PD-1 Immune Checkpoint Inhibition for the Reversal of Squamous Dysplasia in High Risk Current and Former Smokers with or without a History of Lung Cancer

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	PD-1 Immune Checkpoint Inhibition for the Reversal of Squamous Dysplasia in High Risk Current and Former Smokers with or without a History of Lung Cancer
Study Description:	The goal of this clinical research study is to determine whether the PD-1 inhibitor nivolumab improves premalignant bronchial dysplastic lesions in subjects that are at high risk for the development of lung cancer, including those with a prior smoking history, or history of lung cancer or head and neck cancer. The safety and tolerability of nivolumab will also be studied.
Objectives:	***Primary Objective:*** To determine whether immune checkpoint blockade using nivolumab can reverse premalignant histological changes in the bronchial epithelium of subjects at high risk for developing lung cancer as defined by moderate or worse bronchial dysplasia; and either 30 pack-years of tobacco exposure, or history of early-stage lung or early-stage head and neck cancer at least one year after definitive treatment. ***Secondary Objective:*** To assess the safety and tolerability of nivolumab in patients with bronchial dysplastic lesions.

Endpoints:

Primary Endpoint:

The primary endpoint is the dichotomous endpoint of whether a subject responds to immune checkpoint blockade using nivolumab. Response to treatment will be based on the 6-month change (difference between 6-month score and baseline score) in worst (i.e., maximum) histologic classification score, using the 2004 World Health Organization (WHO) classification scale for endobronchial dysplasia.

Secondary Endpoints:

1. Safety and tolerability of nivolumab in patients with bronchial dysplastic lesions.
2. Additional endobronchial histology endpoints
    a. 2-month change (difference between 2-month score and baseline score) in worst (i.e., maximum) histologic classification score
    b. Using all dysplastic (i.e., histology score ≥ 4.0) baseline biopsy pairs, the change in average histology and dysplasia index
    c. Using all matched biopsies, the change in worst histology, average histology, and dysplasia index
    d. Using all matched biopsies from reference sites, the change in worst histology, average histology, and dysplasia index
    e. Response to treatment of completers, based on worst histology

Exploratory Endpoints:

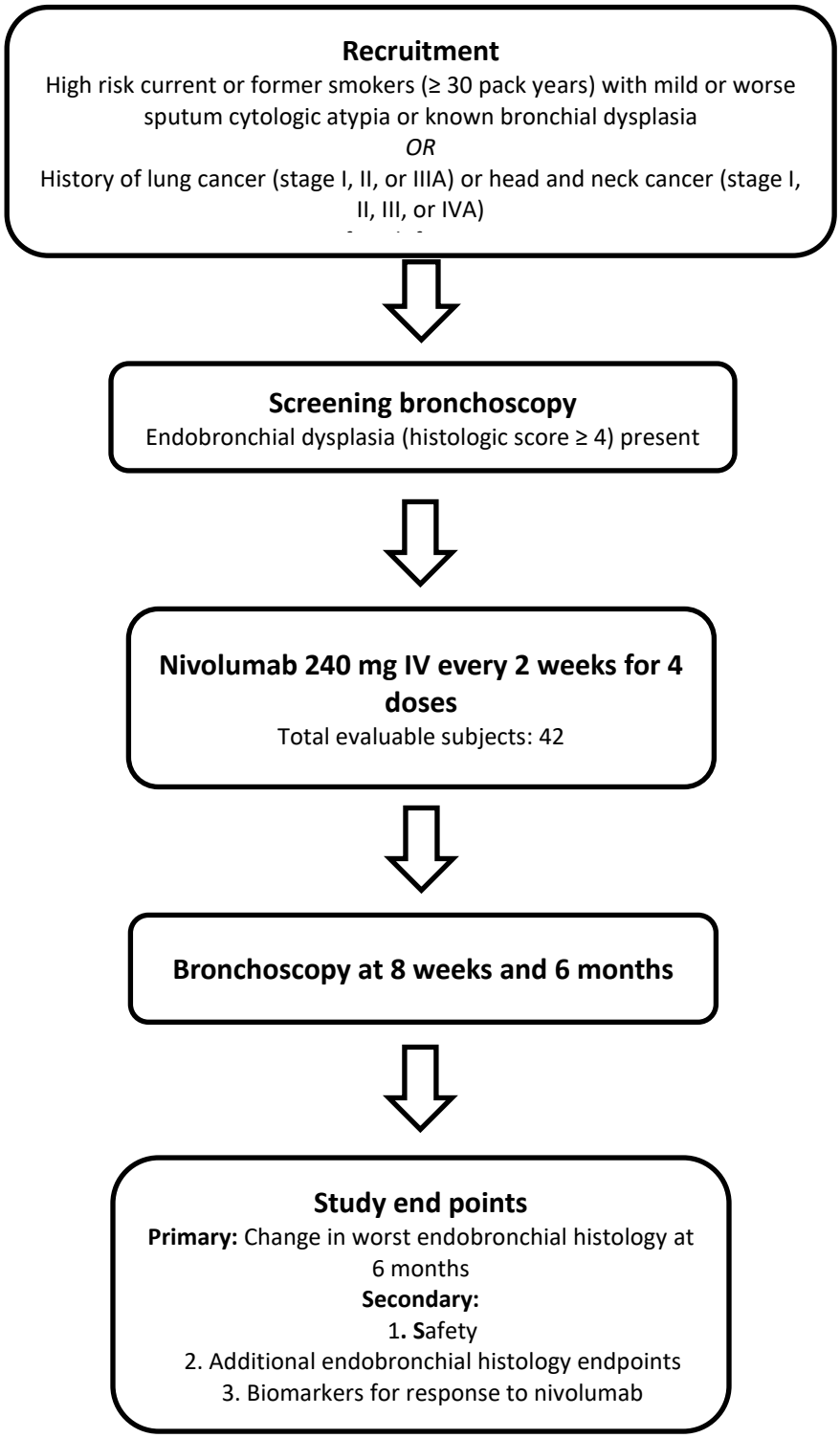
An important aspect of this trial is to identify novel prognostic and predictive markers present at the time of diagnosis. As such, radiologic data and blood will also be collected throughout the study period. The markers to be assessed will be determined according to the best scientific knowledge and technology available. Correlative studies will be interpreted as hypothesis-generating data, to be validated in subsequent trials. Candidate markers to be evaluated include:

1. Expression levels of programmed death receptor 1 (PD-1) on T lymphocytes associated with bronchial dysplastic lesions at baseline and following treatment with nivolumab.
2. Expression levels of programmed death ligand 1 (PD-L1) on macrophages and epithelial cells associated with bronchial dysplastic lesions at baseline and following treatment with nivolumab.
3. Characterization of inflammatory infiltrates (i.e., T lymphocyte and macrophage subsets) in bronchial dysplastic lesions at baseline and following treatment with nivolumab.
4. Total mutational burden of bronchial dysplastic lesions as measured by whole exome sequencing

5. Changes in systemic inflammatory signatures at baseline and during treatment with nivolumab as measured by mass cytometry (CyTOF)

Study Population:	***Sample size:*** This study will use a Simon 2-stage design. The null hypothesis that the true response rate is 0.30 will be tested against a 1-sided alternative. In the first stage, 18 subjects will be enrolled. If there are 6 or fewer responses in these 18 subjects, the study will be stopped. Otherwise, 24 additional subjects will be enrolled for a total of 42 evaluable subjects. If 17 or fewer subjects are responders at the end of the trial, no further investigation of the drug is warranted. The null hypothesis will be rejected if 18 or more responses are observed in the 42 total subjects. This design has 80.2% power to reject the null hypothesis when the true response rate is 0.50, controlling the type I error rate at 0.05 (actual α = 0.044). Up to 240 subjects may be consented to the pre-screening portion of this study. We plan to enroll up to 60 participants in the main/treatment potion of this study for a total of 42 evaluable subjects. ***Gender:*** Male and female ***Age:*** Adults ≥ 18 years of age ***Demographic group:*** Subjects at high risk for developing lung cancer as defined by endobronchial dysplasia; and either 30 pack years of tobacco exposure and sputum cytologic atypia, or history of early-stage lung or head and neck cancer at least one year after definitive treatment. ***General health status:*** ECOG 0-1 ***Geographic location:*** United States
Phase:	2
Description of Sites/Facilities Enrolling Participants:	Academic medical center
Description of Study Intervention:	Nivolumab 240 mg IV every 2 weeks for 4 doses
Study Duration:	5 years
Participant Duration:	1 year

1.2 SCHEMA


Recruitment
High risk current or former smokers (≥ 30 pack years) with mild or worse sputum cytologic atypia or known bronchial dysplasia
OR
History of lung cancer (stage I, II, or IIIA) or head and neck cancer (stage I, II, III, or IVA)
Screening bronchoscopy
Endobronchial dysplasia (histologic score ≥ 4) present
Nivolumab 240 mg IV every 2 weeks for 4 doses
Total evaluable subjects: 42
Bronchoscopy at 8 weeks and 6 months
Study end points
Primary: Change in worst endobronchial histology at 6 months
Secondary:
1. Safety
2. Additional endobronchial histology endpoints
3. Biomarkers for response to nivolumab

2 INTRODUCTION

2.1 STUDY RATIONALE

This study is a phase 2, single-arm, open-label trial of nivolumab in subjects with endobronchial dysplasia; and either 30 pack years of tobacco exposure and either mild or worse sputum cytologic atypia or known bronchial dysplasia, or history of early-stage lung or head and neck cancer (greater than 1 year after definitive treatment). The central question of interest is to determine whether nivolumab improves bronchial dysplastic lesions and prevents the histologic progression of premalignant central airway lesions in subjects that are at high risk for the development of lung cancer. The safety and tolerability of nivolumab will also be studied. Exploratory endpoints will include potential predictive biomarkers of nivolumab efficacy in subjects at high risk for the development of lung cancer.

