Patients will be excluded if they have an active, known or suspected autoimmune disease. Subjects are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger.
4. Patients will be excluded if they have a condition requiring systemic treatment with either corticosteroids (>10mg/day prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses >10 mg daily prednisone equivalents are permitted in the absence or active autoimmune disease.
5. Patients should be excluded if they test positive for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection.
6. Patients should be excluded if they have known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).
7. Allergies and Adverse Drug Reaction: History of allergy to study drug components

3.3. Inclusion of Women and Minorities

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

4. Method of Treatment Assignment/ (Patient Numbering and Treatment Assignment)

4.1. Site Enrollment Requirements

Site must submit all required essential documents including:

- IRB/Regulatory Approval
- Investigator 1572
- Institutional informed consent form
- Essential documents must be submitted to the AFT electronic Trial Master File, accessible via the AFT website, https://alliancefoundationtrials.org/.

4.2. Patient Enrollment/Randomization Procedure

Informed consent: The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and enrollment.

Patients with impaired decision making capacity may be enrolled on this study, where institutional policy and IRB of record allow.

Patient enrollment will be facilitated using the AFT web-based IRT (interactive response technology) system, accessible via the AFT website, https://alliancefoundationtrials.org/.

Patient must be enrolled prior to submission of biospecimens. After written informed consent has been obtained, the study site will obtain a unique patient identifier, which will stay the same throughout the entire study. Patients enrolled but not randomized for any reason have to be documented as a Screening Failure in IRT.

Prior to accessing IRT, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent from and HIPAA authorization form

The AFT IRT system will provide the site with a confirmation of enrollment and treatment randomization information. Please retain this confirmation for your records.

4.3. Patient Numbering

After written informed consent has been obtained, the study site will obtain a unique patient identifier, which will stay the same throughout the entire study.

4.4. Stratification Factors

Patients will be stratified by:

1) Squamous versus non-squamous histology (any histology not specified squamous only will be stratified as non-squamous)
2) History of prior taxane therapy (nab-paclitaxel excluded).
3) History of smoking versus never smoking

4.5. Treatment Assignment

Patients who have progression of disease after first-line platinum based doublet chemotherapy will be randomized to receive nivolumab alone or nivolumab plus nab-paclitaxel.

4.6. Treatment Blinding

N/A

5. Treatment Plan

5.1. Treatment Regimen

Following screening for eligibility, informed consent, and screening procedures, patients will be randomized to one of the following treatment arms:

Arm A: Nivolumab 240 mg via intravenous infusion (IV) over 30 minutes day 1 of each 14 day cycle until disease progression or not tolerated.

Arm B: Nivolumab 360 mg via intravenous infusion (IV) over 30 minutes day 1 of every 21 day treatment cycle until progression or not tolerated. Patients in this arm will also receive nab-paclitaxel at a dose of 100 mg/m2 over intravenous infusion on Days 1 and 8 of each 21 day cycle.

All therapy will be in the outpatient setting.

Patients on both arms will receive a maximum of 12 months of study therapy. Patients who tolerate therapy with tumor control at 12 months may be retreated if they experience tumor progression after discontinuation.

See Section 9.1.1 for expected toxicities.

5.2. Pre-Treatment Criteria

- C1D1 results need to re-meet eligibility parameters Day 1 of each cycle to start treatment.
- Day 1 labs need to be reviewed before initiating treatment.

Laboratory values before C1D1 and each cycle day 1 of study treatment must be within parameters set forth in Section 3.1 (Inclusion Criteria) above. For Arm B day 8 of each cycle see nab-paclitaxel dose modifications Section 6.

5.3. Agent Administration

Arm A: Nivolumab will be administered as an approximate 30 minute IV infusion on Day 1 of every 14 day cycle at a dose of 240mg. Participants may be dosed no less than 12 days from the previous dose of the drug.

Arm B: Nivolumab will be administered as a 30 minute IV infusion on Day 1 of every 21 day cycle at a dose of 360mg. Subjects in this arm will also receive nab-paclitaxel via IV infusion on Days 1 and 8 of each 21 day cycle at a dose of 100 mg/m^2 per institutional standards. Per Investigator's Brochure, limiting the infusion to 30 minutes is recommended to minimize risk of infusion reactions.

On the day of infusion, nivolumab is to be administered first. Infusion of nab-paclitaxel will start at least 30 minutes after completion of the nivolumab infusion.

There are no premedications recommended for nivolumab on the first cycle.
Nab-paclitaxel premedications are as per institutional standard.

Subjects on both arms should be carefully monitored for infusion reactions during nivolumab administration. If an acute reaction is noted, subjections should be managed according to Protocol Section 6.2.7.

Doses of nivolumab may be interrupted, delayed or discontinued depending on how well the subject tolerates the treatment. Dose reductions or escalations of nivolumab are not permitted.

Dose reductions or discontinuation may be needed for nab-paclitaxel based on severe hematologic, neurologic, cutaneous, or gastrointestinal toxicities. Please see Section 6 for more information.

5.4. Order of Administration

On Arm B nivolumab will be administered first followed by nab-Paclitaxel (see above).

5.5. Supportive Care and Concomitant Medications

- **Patients should not receive any other agent which would be considered treatment for the primary neoplasm or impact the primary endpoint.**

- **As there is potential for hepatic toxicity with nivolumab, drugs with a predisposition to hepatoxicity should be used with caution in patients treated with nivolumab-containing regimen.**

- **Patients should receive full supportive care** while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

- **Treatment with hormones** or other chemotherapeutic agents may not be administered except for steroids given for adrenal failure; hormones administered for non-disease-related conditions (e.g., insulin diabetes); and intermittent use of dexamethasone as an antiemetic in solid tumor protocols. Corticosteroids may be given for treatment of drug-related adverse events (see section 17.4).

- **Antiemetics** may be used at the discretion of the attending physician.

- **Diarrhea:** Diarrhea can occur as a part of autoimmune side effect of nivolumab. For diarrhea diagnosed as related to nivolumab, treatment should be according to the nivolumab side effect management algorithms (Appendix II).

  For diarrhea not caused by nivolumab, this could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16mg/day).

  In the event of grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreocide, and antidiarrheals.

  If diarrhea is severe (requiring intravenous rehydration) and/or associated with a fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

- **Palliative radiation therapy** may be administered if repeat imaging demonstrates no new sites of bone metastases and the lesion being considered for palliative radiation is not a target lesion. (see section 13.1.2 for exception regarding pseudoprogression)

  Whole-brain irradiation given for documented CNS disease may NOT be administered. Hold protocol therapy during irradiation. Irradiate a symptomatic lesion, or one that may produce disability (e.g., unstable femur) prior to study initiation, provided other measurable disease is present.

Patients who require radiation therapy due to disease progression during protocol treatment will be removed from protocol therapy. Patients who require palliative radiation due to exacerbation of pain at a pre-existing tumor site that does not qualify as tumor progression may continue on protocol therapy after discussion with and approval from the principal investigator.

5.6. AFT Policy Concerning the Use of Growth Factors

- Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based, Clinical Practice guideline. J Clin Oncol 24(19): 3187-3205, 2006.
- **Epoetin (EPO):** Use of epoetin in this protocol is prohibited OR permitted at discretion of the treating physician.
- **Filgrastim (G-CSF) and sargramostim (GM-CSF)**
    1. Filgrastim (G-CSF)/pegfilgrastim and sargramostim (GM-CSF) treatment for patients on this study is not allowed in patients who have not had febrile neutropenia or another standard clinical indication for CSF support while on study therapy. Nivolumab with or without nab-paclitaxel would be considered low risk for severe neutropenia and/or febrile neutropenia.
    2. Filgrastim/pegfilgrastim and sargramostim may not be used:
        a. To avoid dose reductions, delays or to allow for dose escalations specified in the protocol.
        b. For the treatment of the febrile neutropenia the use of CSFs should not be routinely instituted as an adjunct to appropriate antibiotic therapy. However, the use of CSFs may be indicated in patients who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection, as per the ASCO guidelines. Investigators should therefore use their own discretion in using the CSFs in this setting. The use of CSF (filgrastim/pegfilgrastim or sagramostim) must be documented and reported (e.g. on CRFs per protocol requirements).
        c. If filgrastim/pegfilgrastim or sargramostim are used, they must be obtained from commercial sources.

6. Dose and Treatment Modifications

6.1. Nab-Paclitaxel Dose Modifications

- If multiple adverse events are seen, administer dose modification based on greatest reduction required for any single adverse event observed. Reductions apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.
- Nab-paclitaxel will not be re-escalated once reduced. If more than 2 dose reductions for nab-paclitaxel are required, nab-paclitaxel will be discontinued.

Expedited reporting may be required for some adverse events (See Section 9.1.3).

6.1.1 Nab-Paclitaxel Dose Levels

Table 1

Dose Level	Drug Name	Dose
+1	No dose level +1, not applicable	NA
0*	Nab-paclitaxel	100 mg/m^2 IV
-1	Nab-paclitaxel	75 mg/m^2 IV
-2	Nab-paclitaxel	50 mg/m^2 IV

*Dose level 0 refers to the starting dose.

6.1.2 Hematologic Adverse Event

6.1.2.1 Nab-paclitaxel dose guidelines for Day 1 hematologic adverse events

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

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

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

6.1.2.2 Nab-paclitaxel dose modifications for Day 8 hematologic adverse event

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

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

6.1.2.3 Febrile neutropenia

For febrile neutropenia (defined as temperature ≥ 38.5° C [101° F] sustained for more than one hour concomitant with ANC < 500/mm^3), reduce Nab-paclitaxel by one dose level for this and subsequent cycles.

6.1.3 Nab-paclitaxel dose modifications for gastrointestinal adverse event

For grade 3 or 4 nausea or vomiting despite maximal antiemetic therapy (including 5HT-3 antagonist, corticosterious, and aprepitant), discontinue Nab-paclitaxel.

If the gastrointestinal adverse event is not consistent with autoimmune inflammatory bowel syndrome, continue nivolumab at the previous dose when symptoms resolve to ≤ grade 1.

6.1.4 Neurotoxicity

For grade 3 sensory or motor neuropathy, skip Nab-paclitaxel until the adverse event resolves to ≤ grade 1 and then resume therapy with one dose level reduction of Nab-paclitaxel on Day 1 of the next scheduled cycle. If Nab-paclitaxel is skipped for two consecutive cycles, discontinue Nab-paclitaxel. Treatment with nivolumab may continue.