2.2 BACKGROUND

2.2.1 RATIONALE FOR LUNG CANCER PREVENTION STUDIES

Lung cancer is the leading cause of cancer death in both men and women in the United States with a dismal 5-year survival rate of approximately 16% (1). Although the National Lung Screening Trial (NLST) has shown that yearly low dose chest CT scans can decrease lung cancer mortality by 20% (2), currently less than 25% of patients present with surgically curable disease (stages I and II) (1). Cigarette smoking accounts for 85-87% of all new lung cancer cases and the increased risk of lung cancer persists for more than 20 years after smoking cessation. In the US, the majority of new lung cancer cases are diagnosed in former smokers (3). Therefore, improved success in decreasing lung cancer mortality rates will rely not only on smoking prevention/cessation and CT scanning of high risk populations, but also on effective preventive strategies.

2.2.2 PRIOR LUNG CANCER CHEMOPREVENTION STUDIES

Table 1: Lung Cancer Prevention Trials

CHEMOPREVENTION OF LUNG CANCER:RANDOMIZED TRIALS

STUDY	No.	Therapy	Group	RESULTS
Caret	18,314	Beta Carotene & Retinol vs. placebo	Smokers, Ex-Smoker Asbestos Exp	↑ Inc Risk RR 1.28 (p=.02)
ATBC	29,133	Beta Carotene & Alphatocepherol, Both Placebo	Male Smokers	RR 1.16 (p=.02)
Physician Health	22,071	Beta Carotene Placebo	Male Physician (age 40-84, 11% smokers)	No Benefit
*EORTC	2,592	Retinyl palmitate	Stage I NSCLC	↓ SPT (p=.05)
*Euroscan	2,592	RetinylPalmitate, NAC,both,placebo	Stage I NSCLC Stage I-II H&N	No Benefit
*US InterGroup	1,134	13-Cis Retinoic Acid placebo	Stage I NSCLC	No Benefit

* Second Primary Lung Cancer Endpoint

There have been a limited number of chemoprevention studies in lung cancer. Early trials were based on epidemiological data, which suggested that diets high in vitamin A reduced the risk of lung cancer. Several large randomized primary and secondary lung cancer prevention trials have been conducted (summarized in Table 1) (4-9). Three large trials in primary prevention evaluated β-carotene plus retinol, β-carotene and/or α-tocopherol, or β-carotene alone, while three trials investigating secondary prevention strategies administered retinyl palmitate, retinyl palmitate and/or N-acetylcysteine (NAC) or 13-cis retinoic acid. Unfortunately, the results from these trials

were disappointing. No protective effect against lung cancer was observed, and two trials suggested these agents could increase the risk of lung cancer in the smoking population. Thus, high doses of a single antioxidant vitamin do not appear to be a viable strategy. In addition, these trials were based only on epidemiologic data and required thousands of subjects and years to decades to complete. A study exploring the association of supplemental multivitamins, vitamin C, vitamin E, and folate in a large cohort failed to find a decrease in lung cancer risk (10). In fact, the researchers found a small increased risk associated with supplemental vitamin E. The most recent lung cancer tertiary chemoprevention trial examined the ability of selenium to prevent second primary tumors also failed to show any clinical benefit.

Due to the length and considerable cost to conduct trials with lung cancer incidence as the endpoint, more recent studies have focused on intermediate endpoints (endobronchial dysplasia) that are precursors for invasive squamous cell lung cancer. The World Health Organization (WHO) classification for lung cancer recognizes distinct histological lesions that are precursors of lung cancer (11). Our group at the University of Colorado Anschutz Medical Campus and Denver VA Medical Center showed that bronchial dysplastic lesions can be reproducibly graded, and that persistence of bronchial dysplasia (BD) is associated with the development of invasive squamous cell lung cancer (12). Our group also showed that the oral prostacyclin analog iloprost significantly improves BD in former smokers (13), which suggests that targeted agents such as prostacyclin analogs may prevent the development of lung cancer in former smokers. Unfortunately, oral iloprost is currently unavailable, although we currently have a phase I trial that evaluates the effects of inhaled iloprost. Moreover, agents that prevent the development of lung cancer in active smokers have not been identified. Smaller trials with intermediate endpoints in high-risk subjects are urgently needed.

2.2.3 LUNG CANCER RISK ASSESSMENT AND PATIENT SELECTION

It is critical to define entry criteria for lung cancer prevention trials carefully. Study subjects must be of high enough risk that either lung cancer or intermediate endpoints will be found as frequently as possible. Over the past 25 years, investigators at the Denver VA Medical Center and the University of Colorado SPORE in Lung Cancer have focused on defining risk factors for both the development of lung cancer and the determination of intermediate endpoint biomarkers. The group at highest absolute risk for the development of lung cancer is comprised of survivors of previous lung cancer or head and neck cancer (14). The risk of developing new primary lung cancer in these patients is approximately 1-2% per patient per year.

Table 2: Frequency of bronchial dysplasia in bronchoscopic specimens

A.	BD positive – N (%)	BD negative – N (%)	p-value*
Prevalent Lung CA	13 (81.3)	3 (18.7)	0.46
No Lung CA	101 (72.7)	38 (27.3)	

B.	Multiple BD sites	w/o Multiple BD sites – N (%)	p-value*
Prevalent Lung CA	10 (62.5)	6 (37.5)	0.66
No Lung CA	79 (56.8)	60 (43.2)	

Frequency of bronchial dysplasia in bronchoscopies from various sources: A – Patients with previously diagnosed lung cancer (Prevalent Lung CA) show bronchial dysplasia (BD) in bronchial biopsies as often as in high risk patients without lung cancer (No Lung CA). B – The presence of BD at multiple sites (2 or more) is also common in the prior lung CA group.

Interestingly, bronchial dysplasia is the most common premalignant lesion in lung specimens from patients who underwent resection for invasive lung cancer (15). Our group at the University of Colorado Cancer Center has recruited subjects with previous lung cancer to clinical trials involving sputum collection and serial bronchoscopies. Although not statistically significant, bronchial dysplasia was more frequent in subjects

with a history of prior lung cancer (81.3%) than in high-risk former and current smokers with sputum atypia who did not have a history of lung cancer (72.7%, Table 2). The presence of BD at multiple sites (two or more) was also slightly more common in subjects with a history of lung cancer (62.5%) than in high-risk former and current smokers with sputum atypia (56.8%, Table 2).

Sputum cytologic atypia is also common in subjects with a history of prior lung cancer. Out of 14 subjects with a history of prior lung cancer, 11 (78.6%) showed dysplastic changes in sputa prior to their initial bronchoscopy. Out of the three subjects that had no significant epithelial abnormalities at pre-bronchoscopy sputum evaluation, two demonstrated mild dysplasia in a subsequent sputum sample. Of note, nine out of 14 subjects (64.3%) showed high grade atypia in their sputum, indicating that subjects with a history of prior lung cancer continue to harbor advanced premalignant lesions after definitive treatment. Although survivors of previous lung cancer or head and neck cancer are at the highest risk for developing lung cancer, tobacco smoking is the most common risk factor. However, prevention trials that assess intermediate endpoint biomarkers must further refine entry criteria. Subjects with tobacco smoke exposure and sputum cytologic atypia have rates of lung cancer greater than 1% yearly and are a high-risk group in which lung cancer prevention may have utility (16). Our group has shown that high-risk current and former smokers (≥ 30 pack year smoking history with sputum cytologic atypia) contain premalignant central airway dysplastic lesions that can progress to invasive squamous cell lung cancer (12). Unfortunately, bronchial dysplastic lesions are difficult to visualize during routine white light bronchoscopy. In order to address this limitation, advanced techniques such as LIFE (Laser Induced Fluorescence Endoscopy) and narrow-band imaging (NBI) bronchoscopy have been developed. University of Colorado investigators participated in the first multicenter trial to evaluate LIFE bronchoscopy for the detection of premalignant dysplasia in which LIFE bronchoscopy was shown to have an approximately six-fold increase in sensitivity for detecting moderate or greater dysplasia, compared to white-light bronchoscopy (17). In order to further evaluate the efficacy of LIFE bronchoscopy and to eliminate potential biases related to order of examination (white-light or LIFE first) or bronchoscopist prejudice, we conducted a two-bronchoscopist trial in which the order of examination and the identity of the bronchoscopist for each modality was determined randomly. This trial confirmed the superiority of LIFE for the detection of premalignant dysplasia. Similarly, NBI is superior to white-light bronchoscopy, with 96% sensitivity, 84% specificity, 131 diagnostic odds ratio, and 94% area under the receiver-operating characteristic curve (18). Using our criteria for patient selection (≥ 30 pack years, sputum cytologic atypia, and age) and our techniques for white light bronchoscopy combined with LIFE or NBI, we have been able to detect mild or greater dysplasia on bronchial biopsy in approximately 2/3 of study participants, a rate that is not equaled by any other center. During our more recent oral iloprost and pioglitazone trials, approximately 75% of enrolled subjects had at least one area of mild dysplasia identified during the initial bronchoscopy.

Thus, smoking history (current or former smokers with ≥ 30 pack years) with sputum cytologic atypia, and a prior history of lung cancer or a tobacco related aerodigestive cancer (specifically head and neck) are two of the strongest risk factors for developing lung cancer. As a result, these are the populations we have selected for our trial.

2.2.4 THE ROLE OF NIVOLUMAB IN THE TREATMENT OF LUNG CANCER

The immune system plays a dual role in cancer progression. It suppresses tumor growth by eliminating cancer cells, but also promotes tumor growth by selecting for cancer cells that can evade immunosurveillance. Cancer immunoediting has been proposed to occur in three phases: elimination, equilibrium, and escape, which involve the activation of innate and adaptive immune mechanisms

(19,20). In the elimination phase, transformed cells are destroyed by a competent immune system. Cancer cells that survive immunosurveillance enter the equilibrium phase. Equilibrium represents a functional state of dormancy in which tumor outgrowth is controlled by adaptive immunity. Tumor cells that acquire the ability to circumvent immune recognition will become clinically apparent. Moreover, tumor cells that escape immunosurveillance induce an immunosuppressive state through production of cytokines and growth factors such as VEGF and TGFβ, as well as by recruiting regulatory T cells (Tregs) and myeloid-derived suppressor cells.

Immune checkpoints refer to inhibitory pathways crucial for maintaining self-tolerance. However, tumors use certain checkpoint pathways to escape immune surveillance (21). Inhibitory ligands and receptors that regulate T cell effector functions are commonly overexpressed in tumor cells or in the tumor microenvironment (TME). The blockade of immune checkpoints results in tumor-specific T cell responses. The most studied immune checkpoint receptor in NSCLC is programmed death receptor 1 (PD-1). PD-1 mediates immune resistance in the TME by downregulating the activity of effector T cells in peripheral tissues in the setting of an inflammatory response (22). PD-1 is expressed on tumor-infiltrating lymphocytes (TILs), and upon binding to its ligands PD-L1 and PD-L2, PD-1 inhibits kinases that are involved in T cell activation (23,24). PD-1 is also highly expressed on Tregs and may enhance their proliferation (25). PD-1 ligands are frequently upregulated in human cancer, including NSCLC (26). Inhibition of the PD-1 pathway has been shown to enhance intratumoral immune responses in preclinical studies (27), and blockade of PD-1 has introduced a new era in lung cancer treatment.

Nivolumab (OPDIVO™) is a full human monoclonal immunoglobulin G4 antibody that binds to PD-1. Among patients with advanced, previously treated NSCLC, overall survival, response rate, and progression-free survival were significantly better with nivolumab than with docetaxel (28,29). As a result, the US FDA approved nivolumab for the treatment of locally advanced or metastatic NSCLC after prior chemotherapy in adults. Some of the responses with these agents have proven to be prolonged (30). Even more encouraging than the objective response rate (ORR) with nivolumab in early-phase testing was the durability of the responses, with a median progression free survival (PFS) of 17 months (31). Not surprisingly, these durable responses led to promising overall survival, with 42% and 24% of patients alive after 1 year and 2 years, respectively. The durable responses seen with nivolumab suggest the generation of long-lasting memory T cells that can self-renew, providing a sustained and durable response upon re-exposure to the target tumor antigen. These encouraging clinical results have rightfully placed PD-1/PD-L1 immunotherapy at the forefront of oncological practice. Unfortunately, the overall response rate to PD-1/PD-L1 immune checkpoint inhibition is only modest for patients with advanced NSCLC, ranging from 14-24% (29,32-36).

A large meta-analysis study on the prognostic influence of TILs demonstrated TIL density was associated with favorable clinical outcome across different cancer types, supporting the protective role of host anti-tumor immune response (37). However, the protective impact of TILs faded in later stage cancers, suggesting that the tumor microenvironment in advanced cancers is more immunosuppressive. PD-1/PD-L1 immune checkpoint blockade may therefore have greater responses in patients with early-stage NSCLC, and this area of research is under active investigation. At the 2016 ESMO Congress, Forde and colleagues reported data from 16 patients with Stage I-IIIA NSCLC who received two doses of nivolumab at four and two weeks prior to surgical resection (38). The investigators found that 12 of 15 patients (80%) had regression of their tumors, including six of 15 patients (40%) demonstrating major pathological regression (<10% residual viable tumor) following nivolumab. Although the sample size in this study was small, the response rate to nivolumab observed in patients with early-stage NSCLC (80%) is significantly higher than the response rate observed in patients with advanced NSCLC (~20%).

2.2.5 RATIONALE FOR USING NIVOLUMAB TO PREVENT LUNG CANCER

An alternative approach to cancer immunotherapy that has been proposed is the treatment of premalignant lesions with immune checkpoint inhibitors to prevent progression to cancer. Premalignant lesions are tissues that are not yet invasive but can progress to become malignant. Examples of these precancerous tissues include bronchial squamous dysplasia and atypical adenomatous hyperplasia of the lung. It is not uncommon for multiple premalignant lesions to develop at various times due to the field effect of areas exposed to carcinogens (39). A mouse model of premalignant lung adenomas showed infiltration by immature macrophage-lineage cells that support the premalignant cells and produce inhibitory mediators such as TGF-β (40). Similarly, an immune inhibitory state was demonstrated within HPV-associated respiratory papillomas in patients, as demonstrated by increased levels of Tregs with suppressive activity and an increased Th2-like milieu (41). This study also showed increased expression of the PD-1/PD-L1 inhibitory axis and indications of immune exhaustion. Our preliminary data have shown that PD-L1 expression is up-regulated in bronchial dysplastic lesions from high risk former or active smokers (Figure 3 in Exploratory Endpoints section below). It has also recently been shown that tumor-specific T cell dysfunction is initiated early during tumorigenesis (42). Taken together, these data provide the basis for our primary hypotheses: ***immune evasion contributes to malignant transformation of premalignant bronchial dysplastic lesions into invasive lung cancers. We further hypothesize that blocking PD-1 with nivolumab will allow the immune system to target and eradicate premalignant bronchial dysplastic lesions, thereby preventing the development of lung cancer.***

We propose to test the ability of the PD-1 checkpoint inhibitor nivolumab to improve bronchial dysplastic lesions in subjects who are at high risk for developing lung cancer. High risk subjects will include previously resected lung cancer patients, previously treated head and neck cancer patients, and subjects with heavy smoking history (≥ 30 pack-years) and sputum atypia. We have used these criteria in our previous studies (13), because subjects with tobacco smoke exposure and sputum cytologic atypia have rates of lung cancer greater than 1%/year (43,44) and represent a high risk group in which pharmacologic prevention may have the greatest utility. Moreover, subjects with a prior cancer history develop new primary lung tumors at a rate of 2% yearly (45). Interestingly, whole-exome sequencing of NSCLC samples from patients treated with a PD-1 inhibitor showed that clinical efficacy of nivolumab in NSCLC patients correlated with a molecular smoking signature, which was associated with mutation burden (46). We therefore hypothesize that high risk current or former smokers will be more likely to respond to PD-1 immune checkpoint inhibitors than never smokers, similar to what has been seen in NSCLC treatment trials (31). Unlike other pharmacologic agents whose effects may be lost upon discontinuation of therapy, PD-1 inhibitors may have durable responses by generating memory T cells that will have persistent antitumor activity.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

2.3.1.1 RISK OF NIVOLUMAB

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 70 clinical studies. Across those studies, approximately 12,300 subjects have received nivolumab monotherapy in single- or multiple-dose Phase

1/2/3 studies or studies with nivolumab in combination with other therapeutics, including ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies. All available data suggest that nivolumab monotherapy has a consistent adverse event (AE) profile across tumor types. The only exception is pulmonary inflammation AEs, which may be numerically greater in subjects with NSCLC, possibly because in some cases, it can be difficult to distinguish between nivolumab-related and unrelated causes of pulmonary symptoms and radiographic changes. The safety profile is generally consistent across completed and ongoing clinical trials, with no maximum tolerated dose reached at any monotherapy dose tested up to 10 mg/kg. There was no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. Most related AEs are thought to be due to the effects of inflammatory cells on specific tissues. The most frequently reported treatment-related AE is fatigue, which is almost always of low grade. Across all studies conducted to date, drug-related AEs have included pulmonary toxicity, renal toxicity (including acute renal failure), endocrine abnormalities, GI toxicity, dermatologic toxicity (including rash), and hepatotoxicity. For nivolumab monotherapy, the majority of these AEs have been managed successfully with supportive care and, in more severe cases, a combination of dose delay, permanent discontinuation, and/or use of corticosteroids or hormone replacement therapy (for endocrinopathies).

The safety of nivolumab was evaluated in CheckMate 057 (28), a randomized, open-label, multicenter trial in patients with metastatic non-squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen. Patients received 3 mg/kg of nivolumab (n=287) administered intravenously over 60 minutes every 2 weeks or docetaxel (n=268) administered intravenously at 75 mg/m^2 every 3 weeks. The median duration of therapy was 2.6 months (range: 0 to 24+ months) in nivolumab-treated patients. In this trial, 30% of patients received nivolumab for greater than 6 months and 20% of patients received nivolumab for greater than 1 year. This trial excluded patients with active autoimmune disease, medical conditions requiring systemic immunosuppression, or with symptomatic interstitial lung disease. The median age of all randomized patients was 62 years (range: 21 to 85); 37% of patients in the nivolumab group were ≥65 years of age, 55% were male, and 92% were white. Twelve percent of patients had brain metastases and ECOG performance status was 0 (31%) or 1 (69%).

In CheckMate 057, nivolumab was discontinued in 13% of patients, and was delayed in 29% of patients for an adverse reaction. Serious adverse reactions occurred in 47% of patients receiving nivolumab. The most frequent serious adverse reactions reported in at least 2% of patients receiving nivolumab were pneumonia, pulmonary embolism, dyspnea, pleural effusion, and respiratory failure. In the nivolumab arm, seven deaths were due to infection including one case of *Pneumocystis jirovecii* pneumonia, four were due to pulmonary embolism, and one death was due to limbic encephalitis. The most common adverse reactions (reported in at least 20% of patients) were fatigue, musculoskeletal pain, cough, decreased appetite, and constipation. Table 3 summarizes selected adverse reactions occurring in at least 10% of nivolumab-treated patients and more frequently than in docetaxel-treated patients. Table 4 summarizes selected laboratory abnormalities worsening from baseline occurring in at least 10% of nivolumab-treated patients and more frequently than in docetaxel-treated patients. Table 5 summarizes immune-mediated adverse reactions occurring in nivolumab-treated patients.

Table 3: Selected Adverse Reactions Occurring in ≥10% of Nivolumab-Treated Patients and at a Higher Incidence than Docetaxel (28)

Adverse Reaction	All Grades (% of Patients)	Grades 3-4 (% of Patients)
Cough	30	0.3
Decreased appetite	29	1.7
Constipation	23	0.7
Pruritis	11	0

Toxicity was graded per NCI CTCAE v4.