For grade 4 sensory or motor neuropathy, skip all therapy until resolution to ≤ grade 2, discontinue Nab-paclitaxel; resume nivolumab at the previous dose.

6.1.5 Cardiotoxicity

Cardiotoxicity may include events of cardiac disorders, myocardial disorders, cardiac failure, angina, tachycardia, bradyarrhythmias, or ventricular arrhythmias.

In clinical studies, the frequency of cardiotoxicity was 4% for nab-paclitaxel in monotherapy studies/indications; and was reported in 6% for nab-paclitaxel in combination with gemcitabine.

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

6.1.6 Nab-paclitaxel Hypersensitivity and/or Infusion Reactions

Nab-paclitaxel is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms of allergic-like reactions.

All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE Version 4.0 guidelines.

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

For Grade 1 symptoms: Mild reaction; infusion interruption not indicated; intervention not indicated.

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

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

Stop the nab-paclitaxel infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also e 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 nab-paclitaxel will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nab-paclitaxel administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

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

Immediately discontinue infusion of nab-paclitaxel. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1: 1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1: 10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nab-paclitaxel will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms.

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

6.2. Nivolumab

6.2.1 Nivolumab Dose Modifications

Dose reductions or dose escalations are not permitted for nivolumab.

6.2.2 Dose Delay Criteria

Because of the potential for clinically meaningful nivolumab-related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected AEs of selected categories. See Appendix II.

Dose delay criteria apply for all drug related adverse events (regardless of whether or not the event is attributed to nivolumab). All study drugs must be delayed until treatment can resume.

Dose delay criteria apply for all drug-related AEs. Nivolumab must be delayed until treatment can resume.

6.2.3 Nivolumab administration should be delayed for the following:

Any Grade ≥ 2 non-skin, drug-related AE, with the following exceptions:

1) Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay.
2) Any Grade 2 skin, drug-related AE.
3) Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, leukopenia, AST, ALT, total bilirubin, or asymptomatic amylase or lipase:
    - Grade 3 lymphopenia or leukopenia does not require dose delay.
    - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity.
    - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity.
    - 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.

Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Subjects who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met.

6.2.4 Criteria to Resume Treatment

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

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment, if continued therapy is of likely clinical benefit and after discussion with and approval from the principal investigator.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled time point per protocol. However, if the treatment is delayed past the next scheduled time point per protocol, the next scheduled time point will be delayed until dosing resumes.

If treatment is delayed or interrupted for > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in discontinuation section.

6.2.5 Management Algorithms

Guidelines for the management of immune related events can be found in the current Investigator Brochure AND in the approved USPI in the US. Investigators should decide the appropriate source of AE management for each protocol.

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab is considered an immuno-oncology agent 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 the Nivolumab IB [and in Appendix] of this protocol. The guidance provided in these algorithms should not replace the Investigator's medical judgment but should complement it.

Management Algorithms are provided in Appendix II.

6.2.6 Discontinuation Criteria

Treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis or eye pain 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

- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, and infusion reactions, and endocrinopathies:
    - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
    - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
    - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except those noted below
        - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
        - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
            - AST or ALT > 8 x ULN
            - Total bilirubin > 5 x ULN
            - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN

- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which 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 4 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 principal investigator.
- Any dosing interruption lasting > 6 weeks with the following exceptions:
- Dosing delays or interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted or delayed
- Dosing interruptions or delays lasting > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the Investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing

6.2.7 Treatment of Nivolumab Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms of allergic-like reactions.

All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE Version 4.0 guidelines.

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

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

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

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

Stop the nivolumab 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). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

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

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 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).

6.3. Dose Modifications for Obese Patients

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, all dosing is to be determined solely by actual weight without any modification unless explicitly described in the protocol. This will eliminate the risk of calculation error and the possible introduction of variability in dose administration. Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation. Physicians who are uncomfortable with calculating doses based on actual body weight should recognize that doing otherwise would be a protocol violation. Physicians may consult the published guidelines of the American Society of Clinical Oncology Appropriate

Chemotherapy Dosing for Obese Adult Patients with Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 30(13): 1553-1561, 2012.

7. Study Assessments and Procedures

7.1. Assessment Types

7.1.1 Efficacy Assessments

7.1.1.1 Imaging Assessment Collection Plan

For the purposes of this study, patients should be reevaluated with CT scan imaging to assess for progression of tumor every 6 weeks plus or minus 7 days for 48 weeks. Because progression free survival is the primary endpoint, imaging will be done every 6 week regardless of when therapy is given.

After 48 weeks, imaging will be every 12 weeks and may be adjusted to conform to when the patient will receive therapy.

For patients who cannot have CT scans, MRI may be substituted.

7.1.2 Safety and Tolerability Assessments and Procedures

Medical history will be taken prior to enrollment on the study. The medical history will be reviewed for any changes at Day 1 of each cycle.

Physical Examination and vital signs will be recorded prior to enrollment and at every treatment visit. On nivolumab single agent therapy (Arm A), physical examination and vital signs will be recorded every 14 days. On nivolumab plus nab-paclitaxel combination therapy (Arm B), physical examination and vital signs will be recorded day 1 and day 8 of each treatment cycle. Vitals signs may be measured per institutional standards.

Laboratory Assessments will be done prior to each enrollment and at every treatment visit. On nivolumab single agent therapy (Arm A), laboratory assessments will be done every 14 days. On nivolumab plus nab-paclitaxel combination therapy (Arm B), laboratory assessments will be done day 1 and day 8 of each 1 day treatment cycle. Please see Section 8 below for a full table of study assessments.

7.1.3 Pharmacokinetics

N/A

7.1.4 Biomarkers/Correlative Studies

Nivolumab is FDA approved for non-small cell lung cancer previously treated with platinum based chemotherapy for both squamous and non-squamous histologies with no restriction by biomarker such as program death receptor ligand (PDL-1). PDL-1 tumor positivity enriches the chance of benefit from nivolumab therapy in non-small cell lung cancer.

We will collect a tumor specimen at the time of enrollment in order to retrospectively assess whether expression of PDL-1 is associated with benefit from nab-paclitaxel in combination with

nivolumab. The discovery of blood immune biomarkers is of interest for immune checkpoint therapy, and will be investigated in an exploratory analysis.

Blood and plasma biomarkers: Pre-treatment, post-treatment (at first restaging) and progression blood and plasma samples will be collected from patients in both arms for exploratory of analysis of various immune and inflammatory biomarkers. Additional circulating, cell-free DNA (cfDNA) studies will also be conducted. See Section 12.

Tumor biomarkers: An archival tumor sample from either a prior core needle biopsy or surgical specimen must be available to be submitted for correlative studies as an eligibility requirement prior to registration. The sample must be shipped within 6 weeks of enrollment. Based on the results from other multi-center studies it is estimated that 80% of specimens will be adequate to result PDL-1. FNAs and cytology specimens are not acceptable as the PD-L1 complementary diagnostic is not validated with such tumor collection methods. Biomarker testing such as tumor PDL-1 status will be tested retrospectively and will not be used to guide therapy. Tumor specimens may be archival and prior to first-line therapy. In addition, an additional tumor sample will be collected at progression with patient consent, when clinically feasible.

7.1.5 Patient Reported Outcomes

N/A

8. Study Assessment Table

Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will cared for by physicians experienced in the treatment and supportive care of patients on this trial. Laboratory assessments should be completed within 14 days of randomization. All other screening procedures will be done within 28 days of randomization.

Table 2: Assessments and Procedures – Arm A – Nivolumab

1 cycle = 14 days

	Frequency → Assessments↓	**Screening**	**Cycle 1/Day (+/- 3)**	**Cycle 2+ /Day (+/- 3)**	***End of Treatment/Early Discontinuation***	***Follow Up*** [f]
			1	**1**		
Tests and Observations	History and Physical Exam	***X***	***X***	***X*** ***X***		***X***
	Vital Signs	***X***	***X***	***X***		***X***
	Height	***X***				
	Weight	***X***	***X***	***X***		***X***
	ECG	***X***				
	ECOG Performance Status	***X***	***X***	***X***	***X***	***X***
	Adverse Event Assessment	***X***	***X***	***X***	***X***	***X***
Laboratory Assessments	Complete Blood Count, Differential, Platelets	***X***	***X*** ***X***	***X*** ***X***		***X***
	Serum Creatinine	***X***	***X***	***X***		***X***
	Albumin, Glucose	***X***	***X***	***X***		***X***
	AST, ALT, Alk, Phos, Bili	***X***	***X***	***X***		***X***
	BUN/serum urea	***X***	***X***	***X***		***X***
	Serum Chemistry (Ca, Mg, NA, K, Cl)	***X***	***X***	***X***		***X***

	LDH, Amylase, Lipase	***X***	***X (LDH only)***	***X (LDH only)***		***X***
	TSH (Free T4 and Free T3)	***X***	***Every 6 weeks***			
	Serum or Urine HCG	***X***[a]	***Every 6 weeks***			***X***
	HBV sAg and HCV Ab/ HCV RNA[b]	***X***				
	Pulse Oximetry	***X***	***X***[c]	***X***[c]		
Staging	Central Pathology Review for Eligibility	***X***				
	Brain Imaging (MRI or CT)[d]	***X***				
	Tumor Measurement	***X***[e]				
	CT/MRI Chest/abdomen/pelvis	***X***	***Every 6 Weeks for 48 weeks***		***X***[g]	***Every 12 weeks for 28 months from enrollment X***
	Bone Scan					
	Histologic Review	***X***				
Correlative Assessments	Archival Tumor Sample	***X***				
	Newly Obtained Biopsy (optional)				***X***[i]	
	Whole Blood/Plasma Sample[h]	***X***			***X***	
Study Drug	Nivolumab		***X***	***X***		

a) A serum or urine pregnancy testing is required within 24 hours of study enrollment or randomization. After discontinuation from nivolumab, test should be repeated at approximately 30 days and approximately 70 days.
b) Hepatitis B and C testing should be done within 28 days prior to first dose of nivolumab.
c) Oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) should be assessed at each on-study visit prior to dosing.
d) Brain scan will be performed at screening to identify patients with small asymptomatic brain lesions that should be tested prior to randomization. For patients with lesions at baseline, brain scans will be repeated every 12 weeks or sooner if clinically indicated.
e) Baseline tumor assessments should be done within 28 days of study enrollment/randomization.
f) Follow-Up visit will be 30 days from last dose of study treatment. In the long-term follow up phase, all patients are expected to be followed for progression free survival and overall survival every 6 months for 28 months from enrollment.
g) Scan will be repeated if not performed within 6 weeks of last dose.
h) Whole blood and plasma samples to study immunologic biomarkers will be collected pre-treatment, post-treatment (at first restaging), and at progression.
i) Patients may consent to an optional tumor biopsy at progression.