Table 4: Selected Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Nivolumab-Treated Patients for all NCI CTCAE Grades and at a Higher Incidence than Docetaxel (28)

Chemistry Test	All Grades (% of Patients with Worsening Laboratory Test from Baseline[a])	Grades 3-4 (% of Patients with Worsening Laboratory Test from Baseline[a])
Hyponatremia	35	6
Increased AST	28	2.8
Increased alkaline phosphatase	27	1.1
Increased ALT	23	2.4
Increased creatinine	18	0
Increased TSH[b]	17	N/A

[a] Each test incidence is based on the number of patients who had both baseline and at least on on-study laboratory available, range 280 to 287 patients

[b] Not graded per NCI CTCAE v4

Table 5: Selected Immune-Related Adverse Reactions Occurring in Nivolumab-Treated Patients (28)

Adverse Reaction	All Grades N (% of Patients)	Grades 3-4 N (% of Patients)	Time to Onset Median (Range)
Pneumonitis (including interstitial lung disease)	10 (3.4)	5 (1.7)	7.2 months (2.7 to 13.1 months)
Diarrhea or colitis	50 (17)	3 (0.01)	2.7 months (4 weeks to 19 months)
Hepatitis	1 (0.003)	1 (0.003)	7.8 months
Adrenal insufficiency	1 (0.003)	N/A	Not reported
Hypothyroidism (including thyroiditis)	20 (7)	N/A	2.9 months (1.4 to 11.8 months)
Hyperthyroidism	4 (1.4)	0 (0)	2 months (4.1 weeks to 2.8 months)
Renal dysfunction	1 (0.3)	0 (0)	1.5 months
Rash	17 (6)	4 (1.4)	Not reported
Limbic encephalitis, fatal (Grade 5)	1 (1)	0 (0)	7.2 months

Toxicity was graded per NCI CTCAE v4.

More recently, PD-1/PD-L1 immune checkpoint blockade has been studied to treat early-stage NSCLC in the adjuvant or preoperative setting. At the 2016 ESMO Congress, Forde and colleagues reported the data from 16 patients with Stage I-IIIA NSCLC who received two doses of nivolumab at four and two weeks prior to surgical resection (38). Treatment-related toxicities were consistent with those seen in other studies of nivolumab, and there were no treatment-related deaths. Of 19 patients evaluated for safety, adverse events of any grade were reported by six patients (32%); only one patient (5%) had grade 3/4 toxicity, and this led to treatment discontinuation. Although the sample size was small, these data suggest that nivolumab is safe in patients who have never received chemotherapy or any other cancer therapy.

2.3.1.2 RISK OF BRONCHOSCOPY, ENDOBRONCHIAL BIOPSY, AND BRUSHINGS

Bronchoscopy is a semi-invasive procedure that involves sedation, local anesthesia, and insertion of a bronchoscope into the airways. In large series, the incidence of serious complications was less than 0.05% (5 in 10,000) in over 23,000 bronchoscopies. Adverse events include laryngospasm, bronchospasm, hypoxemia, allergy or adverse reaction to the sedation, fever following the procedure, or infection. The most common adverse event is fever which occurs in approximately 5% of patients and is self-limited. Infection requiring antibiotics occurs in about 0.5% of patients. Some patients report mild chest soreness, hoarseness, or sore throat the day after the procedure, which is self-limited. Endobronchial biopsy and brushings can lead to hemoptysis, which is self-limited. More serious complications such as major bleeding, lung collapse, vocal cord and bronchial spasm, and cardiac irregularity have been reported but are very rare. Since the patient will be sedated for this procedure, arrangements for transportation home after the procedure will be required.

2.3.1.3 RISK OF PHLEBOTOMY

Phlebotomy to monitor for adverse reactions to nivolumab may result in pain and discomfort, as well as anxiety related to additional testing and the implications of test results. In about 10% of cases, a small amount of bleeding under the skin will produce bruising or a hematoma. The risk of infected hematoma or significant blood loss is less than 0.1%.

2.3.1.4 RISK OF IV INFUSIONS

During bronchoscopy, an intravenous catheter will be placed in participants' arms for infusion of fluids and sedation. In addition to possible pain and hematoma, which is similar to that for phlebotomy, the risk of temporary clotting of the vein is less than 1%. Participants can have allergy or adverse reactions to sedation administered during bronchoscopy. In CheckMate 057 (28), Grade 2 infusion reactions requiring corticosteroids occur in 1.0% (3/287) of patients receiving nivolumab.

2.3.1.5 RISK OF SPUTUM COLLECTION

The risks associated with a routine sputum collection are minimal. If the induced sputum technique using saline is performed, there is a minimal risk of chest tightness and bronchospasm. If this occurs, participants will be administered albuterol (either via inhaler or nebulizer) and monitored until symptoms have resolved.

2.3.2 KNOWN POTENTIAL BENEFITS

There has been no clinical trial so far assessing the clinical benefit of nivolumab in patients with premalignant lung lesions. The studies summarized below describe the clinical efficacy of nivolumab in patients with NSCLC.

2.3.2.1 NIVOLUMAB MONOTHERAPY IN ADVANCED SQUAMOUS NSCLC

CheckMate 017 was a randomized (1:1), open-label study enrolling 272 patients with metastatic squamous NSCLC who had experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen (29). Patients received nivolumab (n=135) administered intravenously at 3 mg/kg every 2 weeks or docetaxel (n=137) administered intravenously at 75 mg/m^2 every 3 weeks. This

study included patients regardless of their PD-L1 status. The first tumor assessments were conducted 9 weeks after randomization and continued every 6 weeks thereafter. The major efficacy outcome measure was overall survival (OS). The median age was 63 years (range: 39 to 85) with 44% ≥65 years of age and 11% ≥75 years of age. The majority of patients were white (93%) and male (76%). Baseline ECOG performance status was 0 (24%) or 1 (76%). In this study, median OS was 9.2 months with nivolumab versus 6.0 months with docetaxel (P<0.001). At 1 year, the OS rate was 42% with nivolumab versus 24% with docetaxel. The response rate was 20% with nivolumab versus 9% with docetaxel (P=0.008). The median progression-free survival was 3.5 months with nivolumab versus 2.8 months with docetaxel (P<0.001). Thus, among patients with advanced, previously treated squamous-cell NSCLC, overall survival, response rate, and progression-free survival were significantly better with nivolumab than with docetaxel.

2.3.2.2 NIVOLUMAB MONOTHERAPY IN ADVANCED NON-SQUAMOUS NSCLC

CheckMate 057 was a randomized (1:1), open-label, study of 582 patients with metastatic non-squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen (28). Appropriate prior targeted therapy in patients with known sensitizing EGFR mutation or ALK translocation was allowed. Patients received nivolumab (n=292) administered intravenously at 3 mg/kg every 2 weeks or docetaxel (n=290) administered intravenously at 75 mg/m^2 every 3 weeks. Randomization was stratified by prior maintenance therapy and number of prior therapies. The trial excluded patients with autoimmune disease, medical conditions requiring systemic immunosuppression, symptomatic interstitial lung disease, or untreated brain metastasis. Patients with treated brain metastases were eligible if neurologically stable. The first tumor assessments were conducted 9 weeks after randomization and continued every 6 weeks thereafter. The major efficacy outcome measure was OS. The median age of all randomized patients was 62 years (range: 21 to 85) with 42% of patients ≥65 years of age and 7% of patients ≥75 years of age. The majority of patients were white (92%) and male (55%). Baseline ECOG performance status was 0 (31%) or 1 (69%), 79% were former/current smokers, 3.6% had NSCLC with ALK rearrangement, 14% had NSCLC with EGFR mutation, and 12% had previously treated brain metastases. Prior therapy included platinum-doublet regimen (100%) and 40% received maintenance therapy as part of the first-line regimen. Histologic subtypes included adenocarcinoma (93%), large cell (2.4%), and bronchoalveolar (0.9%). In this study, the median OS was 12.2 months among patients in the nivolumab group and 9.4 months among patients in the docetaxel group (P=0.002). At 1 year, the OS rate was 51% with nivolumab versus 39% with docetaxel; at 18 months, the OS rate was 39% with nivolumab versus 23% with docetaxel. The response rate was 19% with nivolumab versus 12% with docetaxel (P=0.02). Although progression-free survival did not favor nivolumab over docetaxel (median, 2.3 months and 4.2 months, respectively), the rate of progression-free survival at 1 year was higher with nivolumab than with docetaxel (19% and 8%, respectively).

2.3.3 OVERALL RISK/BENEFIT ASSESSMENT

Currently, the only way to prevent lung cancer is smoking cessation. However, roughly 80% of new lung cancers are diagnosed in former and never smokers, highlighting the need for effective prevention strategies. Most chemoprevention studies have been negative, with the only exception being a randomized phase II trial conducted by our group demonstrating that oral iloprost reverses bronchial dysplasia in former smokers (13). High risk subjects include resected lung cancer patients >1 year post resection, head and neck cancer patients >1 year post definitive therapy, and heavy (≥ 30 pack years) current or former smokers with bronchial dysplasia. Thus, it is possible to detect a large population of

patients at very high risk of developing invasive cancer for whom there is no standard therapy. Effective, early intervention in these situations has the potential to reduce the morbidity and mortality from lung cancer in this population. At the same time, since the risk of cancer is not 100%, any proposed intervention must be safe without significant short or long-term toxicity. PD-1/PD-L1 immune checkpoint inhibitors represent a major breakthough in lung cancer therapy, and their clinical activity in NSCLC demonstrates that the immune system plays a critical role in the pathogenesis of lung cancer. There is increasing evidence that short courses of PD-1 immune checkpoint inhibitors are safe and highly effective in patients with early stage lung cancers. In this project we will test the clinical hypothesis that early intervention with nivolumab in patients at high risk of developing lung cancer is safe and can improve bronchial dysplasia, thereby reducing the risk of lung cancer.

3 OBJECTIVES AND ENDPOINTS

3.1 OBJECTIVES

3.1.1 PRIMARY OBJECTIVE

To determine whether immune checkpoint blockade using nivolumab can reverse premalignant histological changes in the bronchial epithelium of subjects at high risk for developing lung cancer as defined by mild or worse sputum cytologic atypia or known bronchial dysplasia; and either 30 pack-years of tobacco exposure with sputum cytologic atypia, or history of early-stage lung or head and neck cancer at least 1 year after definitive treatment.

3.1.2 SECONDARY OBJECTIVE

To assess the safety and tolerability of nivolumab in patients with bronchial dysplastic lesions.

3.1.3 EXPLORATORY OBJECTIVES

An important aspect of this trial is to identify novel prognostic and predictive markers present at the time of diagnosis. As such, radiologic data and blood will also be collected throughout the study period. The markers to be assessed will be determined according to the best scientific knowledge and technology available. Correlative studies will be interpreted as hypothesis-generating data, to be validated in subsequent trials.

3.2 ENDPOINTS

3.2.1 PRIMARY ENDPOINT: IMPROVEMENT IN ENDOBRONCHIAL HISTOLOGY

It has long been established that abnormal bronchial histology (endobronchial dysplasia) is associated with cigarette smoking and increased risk for lung cancer (47-49). However, because of the inaccessibility of the airway mucosa, few studies have documented the extent of abnormalities in bronchial epithelium in at risk subjects prior to the development of lung cancer. Fluorescence bronchoscopy has repeatedly been shown to afford greater accessibility to premalignant lesions in the airways and has increased the need for an acceptable and generally applicable morphological classification of lower airway premalignant lesions. The WHO has recognized the importance of these lesions and added a classification for pre-invasive lesions to the WHO lung cancer classification. The

classification recognizes three distinct grades of dysplasia (mild, moderate, severe) as well as *carcinoma in situ* (11). Using the WHO classification as a template, we have extended the grading scheme, enabling us to evaluate histological responses to lung cancer preventive agents. The histologic classification consists of: normal (grade 1.0), reserve cell hyperplasia (grade 2.0), squamous metaplasia (grade 3.0), mild dysplasia (grade 4.0), moderate dysplasia (grade 5.0), severe dysplasia (grade 6.0), carcinoma in situ (grade 7.0) and invasive cancer (grade 8.0).

The primary endpoint is the dichotomous endpoint of whether or not a subject responds to nivolumab. Response to treatment will be based on the 6-month change (difference between 6-month score and baseline score) in worst (i.e. maximum) histologic classification score. A subject will be considered a responder if his/her worst (i.e. maximum) histology classification score improves (i.e. the score lowers) at the 6 month bronchoscopy as compared with the baseline bronchoscopy. Non-responders will be subjects with similar or higher maximum histologic scores.

3.2.2 SECONDARY ENDPOINTS

3.2.2.1 SAFETY AND TOLERABILITY OF NIVOLUMAB IN HIGH RISK CURRENT AND FORMER SMOKERS

This trial is also designed to evaluate the safety and tolerability of nivolumab in patients at high risk for lung cancer. Results from this trial will be used to support regulatory filing for nivolumab use in patients at high risk for lung cancer. The dosing of nivolumab (240 mg IV every 2 weeks) is based on the dose approved by the US FDA for the treatment of metastastic non-small cell lung cancer (NSCLC), including patients who have been treated for over 2 years. The duration of treatment (4 doses = 8 weeks) is based on published clinical trials that randomized patients with advanced NSCLC who progressed after platinum-based chemotherapy to either nivolumab or docetaxel (28,29). These trials showed a median time to response of 2 months. Similarly, the early stage lung cancer neoadjuvant trial reported by Forde and colleagues demonstrated a high response rate (80%) after two doses of nivolumab (38), and has now been expanded to three doses of nivolumab (NCT02259621).

Patients will be evaluated by one of the study investigators every 2 weeks prior to study drug infusions to determine whether patients have any immune-related adverse events (irAEs) using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). In particular, patients will be monitored closely for evidence of dermatological (e.g., pruritis, rash, vitiligo), gastrointestinal (e.g., diarrhea, colitis, abdominal pain, hepatitis), endocrine (e.g., thyroid dysfunction, diabetes, adrenal insufficiency), renal (e.g., acute renal failure, interstitial nephritis), and pulmonary (e.g., pneumonitis) irAEs. Systemic corticosteroids or other immunosuppressive agents will be initiated at the discretion of the study investigators. Complete blood count, comprehensive metabolic profile, and thyroid function tests (TSH [thyroid-stimulating hormone], free T4, and total T3 levels) will be obtained at baseline and every 3 months for 1 year. A comprehensive metabolic profile will also be checked every 2 weeks before each infusion. Subjects will be followed for a total of 1 year to monitor for development of irAEs after discontinuation of the study drug.

3.2.2.2 OTHER ENDOBRONCHIAL HISTOLOGY ENDPOINTS

Although the primary endpoint will be the change in the worst histology after 6 months, additional histology summary measures (change in average histology and change in dysplasia index = the

percentage of biopsies with dysplasia score ≥ 4.0) will also be analyzed. The three summary measures will be analyzed on different subsets of the data (all matched biopsies vs matched biopsies restricted to the reference sites). Additionally, subjects will be classified as being a responder or non-responder based on the change in their average histology or dysplasia index. The same analyses will be also be conducted on biopsies after 2 months, to determine the rate of change in bronchial dysplasia in response to nivolumab, and to determine whether there may be effects of nivolumab that disappear after discontinuation of the drug.

3.2.3 EXPLORATORY ENDPOINTS

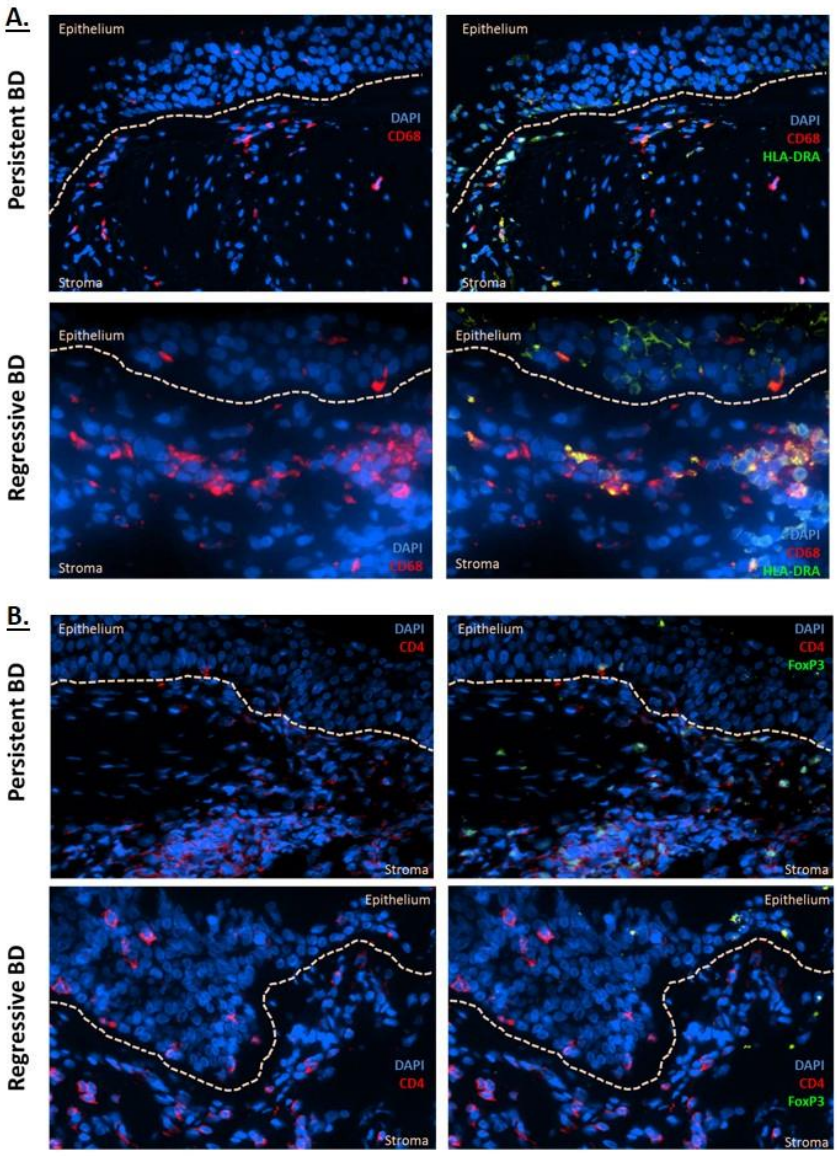


Figure 1. A) A higher proportion of HLA-DRA positive M1 macrophages are present in regressive than persistent BD and HLA-DRA expression is seen in epithelial cells of regressive leisons. B) Regulatory CD4 T-lymphocytes with nuclear FoxP3 positivity more abundant in persistent than regressive BD>

An important aspect of this trial is to identify novel prognostic and predictive markers present at the time of diagnosis. As such, radiologic data and blood will also be collected throughout the study period. The markers to be assessed will be determined according to the best scientific knowledge and technology available. Correlative studies will be interpreted as hypothesis-generating data, to be validated in subsequent trials.

3.2.3.1 PD-1 EXPRESSION ON T LYMPHOCYTES, PD-L1 EXPRESSION ON EPITHELIAL CELLS AND MACROPHAGES, AND CHARACTERIZATION OF INFLAMMATORY INFILTRATES ASSOCIATED WITH BRONCHIAL DYSPLASTIC LESIONS AT BASELINE AND FOLLOWING TREATMENT WITH NIVOLUMAB

Characterizing the polarization state and activation status of inflammatory infiltrates in bronchial dysplasia will represent key assessments in our exploratory endpoints. Our preliminary work has demonstrated that dual immunofluorescence (IF) is an

accurate and sensitive method by which inflammatory infiltrates can be characterized in biopsies of bronchial tissue. We predict that the character of the inflammatory infiltrate in BD will be a determinant of response to PD-1 inhibition. Our gene expression data indicate that decreased M1 versus M2 macrophage ratios, decreased T-helper 1 (Th1) versus T-helper 2 (Th2) lymphocyte ratios, and increased T-regulatory lymphocytes (Treg) support persistence of BD, which leads to a high risk of developing invasive squamous cell carcinoma. An ongoing project employing dual IF has generated preliminary data showing a range of M1:M2 ratios as indicated by CD68/HLA-DRA and CD68/CD206 dual positivity, respectively, and a strong trend toward increased CD4/FoxP3 dual positive Treg infiltrates in persistent BD (Figure 1).