Table 3: Assessments and Procedures – Arm B – Nivolumab + Nab-paclitaxel

1 cycle = 21 days

	Frequency → Assessments↓	**Screening**	**Cycle 1/Day (+/- 3)**		**Cycle 2+ /Day (+/- 3)**		***End of Treatment/Early Discontinuation***	***Follow Up[f]***
			1	**8**	**1**	**8**		
Tests and Observations	History and Physical Exam	***X***	***X***	***X***	***X***	***X***		***X***
	Vital Signs	***X***	***X***	***X***	***X***	***X***		***X***
	Height	***X***						
	Weight	***X***	***X***		***X***			***X***
	ECG	***X***						
	ECOG Performance Status	***X***	***X***	***X***	***X***	***X***	***X***	***X***
	Adverse Event Assessment	***X***	***X***	***X***	***X***	***X***	***X***	***X***
Laboratory Assessments	Complete Blood Count, Differential, Platelets	***X***	***X***	***X***	***X***	***X***		***X***
	Serum Creatinine	***X***	***X***		***X***			***X***
	Albumin, Glucose	***X***	***X***		***X***			***X***
	AST, ALT, Alk, Phos, Bili	***X***	***X***		***X***			***X***
	BUN/serum urea	***X***	***X***		***X***			***X***
	Serum Chemistry (Ca, Mg, NA, K, Cl)	***X***	***X***		***X***			***X***
	LDH, Amylase, Lipase	***X***	***X***		***X***			***X***
	TSH (Free T4 and Free T3)	***X***	***Every 6 weeks***					
	Serum or Urine HCG	***X[a]***	***Every 6 weeks***					***X***
	HBV sAg and HCV Ab/ HCV RNA[b]	***X***						
	Pulse Oximetry	***X***	***X[c]***		***X[c]***			
Staging	Central Pathology Review for Eligibility	***X***						

	Brain Imaging (MRI or CT)[d]	***X***						
	Tumor Measurement	***X***[e]						
	CT/MRI Chest/abdomen/pelvis	***X***	***Every 6 Weeks for 48 weeks***				***X***[g]	***Every 12 weeks for 28 months from enrollment***
	Bone Scan							
	Histologic Review	***X***						
Correlative Assessments	Archival Tumor Sample	***X***						
	Newly Obtained Biopsy (Optional)						***X***[i]	
	Whole Blood/Plasma Samples[h]	***X***					***X***	
Study Drug	Nivolumab		***X***		***X***			
	Nab-paclitaxel		***X***	***X***	***X***	***X***		

a. A serum or urine pregnancy testing is required within 24 hours of study enrollment or randomization. After discontinuation from nivolumab, test should be repeated at approximately 30 days and approximately 70 days.
b. Hepatitis B and C testing should be done within 28 days prior to first dose of nivolumab.
c. Oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) should be assessed at each on-study visit prior to dosing.
d. Brain scan will be performed at screening to identify patients with asymptomatic brain lesions that should be treated prior to randomization. For patients with lesions at baseline, brain scans will be repeated every 12 weeks or sooner if clinically indicated.
e. Baseline tumor assessments should be done within 28 days of study enrollment/randomization.
f. Follow-Up visit will be 30 days from last dose of study treatment. In the long-term follow up phase, all patients are expected to be followed for progression free survival and overall survival every 6 months for 28 months from enrollment.
g. Scan will be repeated if not performed within 6 weeks of last dose.
h. Whole blood and plasma samples to study immunologic biomarkers will be collected pre-treatment, post-treatment (at first restaging), and at progression.
i. Patients may consent to an optional tumor biopsy at progression.

9. Adverse Events

9.1. Adverse Events - General Overview

Per the International Conference of Harmonisation (ICH) guidelines, an adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure.

9.1.1 Expected Toxicities

Nivolumab: The most frequent drug-related AEs occurring in > 5% of subjects included fatigue (28%), rash (15%), diarrhea (13%), pruritis (11%), nausea (9%), decreased appetite (9%), hemoglobin decreased (6%) and pyrexia (6%). The majority of events were low grade, with grade 3/4 drug-related AEs observed in 17% of patients. The most common Grade 3/4 drug-related AEs occurring in > 1% of subjects were fatigue (2%), pneumonitis (1%), diarrhea (1%), abdominal pain (1%), hypophosphatemia (1%), and lymphopenia (1%).

Nab-paclitaxel: The most clinically significant adverse reactions associated with the use of nab-paclitaxel across all studied indications are related to the blood and lymphatic system (neutropenia), the nervous system (peripheral neuropathy), the musculoskeletal system (arthralgia/myalgia), and the gastrointestinal system (nausea, vomiting, and constipation). Other adverse events include myelosuppression, cranial nerve palsies, pneumonitis, sepsis, cardiotoxicity, cystoid macular edema, acute renal failure and hemolytic-uremic syndrome. For a full list of expected toxicities, refer to the Investigator's Brochure.

9.1.2 Routine Adverse Event Reporting

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Baseline conditions will be recorded as part of medical history during Screening. Any new AEs or increase of a documented baseline condition after screening/history will be recorded from the time of signing informed consent through 100 days following cessation of treatment. All adverse events are entered into the eCRF in the Rave® Electronic Data Capture (Rave EDC) system.

SAEs will be collected for 100 days after the last treatment. Treatment-related adverse events should be followed to resolution or stabilization (≤Grade 2). Adverse events should be followed for resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for adverse events that cause interruption or

discontinuation of study drug and for those present at the end of study treatment as appropriate.

Laboratory Test Abnormalities:

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported as such.

The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the subject to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy.

9.1.3 Serious Adverse Event Reporting Requirements

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Investigators are required to notify AFT and their Institutional Review Board if a patient has a reportable serious adverse event. **The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 will be utilized for AE reporting.** The CTCAE is identified and located on the CTEP website at: ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE.

All SAEs must be collected that occur from the time of first protocol-specific study intervention up to within 100 days of last dose. Treatment-related adverse events should be followed to resolution or stabilization (≤Grade 2). SAEs must be entered into the eCRF via Rave Electronic Data Capture System (Rave EDC) as applicable within 24 hours of learning of the event.

Note: All deaths on study require reporting via Rave EDC, regardless of causality. Attribution to treatment or other cause should be provided.

REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS

NOTE: Investigators **MUST** report to the sponsor (AFT) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
7) Or is a new cancer (that is not a condition of the study).
8) Or is associated with an overdose. Overdose is defined as dosing only. On a per dose basis, an overdose is defined as the following amount over the protocol specified dose of nivolumab/nab-paclitaxel assigned to a given patient, regardless of any associated adverse events or sequelae:

   PO: Any amount over the protocol-specified dose

   IV: 10% over the protocol-specified dose

   SC: 10% over the protocol specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule of frequency.

On an infusion rate basis, an overdose is defined as any rate faster than the protocol specified rate. For nab-paclitaxel, an infusion completed in less than 25 minutes may increase Cmax by approximately 20%, therefore a nab-paclitaxel infusion completed in less than 25 minutes will meet the infusion rate criterion for an overdose.

9) Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs Potential drug induced liver injury is defined as:

- ALT or AST elevation > 3 times upper limit of normal (ULN)
  AND
- Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
  AND
- No other immediately apparent possible causes of AST/ALT elevation and

hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

ALL SERIOUS adverse events that meet the above criteria **MUST** be reported to the AFT via Rave EDC within the timeframes detailed in the table below. AFT will send SAE reports to Celgene/BMS within 24 hours of becoming aware of the event.

Hospitalization	**Grade 1 Timeframes**	**Grade 2 Timeframes**	**Grade 3 Timeframes**	**Grade 4 & 5 Timeframes**
Resulting in Hospitalization > 24 hrs	Enter into Rave EDC within 24 hours of the sites awareness of the event			
Not resulting in Hospitalization ≥ 24 hrs	Enter into Rave EDC as routine adverse event			Enter into Rave EDC within 24 hours of the sites awareness of the event

Expedited AE reporting timelines are defined as:

- "All Grade 3, 4 and 5 AEs: 24-Hour; 4 Calendar Days" - The AE must initially be reported via Rave EDC ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ **4** calendar days of the initial 24-hour report.

- "All Grade 1 and 2 AEs resulting in hospitalization or prolonged hospitalization: 24-Hour; 10 Calendar Days" - The AE must initially be reported via Rave EDC ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ **10** calendar days of the initial 24-hour report.

All serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention, through 100 days following cessation of treatment, whether or not related to the investigational product, require reporting into Rave EDC within 24 hours of awareness of the event.

NOTE: Deaths occurring outside of the serious adverse event reporting period that are clearly due to progressive disease should **NOT** be reported as a serious adverse event, but should still be reported via routine reporting methods in the Rave data capture system. Deaths occurring within the reporting window, even if considered to be related to disease progression as the cause of death should be reported within Rave EDC as a serious adverse event with death noted as the outcome of the event.

9.1.4 Assessment of Causality of Adverse Events

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

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

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

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

9.2. Pregnancy Adverse Event Reporting

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

Because the study drug(s) may have an effect on sperm, pregnancies in partners of male subjects exposed to a study investigational drug will be reported by sites within 24 hours of their knowledge of the event using the pregnancy case report form within Rave EDC. AFT will report to Celgene/BMS within 24 hours of the receipt of the event.

Pregnancies that occur from the time of treatment allocation/randomization through 100 days following cessation of the investigational product must be reported by the investigator.

The Investigator will follow the female subject until completion of the pregnancy, and must notify AFT immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the approved form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported by sites within 24 hours of their knowledge of the event using the Pregnancy case report form within Rave EDC. AFT will report to Celgene/BMS within 24 hours of the receipt of the event.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the investigational product should also be reported by sites within 24 hours of their knowledge of the event using the Adverse Event form within Rave EDC. AFT will report to Celgene/BMS within 24 hours of the receipt of the event.

10. Drug Information

10.1. Nivolumab

10.1.1 Description of Study Agent

Nivolumab is manufactured by Bristol Myers-Squibb and is also known as BMS-936558-011. Other names for this agent are MDX1106, ONO-4538, and anti-PD-1. It has a molecular weight of 146,221 Daltons (143,619.17, protein portion).

10.1.2 Form

Nivolumab Injection, 100 mg/10 mL (10mg/mL).

10.1.3 Storage and Stability

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

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

Please refer to the most recent Investigator's Brochure for detailed instructions.

10.1.4 Availability

Bristol Myers-Squibb is the manufacturer of nivolumab and will be supplying it for this study free of charge.

10.1.5 Administration

- Nivolumab will be given every two weeks at a dose of 240mg to be administered as a 30 minute IV infusion.
- Subjects may be dosed no less than 12 days from the previous dose of drug. There are no premedications recommended for nivolumab on the first cycle.
- Subjects should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, subjects should be managed according to Protocol Section 6.2.7.
- Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment.

Nivolumab Injection, 100 mg (10 mg/mL): Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding polyethersulfone membrane in-line filter at the protocol-specified doses. 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 .35 mg/mL. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

Refer to the Investigator's Brochure/Pharmacy Manual for detailed administration instructions for nivolumab.

10.1.6 Ordering

A procedure to determine initial and re-supply of nivolumab will be finalized and provided to sites as an appendix or addendum to this protocol.

Pharmacy supplies not provided by BMS: Empty IV bags/containers, approved diluents, in-line filters and infusion tubing.

10.1.7 Accountability

Site investigators or designated responsible parties must maintain a record of the inventory of distribution of the study drug using the appropriate documentation method. This procedure will be finalized and provided to sites as an appendix or addendum to this protocol.

The investigator is responsible for keeping accurate records of the clinical supplies received from Bristol Myers-Squibb or designee, the amount dispensed to patients and the amount remaining at the conclusion of the trial.

10.1.8 Destruction and Return

Sites may destroy unused study drug according to their institutional policies. If any study drug is lost or damaged, its disposition should be documented in the source documents. Patients will be instructed to return empty vials or unused vials to the clinic site.

10.2. Nab-Paclitaxel

The information provided below is per the most current Investigator's brochure (IB). Please refer to the IB, local prescribing information (package insert), pharmacy manual, or institutional standards for detailed information regarding the storage/stability, compatibility, handling, preparation and administration of study agents used in this trial.

10.2.1 Form

Nab-Paclitaxel for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) is paclitaxel formulated as albumin-bound nanoparticles with a mean particle size of approximately 120 nanometers. Paclitaxel exists in the particles in a non-crystalline, amorphous state. Nab-paclitaxel is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion.

10.2.2 Storage and Stability

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

10.2.3 Availability

Celgene Corporation is the manufacturer of nab-paclitaxel and will be providing it for use in this research study. Labels will bear Celgene's name and address, the protocol number, product name, dosage form and strength, medication identification/kit number, lot number, expiry date, dosing instructions, storage conditions, the quantity of IP contained, and required caution statements, and /or regulatory statements as applicable. No supplies will be shipped to any site until regulatory approval has been obtained. Investigational sites will be supplied with nab-paclitaxel upon identification and screening of a potential trial subject.

Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel.

10.2.4 Administration

Nab-paclitaxel is injected into a vein (intravenous IV) infusion over 30 minutes. The use of an in-line filter is not recommended. Following administration, the intravenous line should be flushed with sodium chloride 9mg/dl (0.9%) solution for injection to ensure complete administration of the complete dose, according to local practice.

10.2.5 Ordering

A procedure to determine initial and re-supply of nab-paclitaxel will be finalized and provided to sites as an appendix or addendum to this protocol.

10.2.6 Accountability

Site investigators or designated responsible parties must maintain a record of the inventory of distribution of the study drug using appropriate documentation for accountability purposes. This procedure will be finalized and provided to sites as an appendix or addendum to this protocol.

The investigator or his/her designee is responsible for keeping accurate records of the clinical supplies received from Celgene, the amount dispensed to patients and the amount remaining at the conclusion of the trial.

10.2.7 Destruction and Return

Sites may destroy unused study drug according to their institutional policies. If any study drug is lost or damaged, its disposition should be documented in the source documents. Patients will be instructed to return empty vials or unused vials to the clinic site.

11. Data Collection and Management/ Data and Specimen Submission

11.1. Data Collection and Submission

Data collection for this study will be done through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in AFT CTMS System. See Data Entry Guidelines for additional instructions.

11.2. Specimen Collection and Submission

11.2.1 Biospecimen Collection

Screening/Registration

The following biospecimens will be collected:

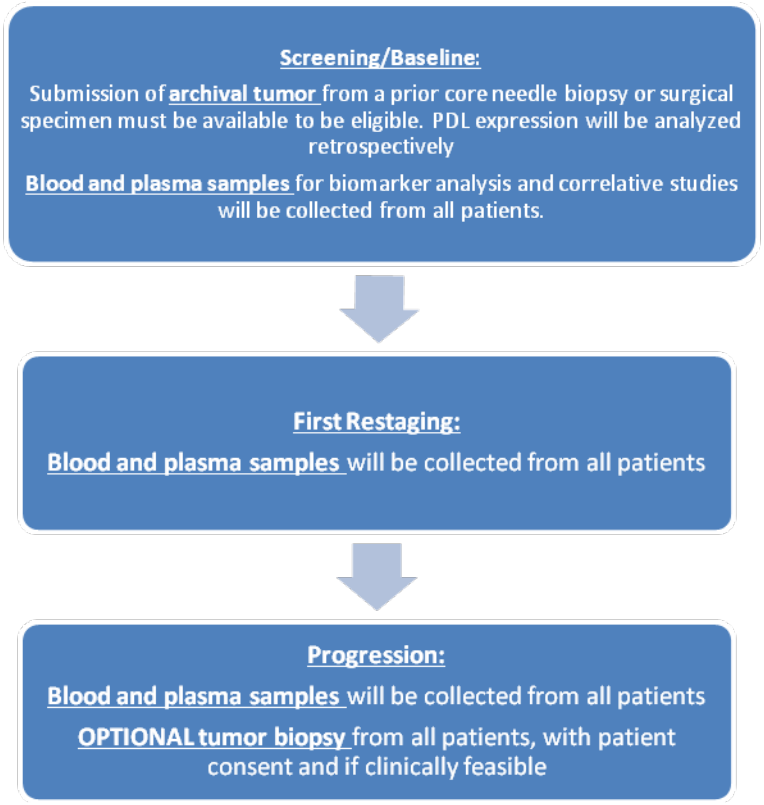
- **A.** An archival tumor specimen from a prior core needle biopsy or surgical specimen will be collected and submitted within 6 weeks of enrollment. Availability of this tissue is required for eligibility.
- **B.** Whole blood and plasma samples will be collected for biomarker analysis.

On Study:

A. Whole blood and plasma samples will be collected from all patients at the following time points:
   a. First restaging
   b. Progression

Please see the biospecimen collection schema below. Detailed information regarding the collection, processing and shipping of samples collected for screening are included in the correlative sciences manual.

11.2.2 Biospecimen Collection Schema



*At screening, patients must be determined to have tissue available to be sent within 6 weeks of enrollment.

12. Correlative Studies

12.1. PDL1 Expression

Nivolumab is FDA approved for non-small cell lung cancer previously treated with platinum based chemotherapy for both squamous and non-squamous histologies with no restriction by biomarker such as program death receptor ligand (PDL-1). PDL-1 tumor positivity enriches the chance of benefit from

nivolumab therapy in non-small cell lung cancer. However even tumors that are completely PDL-1 negative can have durable responses to nivolumab therapy. We will collect a tumor specimen at the time of enrollment in order to retrospectively assess whether expression of PDL-1 is associated with benefit from nab-paclitaxel in combination with nivolumab. A tumor specimen will also be obtained from patients who consent to an additional biopsy at progression. Program death receptor ligand 1 (PDL1) Dako IHC 28-8 assay is an FDA approved complementary diagnostic for nivolumab. PDL1 will be assessed retrospectively to determine whether PDL1 status is associated with benefit for the nivolumab and nab-paclitaxel study combination.

12.2. Plasma - Protein Markers Associated with Sensitivity or Resistance to Nivolumab

Multiplex ELISA assays have been developed to analyze over 25 inflammatory and immune-related markers in less than 0.5 ml of plasma. Coefficients of variation for most analytes are <10%. This platform has been successfully applied to several in-house phase I and II studies, as well as several phase III, Alliance-conducted studies at Duke University. Markers of inflammation will be analyzed in the Duke Phase I Biomarker Lab, which serves as a core lab for these analyses for the NCI's NCTN Alliance Trials Group.
Analyses will be performed on pre-treatment and on-treatment plasma samples and on samples at disease progression. Analyte levels, and changes in analyte levels, will be correlated with clinical outcome (ORR, PFS, and OS). These may include CRP and other markers of inflammation, including but not limited to IFNγ, IL1β, IL6, sILR6R, sGP130, IL4, IL7, IL10, IL12, IL17A, IL17E, and IL23. Additional markers of proteins regulated by the PD-1/PD-L1 interaction and the IL6/JAK-STAT axis may also be assessed, including but not limited to VEGF, HER and TGFβ family members.

12.3. Plasma – Circulating, Cell-Free Tumor DNA

Apoptotic and necrotic cells release DNA fragments into the circulation creating a pool of circulating cell-free DNA (cfDNA). Tumor-derived cfDNA (ctDNA) has become the focus of intensive investigation in the search for genomic biomarkers that can be used to monitor the presence or absence of disease, disease progression, or the development of resistance mechanisms during the course of treatment. Isolation of ctDNA from patient plasma samples will be done in the laboratory of Dr. Andrew Nixon at Duke University Medical Center. The Maxwell® RSC (Promega) instrument will be used for the automated extraction of high-quality ctDNA. All cfDNA will be quantified using a fluorescent dye method. Additional quantification methods such as real-time PCR may be used if they are deemed necessary for downstream applications.

A targeted NGS panel will be constructed to measure multiple target genes in parallel. The NGS panel will include genes commonly associated with lung cancer, as well as genes associated with immune function and checkpoint inhibition. NGS libraries will be generated using standardized protocols. All procedures have been optimized for use with plasma samples similar to those collected during this study. If NGS assays lack the sensitivity to detect rare mutations in cfDNA, or if the cfDNA isolated from a sample is insufficient for NGS, then Taqman assays will be used as secondary analyses. Taqman assays are ideal for identifying the presence of specific, known genomic alterations.

Associations between fluorescent quantification of total cfDNA and markers of clinical benefit (DFS and OS) will be modeled using Cox proportional hazards models. Associations between a potentially predictive SNP or genomic alteration and markers of clinical benefit (DFS and OS) will be modeled

using Cox proportional hazards models.