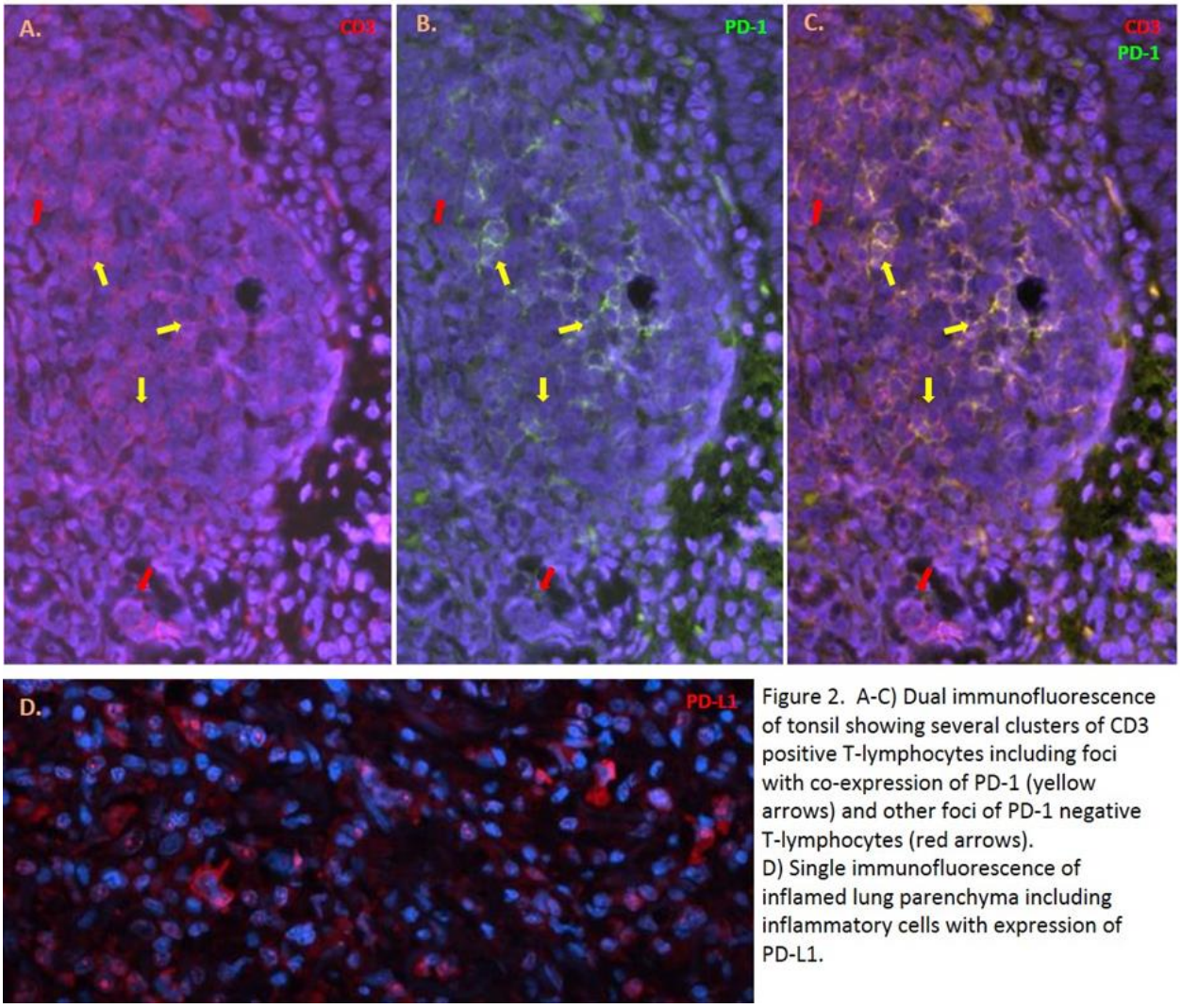


Figure 2. A-C) Dual immunofluorescence of tonsil showing several clusters of CD3 positive T-lymphocytes including foci with co-expression of PD-1 (yellow arrows) and other foci of PD-1 negative T-lymphocytes (red arrows).
D) Single immunofluorescence of inflamed lung parenchyma including inflammatory cells with expression of PD-L1.

For this current study, we will characterize the inflammatory infiltrate in baseline and post-treatment biopsy tissue, and correlate inflammatory infiltrate composition with response to nivolumab by multiplex immunohistochemistry using a Vectra 3 automated quantitative pathology imaging system (University of Colorado Human Immune Monitoring Shared Resource), which detects and distinguishes up to seven stains by immunofluorescence using formalin-fixed, paraffin-embedded tissue sections. Comparison of the infiltrates in the pre- and post-treatment biopsies will identify changes in both the inflammatory cells and the epithelium that correspond to response. These will be assessed using the M1

and M2 macrophage and Th1, Th2 and Treg IF stains described above. We have also optimized IF assays to assess PD-1 expression by T lymphocytes via dual CD3/PD-1 IF (Figure 2 A-C).

Multiplex immunohistochemistry will also provide the ability to detect PD-L1 expression both by macrophages (CD68) as well as by epithelial cells (pan-cytokeratin)and will allow us to assess whether premalignant epithelial cell PD-L1 expression is predictive of response to nivolumab, as has been seen in invasive lung cancer. Currently, PD-L1 staining has been optimized in single primary antibody assays in lung tissue (Figure 2D).

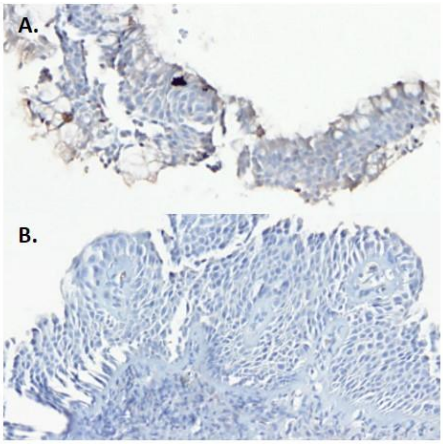


Figure 3. PD-L1 IHC stain showing 1-2+ positive stain in site of BD (A) and lack of stain at different site (B).

Although relatively modest in intensity, preliminary data have shown the presence of PD-L1 expression in the epithelial cells of a subset of bronchial dysplasias (Figure 3). These data will help establish the mechanism by which potential responses are achieved. Furthermore, it may identify biological markers of desired responses that could be used for clinical management in patients receiving PD-1 checkpoint inhibitor-based immunoprevention. Indeed, an important aspect of lung cancer prevention is accurately identifying patients that are likely to benefit from therapy so that associated side effects can be avoided in those that are unlikely to respond.

3.2.3.2 MUTATIONAL BURDEN OF BRONCHIAL DYSPLASTIC LESIONS

The use of mutational burden has been studied as a predictive biomarker in patients given checkpoint inhibitor immunotherapies. Rizvi and colleagues showed that higher mutational burden based on tumor whole-exome sequencing was associated with durable clinical benefit (partial or stable response lasting >6 months) in a study of patients with NSCLC given the PD-1 inhibitor pembrolizumab (46). High mutational burden (≥ 178 non-synonymous mutations) was associated with significantly longer progression-free survival. Similar results have been shown in a study by Johnson and colleagues of patients with advanced melanoma treated with anti-PD-1 and anti-PD-L1 immune checkpoint inhibitors (50). High mutational load (measured by targeted next-generation sequencing) was associated with improved response rate, progression-free survival, and overall survival. In addition, the phase 2 study of atezolizumab for locally advanced and metastatic urothelial carcinoma showed that patients who achieved a complete or partial response had a higher mutational load than patients with stable disease or progressive disease as their best response (51). Thus, to determine whether mutational burden predicts response to nivolumab, we will perform whole-exome sequencing of bronchial dysplasia samples obtained in our study.

3.2.3.3 PERIPHERAL BLOOD MARKERS

Testing of peripheral blood markers is a non-invasive source of potential biomarkers in patients receiving anti-PD-1/PD-L1 immune checkpoint therapies. Although associations with clinical benefit and survival have been noted, none so far have been validated as predictive biomarkers in prospective studies. In this study, we will collect and store peripheral blood for future potential biomarker analysis. A variety of factors that could potentially predict clinical response to nivolumab will be investigated in peripheral blood from subjects prior to treatment. Data from these investigations will be evaluated for

associations with response and/or safety (adverse event) data. All samples collected may also be used for further exploratory analyses to assess biomarkers associated with bronchial dysplastic lesions or nivolumab treatment. Candidate markers to be evaluated may include (depending on specimen availability and resources):

1. Exploratory serum biomarkers: Blood samples for exploratory serum biomarker analyses will be drawn at baseline, at 2 months, and at 6 months. Blood samples will be processed to collect serum and then put in frozen storage. Samples may be assessed by ELISA, seromics, and/or other relevant multiplex-based protein assay methods for immune or NSCLC-related factors that will predict for nivolumab benefit or correlate with nivolumab efficacy. Numerous potential serum-based biomarkers are currently under investigation for their potential to predict or correlate with efficacy to nivolumab or other immunotherapy, including but not limited to levels of soluble PD-L1, cytokines, chemokines, inflammatory factors, and microRNAs.
2. Characterization and immunophenotyping of immune cell populations in peripheral blood by mass cytometry. Mass cytometry offers single-cell analysis of over 40 parameters without issues of spectral overlap. This technique utilizes rare earth metal isotopes in the form of soluble metal ions as tags bound to antibodies, instead of fluorophores to detect multiple analytes. The high-dimensionality of mass cytometry enables simultaneous measurement of both phenotypic cell surface markers and intracellular cytokine networks. We propose to analyze the major immune cell subsets found in human peripheral blood, including neutrophils, eosinophils, basophils, monocytes, dendritic cells, T cells, B cells, and NK cells (and their subsets). Within these immune cell subsets, we will monitor changes in signaling activation of protein involved in JAK (Janus Kinase)/STAT (Signal Transducer and Activator of Transcription), MAPK (Mitogen Activated Protein Kinase), NF-κB (Nuclear Factor Kappa-light-chain enhancer of activated B cells), PI3K (PhosphoInositide 3-Kinase), TCR (T cell Receptor), and BCR (B cell Receptor) signaling pathways, and downstream cytokines (Th1, Th2, Th17, type I and type II interferons). This detailed analysis will potentially translate into new biomarkers that can be used to stratify patients into categories based on peripheral blood “immune profile.” Serum from enrolled participants will also be collected for proteomic analysis should the above mass cytometry analysis yield candidate proteins that may be identified as predictors of response to nivolumab.
3. Peripheral T cell repertoire analysis. One theory in immune-oncology suggests a diverse and activated immune environment is more adept at eradicating premalignant lesions and tumors than a skewed repertoire of naïve and tolerized T cells. In a pilot study by Postow and colleagues, increased T-cell receptor gene richness (i.e., a repertoire containing many different V-J rearrangements) and evenness (i.e., evenly distributed frequencies) in pretreatment peripheral blood samples were associated with clinical benefit to the immune checkpoint inhibitor ipilimumab (response or stable disease lasting ≥9 months) (52). Thus, pretreatment T cell receptor repertoire may have a potential role as a predictive biomarker of response to nivolumab. In order to explore whether a diverse T cell repertoire is predictive of response to nivolumab, next generation, high-throughput, DNA sequencing will be performed on DNA isolated from peripheral blood to quantify the composition of the T cell repertoire prior to and after nivolumab therapy.