13. Measurement of Effect

13.1. Imaging Assessment Collection Plan

For purposes of this study, patients should be reevaluated with imaging to assess for progression of tumor every 6 weeks for 48 weeks and thereafter every 12 weeks for 28 months from enrollment until disease progression, initiation of an alternate treatment, or withdrawal from study protocol.

Testing, including imaging performed as routine clinical management, are acceptable for use in screening as long as they are in compliance with time parameters in Section 7.

13.2. Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria[8]

13.2.1 Definitions

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

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

13.2.2 Disease Parameters

Measurable Disease

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

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

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

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

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

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

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

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

13.2.3 Methods for Evaluation of Disease

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

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

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

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

prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

13.2.4 Measurement at Follow-up Evaluation

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

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

13.2.5 Response Criteria

All target lesions and target lymph nodes followed by CT/MRI/PET-CT/Chest X-ray/physical examination must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

13.2.5.1 Evaluation of Target Lesions

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

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

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

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

13.2.5.2 Evaluation of Non-Target Lesions

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

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

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

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

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

13.2.5.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered (see Section 14.1.2 regarding pseudoprogression).

13.2.5.4 Evaluation of Best Overall Response

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

For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**

PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

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

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

For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

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

13.2.6 Duration of Response

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

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

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

13.2.7 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following table:

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

13.2.8 Symptomatic Deterioration

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration.

13.2.9 Progression-Free Survival

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

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

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

13.2.10 Review of Response

13.2.10.1 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 13.2.2) up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. These lesions can be non-nodal or nodal (as defined in Section 13.2), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.
- **Baseline Sum of Dimensions (BSD):** A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.
- **Post-Baseline Sum of the Dimensions (PBSD):** A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.
- **The minimum sum of the dimensions (MSD)** is the minimum of the BSD and the PBSD.

13.2.10.2 Non-Target Lesions and Non-Target Lymph Nodes

Non measurable sites of disease (Section 13.2.2) are classified as non-target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accordance with Section 12.2.2.

13.2.10.3 New Lesions

New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least15 mm). Any new lesion considered non-measureable at the time of initial progression may become measureable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

13.3. Antitumor Effect – Hematologic Tumors

14. End of Treatment

14.1. Duration of Treatment

14.1.1 CR, PR, or SD

Patients who are in CR, PR or SD (as defined in Section 14) will continue on therapy for a total of 12 months. Patients with CR, PR, or SD at 12 months, and then have progression are potentially eligible for retreatment. After treatment is discontinued, patients will be followed per the study calendar in Section 8.0.

14.1.2 Disease Progression

Remove from protocol therapy any patient with disease progression on study therapy. Details of progression, including tumor measurements, should be documented on the appropriate form.

After disease progression, patients should be followed for survival per the study calendar (Section 8.0).

Patients receiving immune therapy sometimes have symptomatic and/or radiographic progression as enlarged pre-existing lesions or new lesions that constitute “pseudoprogression” from an inflammatory anti-tumor effect. Patients who are felt to be clinically benefiting from study therapy may be allowed to continue on study therapy, if the patient is not having clinical deterioration consistent with true cancer progression. Treating “beyond progression” must be discussed and approved by the principal investigator or their designee (See Section 14.1.3).

14.1.3 Treatment Beyond Progression

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

Subjects will be permitted to continue treatment beyond initial RECIST 1.1 defined PD as long as they meet the following criteria determined by the investigator:

- Investigator-assessed clinical benefit and subject is tolerating study drug.
- Tolerance of study drug
- Stable performance status

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment.

Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases) A radiographic assessment/ scan should be performed within 6 weeks of initial investigator-assessed progression to determine whether there has been a decrease in the tumor size or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab.

15. Statistical Considerations

15.1. Overview of the Study Design

Eligible patients will be randomized with equal allocation to nivolumab alone (arm A) and nivolumab plus nab-paclitaxel (arm B). Randomization will be done through stratified permuted block design algorithm with stratification on (a) Histology (Squamous vs. non-squamous); (b) History of prior taxane therapy (Yes vs. No); and (c) smoking history.

Assuming 5% rate of cancellation prior to treatment and ineligibility, a total of 200 patients will be randomized. All patients will be evaluated for response rate and adverse events during protocol treatments. All patients will be assessed for progression-free survival by repeated CT scans every 6 weeks for 48 weeks and then every 12 weeks until 28 months from enrollment, until lost to follow-up, withdrawal, progression or death. All patients are expected to be followed for progression free survival and overall survival for 28 months after enrollment.

It is now recognized that a subset of patients $\leq$ 5% with non-small cell lung cancer will have pseudoprogression when treated with nivolumab. In this context pseudoprogression means that when the immune system attacks tumors, the radiographic images show tumor enlargement or new lesions prior to the tumors shrinking. Therefore it has become common practice in immune therapy trials to allow "treatment beyond progression" when the patient seems to be having clinical benefit despite evidence of disease progression by radiograph images.

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

15.2. Sample Size, Accrual Time and Study Duration

The sample size of this randomized phase II trial is justified by having adequate statistical power to test an improvement of progression-free survival in a second line setting for advanced NSCLC patients receiving nivolumab plus nab-paclitaxel (arm B) as compared to those receiving nivolumab alone (arm A).

Nivolumab was compared to docetaxel as second-line therapy in advanced stage NSCLC in two randomized phase 3 trials. In the BMS017 trial for second-line squamous cell lung cancer, overall survival was 9.2 months with nivolumab and 6.0 months with docetaxel, HR 0.59 and $p < 0.001$. In the

BMS057 trial for second-line non-squamous lung cancer, overall survival was 12.2 months for nivolumab and 9.4 months for docetaxel, HR 0.73 and p = 0.0015. For the BMS057 non-squamous trial, the median PFS was 2.3 months and for BMS017 squamous trial, the median PFS was 3.5 months. We would expect 2/3 of patients to be non-squamous for this concept. Based on these findings, we design the trial to test an expected median PFS improvement of 1.5 months (approximately 50% increase) from 3 months to 4.5 months.

The following assumptions are made while determining the statistical power:

(i) the median PFS is 3 months for patients on nivolumab alone (arm A) and 4.5 months for nivolumab plus nab-paclitaxel (arm B), a 50% increase in median PFS and a corresponding hazard ratio $\lambda_B/\lambda_A = 0.67$ under constant hazards;
(ii) 190 eligible patients (95 per arm) will be randomized with 1:1 allocation;
(iii) an accrual period of 20 months (approximately 10 patients per month) ; and
(iv) an additional follow-up of 8 months for PFS after the enrollment of the last patient. Using a stratified log rank test at a two-sided significance level of 0.10, the study has approximately 85.5% power to reject the null hypothesis $\lambda_B/\lambda_A = 1$ and accept the alternative hypothesis $\lambda_B/\lambda_A < 1$ when the true $\lambda_B/\lambda_A = 0.67$. At the time of analysis, or approximately 28 months after the first enrollment, a total of 178 events (92 on arm A and 86 on arm B) are anticipated under the alternative hypothesis. After adjusting for the small loss of power due to interim analysis (see next section for details), the actual power will be approximately 84.5%.

After the initiation of protocol treatment, all registered patients will be followed for 28 months from enrollment to observe progression-free survival and overall survival.

15.3. Stratification Factors

Patients will be stratified by:

1) Squamous versus non-squamous histology (any histology not specified squamous only will be stratified as non-squamous)
2) History of prior taxane therapy (nab-paclitaxel excluded).
3) Smoking history

15.4. Statement for Primary Endpoint

The primary objective is to determine whether the progression free survival of patients with advanced stage non-small cell lung cancer whose cancer has progressed after first-line chemotherapy is improved with nivolumab plus nab-paclitaxel compared to nivolumab alone.

15.5. Interim Analysis Design for Primary Endpoint (include DSMB reporting, if applicable)

AFT DSMB will review the study data at each of its semiannual meetings after first enrollment. This will include toxicity, progression free survival and overall survival information. In determining whether the trial should be continued, the DSMB will use its discretion in weighing the combined impact of treatment-related toxicity, disease recurrence and overall survival. The first formal interim analysis for efficacy will occur once 104 events (58% information) have been observed with two treatment arms combined or approximately 16 months after first enrollment. After that, 2nd formal interim analyses will

be conducted at 156 events (approximatively at months 22) and the final analysis at 178 events (months 28). Early stopping at any of these times could occur for superiority (arm B is superior to arm A) and for futility (arm B is equivalent or inferior to arm A) on progression-free survival. The log rank test will be used to generate the one-sided p-values for both tests. Using RCTdesign (9), we will construct two-sided boundaries in the spirit of O'Brien and Fleming (10). We will truncate alpha level at 0.001 for the futility boundary to echo the spirit of the paper by Freidlin and Korn (11). The final analysis at 28 months after study activation will conclude a superiority of arm B to arm A if the p-value of a two-sided log rank test for superiority is less than 0.10 as the alpha spent under such early stopping boundaries is minimal. The following table displays operating characteristics, including actual power, average study size, stopping probabilities under true hazard ratios of 0.6, 0.667, 0.7, 0.8, 0.9, 1.0.

Table 4

Hazard Ratio (λ_B/λ_A)	Expected Number of Events	Prob. to Reject H0: $\lambda_B/\lambda_A = 1$ (Power)	Prob. of early stop prior to final analysis for superiority	Prob. of early stop prior to final analysis for futility
0.6	125	0.9568	0.9091	0.0002
0.67	140	0.8457	0.7522	0.0017
0.7	147	0.7567	0.6476	0.0041
0.8	163	0.4269	0.3271	0.0322
0.9	168	0.1692	0.1201	0.1274
1	162	0.0500	0.0343	0.3099
1.2	138	0.0024	0.0017	0.7337

15.6. Secondary Objectives

The secondary objectives for this study are as follows:

1) To evaluate the difference of response rates between two treatments;
2) To evaluate the difference of overall survivals between two treatments;
3) To characterize the treatment related adverse events
4) To characterize progression free survival for PDL1 positive (>1% tumors positive) and PDL1 negative tumors
5) To study immunologic biomarkers in the blood before and after nab-paclitaxel plus nivolumab.
6) To study immunologic biomarkers in the tumor at baseline before nab-paclitaxel plus nivolumab.
7) To evaluate the difference of response rates in squamous cell lung cancer between the two treatments.
8) To evaluate the difference in progression free survival in squamous cell lung cancer between the two treatments.
9) To evaluate the difference in overall survival.
10) To compare clinical outcomes for PDL1 positive and PDL1 negative tumors.
11) To compare rate of deaths in the first 3 months between the two treatments.

12) To compare characteristics of tumors for deaths in the first 3 months compared to those living more than 3 months.

15.7. Supplementary/Secondary Analysis Plans/Statistical Analysis Plan

A modified ITT approach will be used for the statistical analyses. In other words, ineligible patients, who have received at least one cycle of protocol treatment will be included in the analysis of adverse events. The statistical analysis cohort for treatment efficacy will include all randomized patients but exclude in eligible patients or patients who cancel this study before receiving any protocol treatment. The primary efficacy endpoint is progression-free survival (PFS), which is the time from the date of randomization to the date of the earliest radiographic disease progression or death, the data will be censored at the date of the last disease assessment.

PFS will be analyzed by Kaplan Meier methodology and compared between arm A and arm B, using a log-rank test stratified by histology, history of prior taxane therapy and smoking history (12). A two-sided p value will be provided. Median PFS will be estimated and its 95% confidence interval for median PFS will be presented for each arm. Overall survival (OS), which is the time from randomization to deaths of all causes, will be analyzed in a similar manner as PFS.

All subjects who receive at least one dose of the study drug will be included in safety analysis. Treatment-related toxicity will be summarized by grade, type and system organ class. Comparisons of the percentages of subjects experiencing an adverse event between arm A and arm B will be performed using Fisher's exact test (13).

The objective of the correlative sciences study is to study immunologic biomarkers in the blood before and after nab-paclitaxel plus nivolumab and to study immunologic biomarkers in the tumor at baseline before nab-paclitaxel plus nivolumab. The association of baseline value and the changes of these biomarkers with clinical outcomes will be evaluated. The association of these biomarker measures with response will be evaluated with Wilcoxon rank sum test and multivariable logistic regression with adjustment for other risk factors. The association between these biomarker measures and survival endpoints, including PFS and OS, will be using single-predictor and multivariable Cox models (14). The biomarkers measured in tumor samples at baseline will be evaluated in similar approaches. The PDL status determined by biomarker analysis will be used to test the interaction between PDL status and treatments and the treatment effect on PDL positive will also be estimated (15).

15.8. Adverse Event/Accrual Monitoring Stopping Rule

Overall, if 5 or more of the first 20 patients in the nivolumab plus nab-paclitaxel arm (arm B) experience grade 4/5 non hematologic adverse events (excluding diarrhea and rash) that are probably, possibly, or definitely related to study treatment, OR if the rate of treatment-related deaths within the first 60 days of the first dose of the protocol treatment exceeds 4 or more in either arm among the first 20 patients at any time, accrual to the study will be suspended to allow for one investigation. After consideration by the study team and the primary IRB, a decision will be made as to whether accrual can be resumed potentially with modifications to entry criteria and/or study conduct.

15.9. Criteria for Taking a Patient Off Protocol Therapy

Patients in Arm A and Arm B will receive study therapy until progression or not tolerated. Patients having durable disease control after 12 months will stop study therapy. If the cancer then progresses during the 28

months of planned follow-up after enrollment, the patient may receive an additional 12 months of therapy, if the patient otherwise meets all criteria to receive study therapy. Dose reductions established during the first 12 months of therapy will continue in the potential second 12 months of therapy.

Patients will be removed from study for one of the following:

- Unacceptable toxicity
- Progression of disease
- Patient/physician withdrawal

The reason for treatment discontinuation must be entered into the eCRF. Patients who discontinue treatment will remain on study in Follow-Up Phase.

15.10. Duration of Follow-Up

Patients will be followed for 28 months after enrollment. After the end of treatment visit, the patient should be followed by institutional standard. Follow-up data may be acquired by phone for patients who are no longer returning to the treating institution for follow-up.

15.11. Criteria for Taking a Patient Off Study

Patients will continue study therapy until one of the following, whichever occurs first:

- Lost to follow up
- Withdrawal of consent for data submission
- Death

The date of death or last known alive should be entered into the eCRF when a patient is removed from study.

15.12. Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

15.13. Managing Ineligible Patients and Registered Patients Who Never Receive Protocol Intervention

Definition of ineligible patients: A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible. Patients who are deemed ineligible may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

Study participants who are registered to the trial but never receive study intervention (for a reason other than because they were deemed ineligible) must still complete follow-up requirements as specified below:

Baseline, on-study, endpoint (e.g. relapse or progression), off treatment, and survival data submission required.

15.14. Data and Safety Monitoring

Interim Reports from the statistical team will be generated for the Data and Safety Monitoring Board (DSMB), as per the safety monitoring plan.

16. General Regulatory Considerations and Credentialing (Ethical Considerations and Administrative Procedures)

16.1. Compliance with Trial Enrollment 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 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. Information posted will allow patients 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 trial site contact information.

16.2. Regulatory and Ethical Compliance

By signing the Protocol the investigator agrees to treat all of the information that is provided with the strictest confidentiality and to require the same of his personnel as well as the IRB. Study documents (protocols, investigator`s brochures, eCRFs, etc.) provided by the AFT will be stored in an appropriate manner in order to ensure confidentiality. The information provided to the investigator by AFT must not be made available to other parties without a direct written authorization by the aforesaid parties, with the exception of the extent to which disclosure is necessary in order to obtain informed consent from the patients who wish to participate in the study.

This study will be conducted in compliance with the study protocol, subsequent amendment(s) and with the study-specific manuals/guidelines, if applicable. These documents ensure that the ICH E6 guideline for Good Clinical Practice is maintained as well as compliance with the principles of the Declaration of Helsinki (World Medical Association), or the laws and regulations of the country in which the research is conducted, whichever afford the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulation and applicable local, state and federal laws.

By signing the study protocol the investigator agrees to comply with the instructions and procedures described therein and thus to adhere to the principles of good clinical practice, which these instructions and procedures reflect.

16.3. Informed Consent

It is the responsibility of the Investigator, or a person designated by the Investigator (if acceptable by local regulations), to obtain written Informed Consent from each patient participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. This information must be provided to the patient prior to undertaking any trial-related procedure which is not part of the routine clinical management of the patient (i.e. would not be indicated outside the study).

For patients not qualified or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. In the case where both the patients and his/her legally acceptable representative are unable to read, an impartial witness should be present during the entire informed consent discussion. After the patient and representative have orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. The Investigator or designee must also explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

Furthermore, it is the investigator's responsibility to obtain the signed Informed Consent Form, and a signature from the person conducting the informed consent discussion, prior to undertaking any trial-related procedure. The proposed Informed Consent Form must comply with the ICH GCP guideline and regulatory requirements.

16.4. Responsibilities of the Investigator/IRB/IEC/REB

The regulatory requirements for the Investigator can be found in Subpart D of 21CFR312 (21CFR 312.60: General Responsibilities of Investigators) and in ICH E6 Section 4.

Additional requirements are also outlined in the Statement of Investigator Responsibilities (Form FDA 1572) and the Site Services Agreement. Alliance Foundation Trials, LLC (AFT) will supply the protocol and subsequent amendments.

The Investigator is responsible for ensuring all patients and/or parents or legal guardian of each patient, if applicable, are informed about the study and that written consent is obtained prior to the conduct of any study related procedures.

In addition, the Investigator is responsible for reviewing all health related information collected for each study patient in order to identify any safety related issues/adverse events (AE) or Infusion Associated Reactions (IAR). All Serious Adverse Events (SAEs) and IARs are to be reported within 24 hours to AFT via the Rave Electronic Data Capture system of becoming aware of the event. If this is not reported within 24 hours, a Protocol Deviation will be documented.

As specified in 21CFR 312.62 (Investigator Record Keeping and Record Retention) and ICH E6 Sections 4.9 and 8, the Investigator is responsible for ensuring that their study staff maintains and retains all study related documentation, including but not limited to: signed Informed Consent forms, medical records that are applicable for this study and source documents, the AFT-31 protocol, Institutional Review Board (IRB) approvals, relevant IRB and Sponsor correspondence, and assorted regulatory documents. The Investigator is responsible for retaining and keeping safe all patient related

documentation. In order to do this, the site staff will complete electronic case report forms (eCRFs) in a timely manner.

16.5. Financial Disclosures

Investigators will provide AFT with adequate and accurate financial information in accordance with local regulations and laws in order to allow AFT to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing updated information on financial interests during the course of the study as well as for 1 year after completion of the study.

16.6. Protocol Deviations

The investigator is responsible to document and explain any deviations from the approved protocol. The investigator should promptly report any deviations that might impact patient safety and data integrity to AFT and if locally applicable, to the respective IRB in accordance with local IRB policies and procedures.

A deviation is a departure from the protocol. If deviations are discovered by the monitor or data manager, other member of study staff or otherwise, they will be discussed with the Investigator and study staff. AFT does not provide waivers for protocol deviations.

16.7. Protocol Amendments

Any modifications to the protocol or the Informed Consent Form which may impact on the conduct of the study, potential benefit of the study, or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be released by AFT, agreed by the investigator(s) and approved by relevant IRBs prior to implementation. A signed and dated statement that the protocol, any subsequent relevant amended documents and the Informed Consent Form have been approved by relevant IRBs must be provided to AFT before the study is initiated.

Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be released by the AFT, agreed by the investigator(s) and notified to the IRB.

16.8. Retention of Records (Study Documentation, record keeping, and retention of records)

Any records and documents relating to the conduct of this study and the distribution of investigational drug, including ICFs, eCRFs, PRO data, laboratory test results, and medication inventory records, must be retained by the study chair until notification by AFT, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations. No records may be disposed of without the written approval of AFT. Written notification should be provided to AFT prior to transferring any records to another party or moving them to another location.

16.9. Data and Safety Monitoring Board (DSMB)

The Alliance Foundation Trials Data Safety Monitoring Board will be monitoring this study.

16.10. Regulatory Reporting

Serious adverse events will be forwarded to FDA by the IND Sponsor according to 21 CFR 312.32.

It is the responsibility of the investigator and the research team to ensure that serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices (GCP), the protocol guidelines, AFT's guidelines, and Institutional Review Board (IRB) policy.

16.11. Data Confidentiality

Patient medical information both, associated with biologic specimens or not, is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorization for use and disclosure of personal health information) which has been signed by the patient, unless permitted or required by law. Data derived from biologic specimen analysis on individual patients will in generally not be provided to study investigators unless a request for research use is granted. The overall results of any research conducted using biologic specimens will be available in accordance with the effective AFT policy on study data publication.

16.12. Database Management and Quality Control

The Site Principal Investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study.

Rave EDC will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an eCRF, and transmitted in a secure manner to AFT within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the eCRF.

The Clinical Research Coordinator (CRC) or designated study site personnel will complete the eCRFs in a timely manner after the information is collected, preferably within 3-5 business days after the study procedure has been performed. The Investigator will review and approve the completed eCRFs. Subjects will not be identified by name in the study database or on any study documents to be collected by the AFT (or designee), but will be identified by a site number, subject number.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto eCRFs.

At study completion, when the database has been declared to be complete and accurate, the database will be locked.

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis.

AFT will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the AFT; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the clinical study database they will be verified for accuracy and consistency with the data sources. Queries are entered, tracked, and resolved through the EDC system directly. The study database will be updated in accordance with resolved queries. All changes to the study database will be documented.

At critical junctures of the protocol (e.g., production of interim and final reports), data for analysis is locked and cleaned per established procedures.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (e.g. retirement, relocation), AFT should be prospectively notified. The study records must be transferred to a designee acceptable to AFT, such as another investigator, another institution, or to AFT itself. The Investigator must obtain AFT's written permission before disposing of any records, even if retention requirements have been met.

16.13. Site Monitoring

Monitoring visits will be conducted by representatives of the Alliance Foundation according to the US CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to AFT (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

16.14. Audits and Inspections

To enable evaluations and/or audits from regulatory authorities or AFT, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., eCRFs and hospital records), all original signed informed consent forms, copies of all eCRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports).

The records should be retained by the Investigator according to ICH, local regulations, or as specified in the Clinical Trial Agreement, whichever is longer, but at a minimum, all study documentation must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of AFT-31.

16.15. Early Discontinuation of the Study

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
4. Plans to modify or discontinue the development of the study drug

16.16. Publication of study protocol and results

AFT prioritizes the timely presentation and publication of study results. Publications and any kind of presentations of any results from the study shall be in accordance with accepted scientific practice, academic standards and customs and must be approved in writing by AFT as the sponsor of this trial. No investigator may present or publish any portion of this trial without written approval by AFT.

17. References

1. Brahmer J, et al. N Engl J. Med. 2015 Jul 9; 373(2): 123-35.
2. Borghai H, et al. N Engl J Med. 2015 Sept. E Pub
3. Socinski MA, et al. J Clin Oncol 2012; 30:2055-62.
4. Liu Z, et al. Med Oncol. 2015 Aug; 32(8):216.
5. Camidge R. et al. World Lung Cancer Meeting, Denver, CO September 2015.
6. Adams S, et al. San Antonio Breast Cancer Meeting, San Antonio, TX December 2015.
7. Antonia SJ, et al. ASCO Annual Meeting, Chicago, IL 2014
8. E.A. Eisenhauer, P. Therasse, J. Bogoaerts, L.K. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (Version 1.1). Eur J Cancer. 2009 Jan; 45(2): 228-47.
9. Emerson, S., S+SEQTRIAL: technical overview, in Data Analysis Products Division, MathSoft, Inc. 2000.
10. O'Brien, P.C. and T.R. Fleming, A multiple testing procedure for clinical trials. Biometrics, 1979. 35(3):p. 549-56.
11. Freidlin, B., E.L. Korn, and S.L. George, Data monitoring and committees and interim monitoring guidelines. Control Clin Trials, 1999. 20(5): p. 395-407.
12. Kaplan, E.L., Meier, P., Nonparametric estimation from incomplete observations. J Am Stat Assoc, 1958. 53(282): p. 457-481.
13. Mantel, N., Evaluation of survival and data and two new rank order statistics arising in its consideration. Cancer Chemotherapy Rep. 1966. 50(3): p. 163-70.
14. Cox, D.R. Regression models and life-tables. J R Stat Soc 1972 34: p.187-220.
15. Fine, J., Gray R., A proportional hazards model for the sub distribution of a competing risk. J Am Stat Assoc, 1999. 94: p. 496-509.

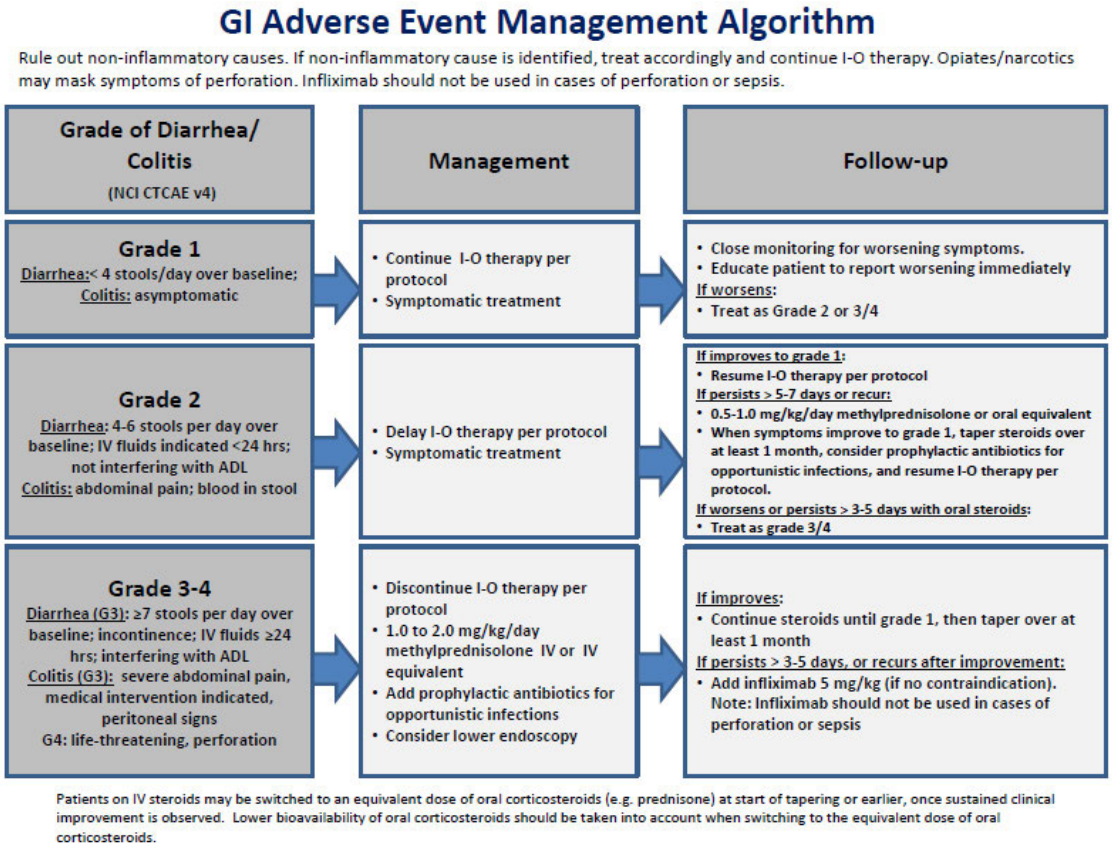
18. Appendices

18.1. Appendix I: ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
*As published in Am. J. Clin. Oncol. *Oaken, M.M., Creech, R.H., Toomey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Is J Clin Oncol 5:649-655, 1982?* The Eastern Cooperative Oncology Group, Robert Comes M.D., Group Chair.	

18.2. Appendix II: Adverse Event Management Algorithms

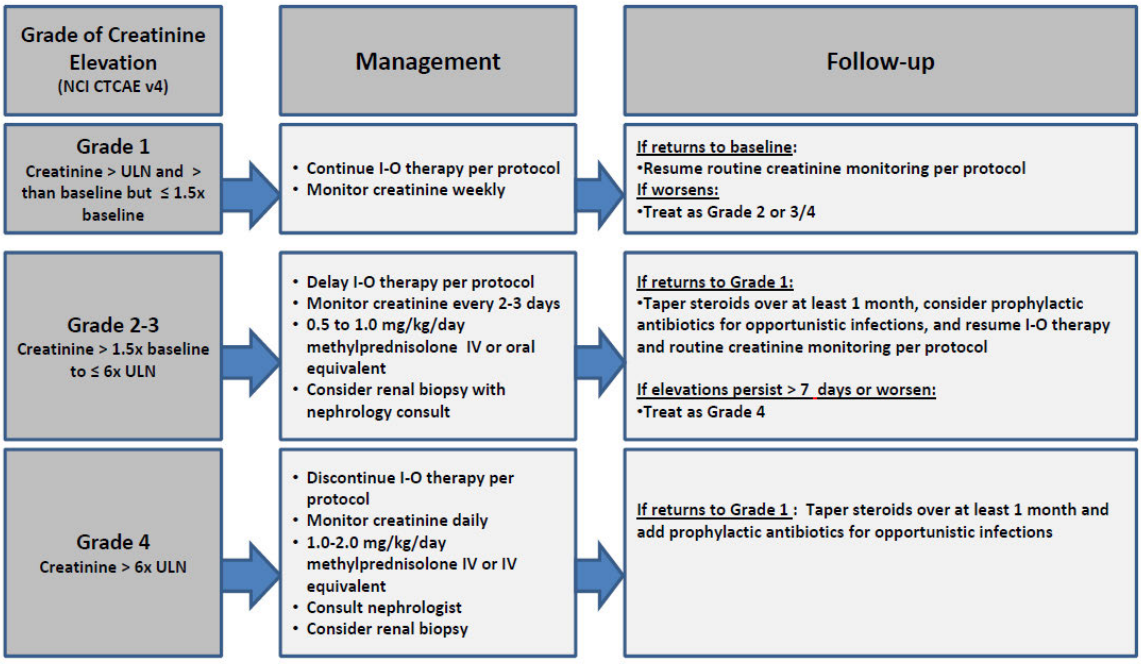
18.2.1 Genitourinary Adverse Events



18.2.2 Renal Adverse Events

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.

18.2.3 Pulmonary Adverse Events

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.

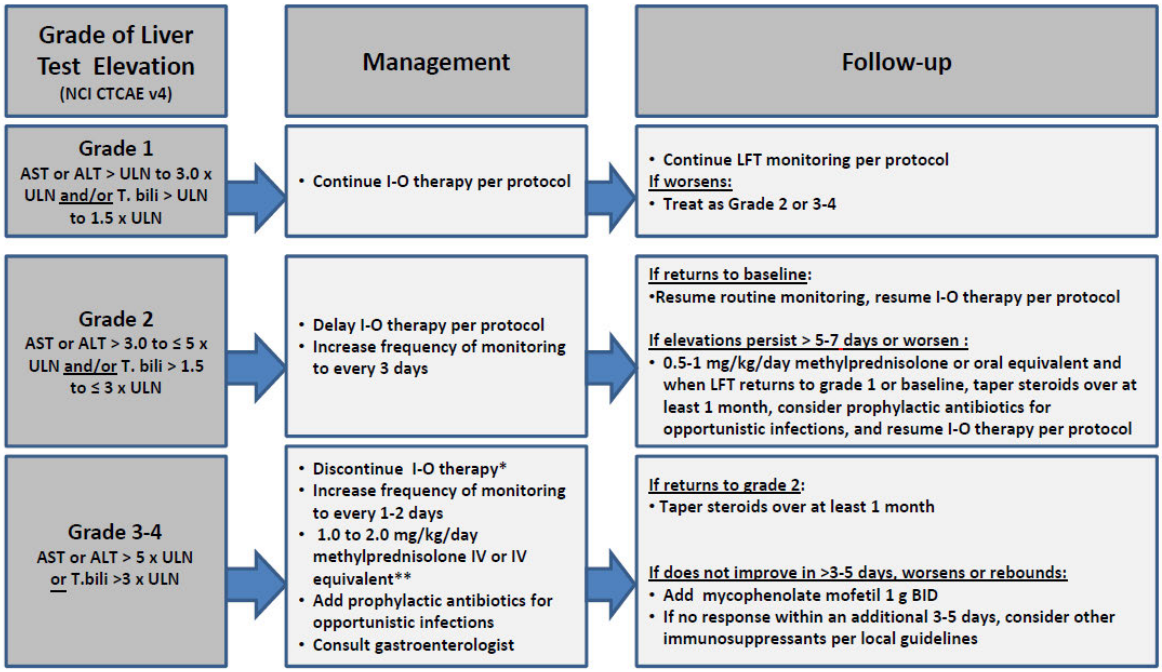
Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• 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.

18.2.4 Hepatic Adverse Events

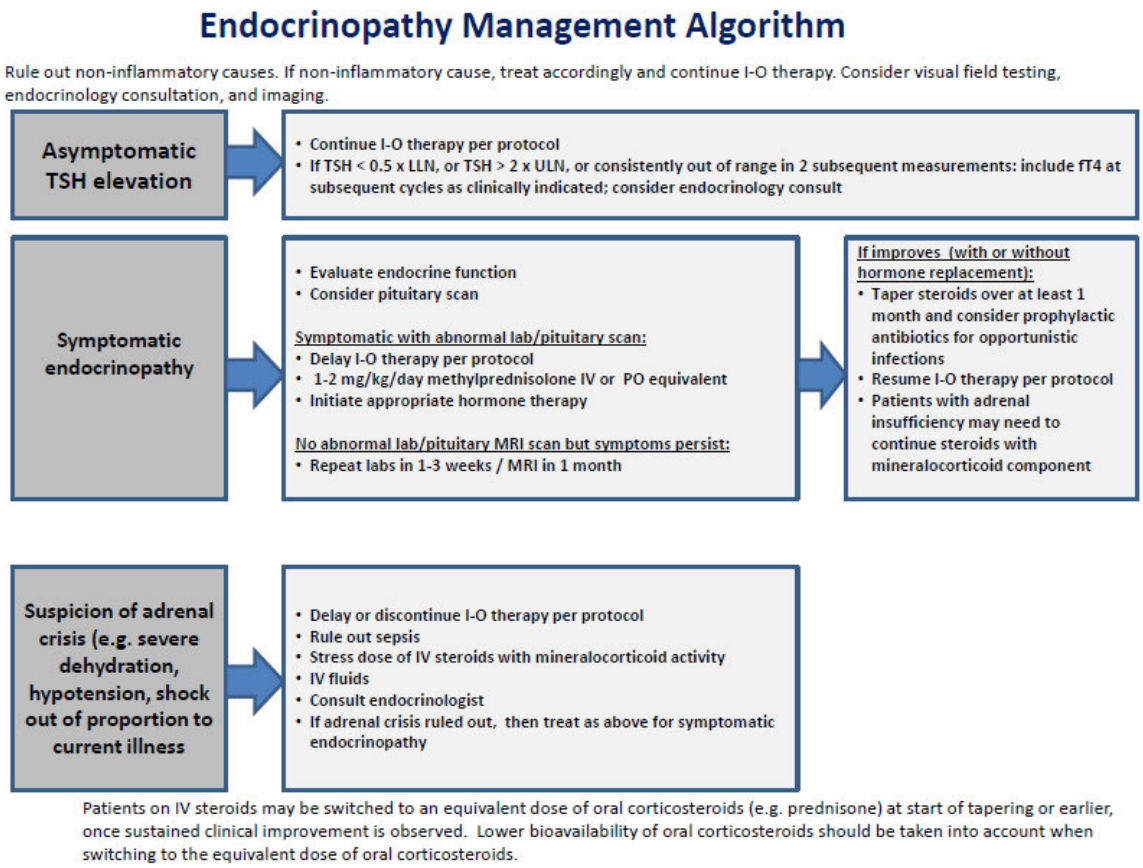
Hepatic Adverse Event Management Algorithm

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

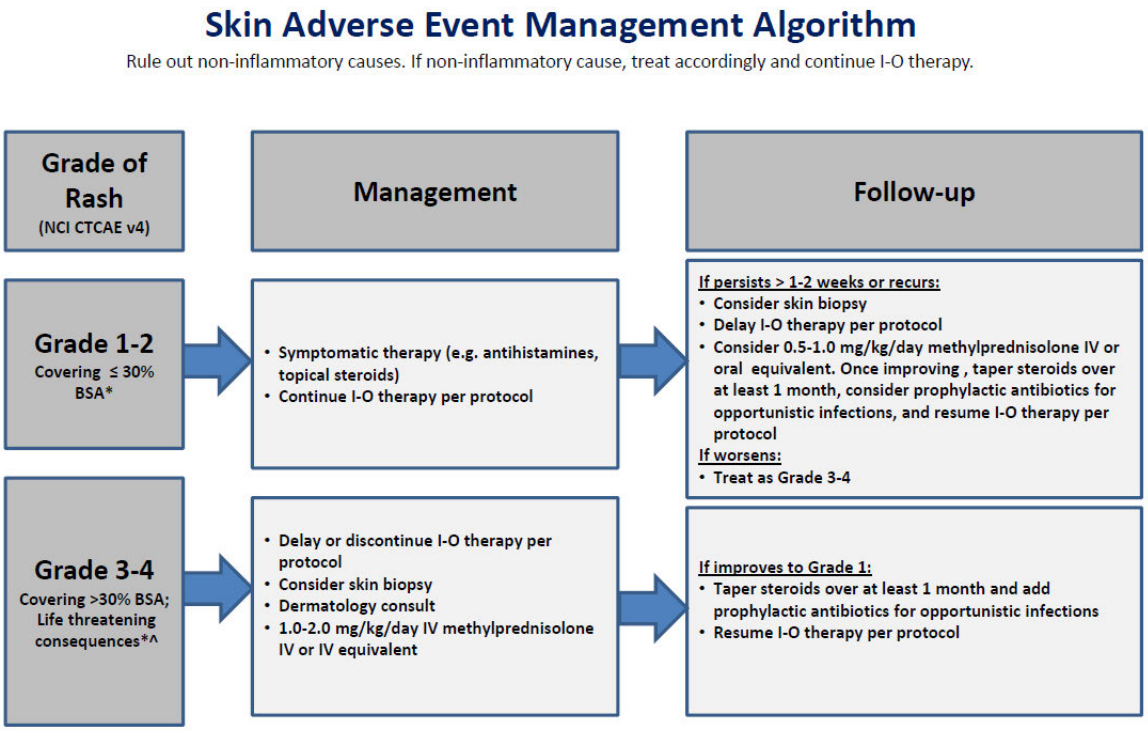


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

18.2.5 Endocrine Adverse Events

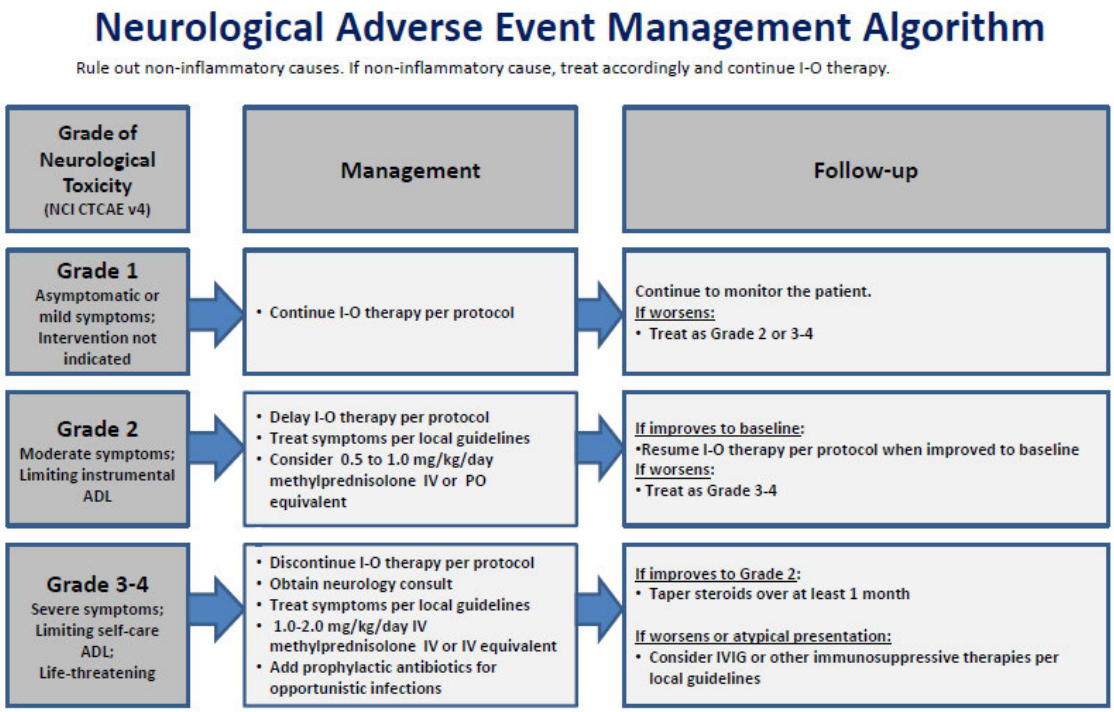


18.2.6 Skin Adverse Events



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.

18.2.7 Neurological Adverse Events



19. Approval Signatures

Printed	Signature	Title	Date
Suzanne George, M.D.			
Xiaofei Wang, Ph.D.			
Neal Ready, MD PhD			