3.2.3.4 SPUTUM INFLAMMATORY CELL ANALYSIS

Because BD is a lesion of the central airways, evidence of the process can be detected in sputa from at risk individuals. Sputa contain atypical epithelial cells that are shed from dysplastic lesions, but also

contain abundant inflammatory cells. Sputa will be collected and used to identify at risk subjects that qualify for enrollment, and thus a baseline sputum sample will be available on many trial participants. In conjunction with the analyses planned above, trial associated sputa provide an excellent resource to assess the potential value of using these specimens for non-invasive predictive testing. Initial analyses will focus on comparing the features of the inflammatory cells with those seen in the biopsy tissue to determine how closely the inflammatory cells in sputa represent the findings seen in the bronchial dysplastic lesions. This will help inform the second objective, which will focus on identifying a signature in sputa that would predict response to nivolumab. Sputa are collected in the mild, methanol-based Carnoy's fixative and thus would be expected to preserve antigen epitopes in a relatively unaltered state.

3.2.3.5 EPITHELIAL CELL CULTURE

Bronchial epithelial cells will be cultured from one or more endobronchial biopsies in serum free media. Epithelial progenitor cells will be isolated and assessed for the ability to self replicate and differentiate into basal, ciliated and secretory cells. Gene expression by RNAseq and mutational load by whole exome sequencing will be performed on a subset of these cells.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a single-institution, open-label, single-arm, two-stage, phase II study of the PD-1 inhibitor nivolumab in patients at high risk for lung cancer. Simon's two-stage design will be used. In the first stage, 18 subjects will be enrolled. If at least 7 subjects respond to nivolumab, then an additional 24 subjects will be enrolled for a total of 42 subjects. The central hypothesis to be tested by this trial is that immune evasion contributes to malignant transformation of premalignant bronchial dysplastic lesions into invasive lung cancers, and that blocking PD-1 will allow the immune system to target and eradicate premalignant bronchial dysplastic lesions, thereby preventing the development of lung cancer.

Nivolumab 240 mg IV will be administered every two weeks for a total of four doses (8 weeks). Participants will undergo bronchoscopy with endobronchial biopsy at study entry, 2 months, and 6 months. The primary endpoint will be change in bronchial dysplasia between study entry and the 6 month timepoint. Secondary endpoints include safety and tolerability of nivolumab in patients with bronchial dysplastic lesions, and additional endobronchial histology endpoints. Exploratory endpoints will be used to identify predictive markers of response to nivolumab.

The estimated time to accrue 42 evaluable subjects (accounting for subject dropout) is two years and the total proposed study time is 3 years. The duration of participation for each subject will be one year. Assuming the study progresses to stage two, enrollment will be stopped once 42 subjects have completed the study.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This trial utilizes a Simon's two-stage design. Patient enrollment will occur in two successive stages. During stage one of the study, 18 subjects will be enrolled. If there are less than or equal to six positive responses (defined as improvement in worst histology score by ≥1.0 histology unit after six months) in these 18 subjects, the study will be terminated for lack of efficacy. If at least seven responses are

observed (i.e., seven subjects who have improvement in their worst histology score), the study will progress to stage two, where an additional 24 subjects will be enrolled. This study design minimizes the number of people exposed to a potentially ineffective treatment.

4.3 JUSTIFICATION FOR DOSE

Although nivolumab was originally approved for NSCLC at a single dose of 3 mg/kg IV every 2 weeks, the new recommended dosage regimen for nivolumab is 240 mg IV every 2 weeks. The safety and efficacy of 240 mg q2w flat dose of nivolumab is expected to be similar to 3 mg/kg q2w dosing regimen. A flat dose of nivolumab 240 mg q2w was selected since it is identical to a dose of 3 mg/kg for subjects weighing 80 kg, the observed median body weight in nivolumab treated cancer patients. Using a population pharmacokinetics model, the overall distributions of nivolumab exposures (Cavgss, Cminss, Cmaxss, and Cmin1) are comparable after treatment with either 3 mg/kg or 240 mg nivolumab. The predicted range of nivolumab exposures (median and 90% prediction intervals) resulting from a 240 mg flat dose across the 35 to 160 kg weight range is maintained well below the corresponding exposures observed with the well tolerated 10 mg/kg nivolumab q2w dosage. Across various tumor types, nivolumab has been shown to be safe and well tolerated up to a dose of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy and safety has been found to be relatively flat. Given the similarity of nivolumab pharmacokinetics across tumor types and the similar exposures predicted following administration of 240 mg flat dose compared to 3 mg/kg q2w regimen, it is expected that the safety and efficacy profile of 240 mg q2w nivolumab will be similar to that of 3 mg/kg nivolumab.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 8.1.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged $\geq$ 18 years
4. A current or ex-smoker with a $\geq$ 30 pack-year history of smoking and mild or worse sputum cytologic atypia or known bronchial dysplasia, *OR* history of non-small cell lung cancer (stage I, II, or IIIA) with $\geq$ 10 pack-year history of smoking and no evidence of active disease at least 1 year after definitive treatment, *OR* history of head and neck cancer (stage I, II, III, or IVA) with $\geq$ 10 pack-year history of smoking and no evidence of active disease at least 1 year after definitive treatment. An ex-smoker is defined as no tobacco use in the prior 12 months
5. Endobronchial dysplasia (score $\geq$ 4) on screening bronchoscopy
6. Total granulocyte count > 1500
7. Platelet count > 100,000
8. Serum creatinine $\leq$ 1.5 mg/dL

9. Total bilirubin $\leq$ 2.0 mg/dL
10. Transaminases and alkaline phosphatase $\leq$ 2.5x upper limit of normal (ULN)
11. Albumin $\geq$ 2.5 mg/dL
12. ECOG performance status ≤ 1 (Appendix 1)
13. Participants must be able and willing to undergo three bronchoscopies: before, after four doses of nivolumab (8 weeks), and after 6 months

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Participants may not be currently receiving immune checkpoint inhibitor treatment or have been treated with immune checkpoint inhibitors in the past (including anti-programmed cell death receptor [PD]-1, anti-programmed death ligand 1 [PD-L1], and anti-cytotoxic T-lymphocyte associated protein 4 [CTLA4] monoclonal antibodies)
2. Patients cannot receive any other investigational anti-cancer agents while participating in the study
3. Participants cannot have used any other investigational agents within the previous six months
4. History of allergic reactions attributed to compounds of similar chemical or biologic composition to nivolumab
5. Clinically apparent bleeding diathesis (*i.e.*, bleeding that is spontaneous, excessive, or delayed in onset following tissue injury results from a localized pathologic process or a disorder of the hemostatic process, involving a complex interplay among vascular integrity, platelet number and function, coagulation factors, and fibrinolysis)
6. Cardiac dysrhythmia that is potentially life-threatening, such as ventricular tachycardia, multifocal premature ventricular contractions or supraventricular tachycardias with a rapid ventricular response. Well-controlled atrial fibrillation or rare (< 2 minute) premature ventricular contractions are not exclusionary
7. History of coronary artery disease, including myocardial infarction, congestive heart failure (LV ejection fraction <50% or clinically significant diastolic dysfunction), or any serious medical condition which would preclude a patient from undergoing a bronchoscopy or would jeopardize the goals of the study
8. Individuals who are HIV-positive will be considered on a case-by-case basis, but will be required to meet criteria related to patient safety and data integrity, as assessed by the study investigators
9. History of hepatitis B or hepatitis C infection that is untreated and/or with a detectable viral load
10. Hypoxemia (less than 90% saturation with supplemental oxygen)
11. Severe obstructive lung disease (GOLD Stage III or IV, FEV1<30% predicted)
12. Prior chemotherapy or thoracic radiation within the past 1 year
13. Participants with findings on CT chest suspicious for lung cancer (Lung-RADS category 4) will not be allowed to enroll until they have undergone additional evaluation for malignancy and an alternative (i.e., non-malignant) diagnosis has been established
14. Current malignancy, with the exception of non-melanoma (*i.e.*, basal cell or squamous cell) skin cancer. Patients with lung carcinoma in situ found during the study biopsy are also excluded.
15. History of a malignancy except for adequately treated non-melanoma (i.e., basal cell or squamous cell) skin cancer or in situ cervical cancer for which the subject has not been disease-free for 5 years. Patients with a history of non-small cell lung cancer (stage I, II, or IIIA) or head

and neck cancer (stage I, II, III, or IVA) must have no evidence of active disease at least 1 year after definitive treatment.

16. History of stage IIIA NSCLC for which the only treatment was chemoradiation without surgery
17. Known or suspected autoimmune disease; subjects with type I diabetes mellitus, hypothyroidism requiring hormone replacement, or skin disorders not requiring systemic treatment are permitted to enroll
18. Conditions requiring systemic corticosteroids equivalent to > 10 mg prednisone per day or other immunosuppressive medications within 2 weeks of enrollment
19. Known interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity
20. History of interstitial pneumonitis requiring treatment with systemic corticosteroids or other immunosuppressive agents (e.g., mycophenolate, azathioprine)
21. Life expectancy of < 1 year
22. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 4 weeks prior to the start of nivolumab
23. Women must not be breastfeeding
24. Inability to give informed consent
25. Pneumonia or acute bronchitis for at least 2 weeks prior to enrollment

5.3 REPRODUCTIVE STATUS

Women of childbearing potential (WOCBP) are defined as females who have experienced menarche, who have not undergone surgical sterilization (hysterectomy or bilateral oophorectomy)and are not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over the age of 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone (FSH) level >40 mIU/mL to confirm menopause.

Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab and for at least five months following the last dose of nivolumab. WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements, but still must undergo pregnancy testing as described in this section.

Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab and for at least seven months following the last dose of nivolumab. Azoospermic males are exempt from contraceptive requirements.
At a minimum, WOCBP and female partners of male subjects, who are WOCBP, must agree to the use of two methods of contraception, with one method being highly effective and the other method being highly or less effective as listed below:

1. Highly effective methods of contraception (failure rate <1% when used consistently and correctly):
    a. Progestogen only hormonal contraception associated with inhibition of ovulation
    b. Hormonal methods of contraception including oral contraceptive pills containing combined estrogen + progesterone, vaginal rings, injectable, implants and intrauterine devices (IUDs) such as Mirena
    c. Nonhormonal IUDs, such as ParaGard
    d. Bilateral tubal occlusion

e. Vasectomied partner with documented azoospermia 90 days after procedure
f. Intrauterine hormone-releasing system (IUS)
g. Complete abstinence
    i. Complete abstinence is defined as the complete avoidance of heterosexual intercourse
    ii. Complete abstinence must be used throughout the duration of study and for the duration of time as specified above following the last dose of nivolumab
    iii. It is not necessary to use any other method of contraception when complete abstinence is elected
    iv. Subjects who choose complete abstinence must undergo pregnancy testing as described in this section
    v. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence
    vi. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject

2. Less effective methods of contraception:
    a. Diaphragm with spermicide
    b. Cervical cap with spermicide
    c. Vaginal sponge with spermicide
    d. Male or female condom with or without spermicide
    e. Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
3. Unacceptable methods of contraception:
    a. Periodic abstinence (calendar, symptothermal, post-ovulation methods)
    b. Withdrawal (coitus interruptus)
    c. Spermicide only
    d. Lactation amenorrhea method (LAM)

5.4 RECRUITMENT PLAN

Patients for this trial will be recruited from the Rocky Mountain Regional Veterans Affairs Medical Center (RMR VAMC), the University of Colorado Cancer Center, and affiliated clinics. Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research staff. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The investigators and research staff may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study. Specifically, medical records of patients being treated at the DVAMC Chest Clinic and the University of Colorado Pulmonary Nodule Clinic will be screened for cigarette smoking history. Medical records of patients with lung cancer or head and neck cancer being treated at the University of Colorado Cancer Center and DVAMC Oncology Clinic will be screened for patients who have undergone definitive therapy at least one year prior to study enrollment.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at DVAMC

and the University of Colorado in order to assess eligibility further. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient is ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

Participants will be recruited for this study protocol by the investigator or research staff to reach a target sample size of 48 participants. A HIPAA authorization form will be provided to the subject at the time of consent. This authorization will designate the specific health information that will be required to be released and to whom. We have experience with a cohort study collecting sputum samples on patients with 30 pack years of smoking. This study will include individuals with biopsy proven endobronchial dysplasia and either $\geq$ 30 pack years of smoking or previous history of non-small cell lung cancer (stage I, II, or IIIA) or head and neck cancer (stage I, II, III, or IVA).

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

All protocol-specified investigational products are considered study drug. An investigational product, also known as investigational medicinal product in some regions, is defined as a pharmaceutical form of an active substance being tested in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, the investigational product is: BMS-936558 (nivolumab). Nivolumab is a human monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Nivolumab is an IgG4 kappa immunoglobulin that has a calculated molecular mass of 146 kDa.

6.1.2 DOSING AND ADMINISTRATION

Subjects will receive nivolumab 240 mg IV every two weeks until subject discontinuation or until they have completed four cycles. Subjects will receive treatment with nivolumab as a 30 minute IV infusion on Day 1 of a treatment cycle every two weeks (14 days). There will be no dose escalations or reductions allowed. Treatment may be delayed for up to a maximum of 2 weeks from the scheduled re-treatment date. Subjects may be dosed no less than 12 days from the previous dose.

Subjects will receive nivolumab infusions at the site of enrollment (*i.e.*, research subjects enrolled at UCHealth will receive nivolumab infusions at UCHealth and research subjects enrolled at the RMR VAMC will receive nivolumab infusions at the RMR VAMC).

Subjects will be monitored continuously for AEs while on study. Treatment modifications (e.g., dose delay) will be based on specific laboratory and adverse event criteria.

Nivolumab infusion must not be administered as intravenous push or bolus injection. The nivolumab infusion will be administered intravenously over a period of 30 minutes. Nivolumab infusion should not be infused at the same time in the same intravenous line with other agents. A separate infusion line must be used for the infusion.

An infusion set and an in-line, sterile, non-pyrogenic, low protein binding filter (pore size of 0.2 μm to 1.2 μm) will be used.

Nivolumab infusion is compatible with PVC and polyolefin containers, glass bottles, PVC infusion sets and in-line filters with polyethersulfone membranes with pore sizes of 0.2 μm to 1.2 μm.

After administration of the nivolumab dose, the line will be flushed with sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection.

Any unused portion of the infusion solution should not be stored for reuse. Any unused medicinal product or waste material will be disposed of in accordance with local requirements.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Nivolumab will be provided by the manufacturer, Bristol-Myers Squibb (BMS).

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

OPDIVO is a sterile, preservative-free, non-pyrogenic, clear to opalescent, colorless to pale-yellow liquid that may contain light (few) particles. OPDIVO injection for intravenous is supplied in single-dose vials. Each mL of OPDIVO solution contains nivolumab (10 mg), mannitol (30 mg), pentetic acid (0.008 mg), polysorbate 80 (0.2 mg), sodium chloride (2.92 mg), sodium citrate dehydrate (5.88 mg), and water. OPDIVO may also contain hydrochloric acid and/or sodium hydroxide to adjust pH to 6.

OPDIVO will be packaged in an open-label fashion. Each mL of OPDIVO concentrate contains 10 mg of nivolumab. OPDIVO is available as 40 mg/4 mL single-dose vials and 100 mg/10 mL single-dose vials. The vials are not subject specific, although there will be specific vial assignments by subject in order to track drug usage and re-supply.

6.2.3 PRODUCT STORAGE AND STABILITY

OPDIVO should be stored under refrigeration at 2°C to 8°C (36°F to 46°F). OPDIVO should be protected from light by storing in the original package until time of use. OPDIVO should not be frozen or shaken. Unopened, OPDIVO is stable for 2 years. From a microbiological point of view, once opened, the medicinal product should be infused or diluted and infused immediately. If not used immediately, chemical and physical in-use stability of OPDIVO has been demonstrated for 24 hours at 2°C to 8°C protected from light and a maximum of 4 hours at 20°C-25°C and room light (this 4-hour period of the total 24 hours should be inclusive of the product administration period).

6.2.4 PREPARATION

The prescribed dose for the patient is 240 mg. The volume of OPDIVO concentrate to prepare the dose is 24 mL. Care will be taken to ensure aseptic handling when preparing the infusion. The infusion should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents.

OPDIVO can be used for intravenous administration either:

- without dilution, after transfer to an infusion container using an appropriate sterile syringe; or
- after diluting to concentrations as low as 1 mg/mL. The final infusion concentration should range between 1 and 10 mg/mL. OPDIVO concentrate may be diluted with either:
    - sodium chloride 9 mg/mL (0.9%) solution for injection; or
    - 50 mg/mL (5%) glucose solution for injection.

STEP 1

- OPDIVO concentrate will be inspected for particulate matter of discoloration. The vial should not be shaken. OPDIVO concentrate is a clear to opalescent, colorless to pale yellow liquid. The vial will be discarded if the solution is cloudy, is discolored, or contains particulate matter other than a few translucent-to-white particles.
- The required volume (24 mL) of OPDIVO concentrate will be withdrawn using an appropriate sterile syringe.

STEP 2

- The concentrate will be transferred into a sterile, evacuated glass bottle or intravenous container (PVC or polyolefin).
- If applicable, the concentrate will be diluted with the required volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection. The infusion will be gently mixed by manual rotation. The infusion should not be shaken.

After preparation, the OPDIVO infusion will be stored either:

- at room temperature for no more than 4 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion or
- under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of infusion preparation.

6.2.5 DESTRUCTION OF STUDY DRUG

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials, and syringes, may be destroyed on site. The unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor. On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal (i.e., incinerator, licensed sanitary landfill, or licensed waste disposal vendor) must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met, the responsible BMS Study Monitor will make arrangements for return of study drug.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

6.2.6 RETURN OF STUDY DRUG

Study drug will not be returned. All unused and/or partially used study drug may be destroyed on site providing the site has an applicable standard operating procedure on file.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This is a single-institution, open-label, single-arm study. Thus, subjects, investigators, and research staff will be unblinded. However, blinding of endobronchial biopsies will be utilized to minimize bias by the pathologist.

6.4 STUDY INTERVENTION COMPLIANCE

Treatment compliance will be monitored by drug accountability as well as the subject's medical record and case report form (CRF).

6.5 CONCOMITANT THERAPY

All concomitant prescription medications taken during study participation will be recorded. For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications reported on the CRF include concomitant prescription medications, over-the-counter medications, and non-prescription medications.

History of prior cancer therapy will be recorded at screening on the CRF for each participant. Reasonable effort will be made to collect information on all prior cancer therapy received by the participant (e.g.,

surgeries, chemotherapy, radiotherapy, immunotherapy, biologics). The information must be obtained from the participant's medical chart and recorded on the appropriate CRF.

Concomitant medications for all ongoing medical history conditions or AEs must be reported from the date the informed consent is signed until the last study visit, and for all concomitant medications related to serious or study drug-related toxicities until the medication is no longer taken or until participant contact discontinues.

To account for any potential interaction with nivolumab, concomitant medications, treatments, or procedures should be reviewed with study participant and updated on the participant's medical record at every study visit.

6.5.1 PROHIBITED AND/OR RESTRICTED TREATMENTS

The following medications are prohibited during the study (unless utilized to treat a drug-related adverse event):

- Immunosuppressive agents (e.g., mycophenolate, azathioprine)
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 6.5.3)
- Any concurrent antineoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, extensive radiation therapy, or stand or investigational agents for treatment of lung cancer or head and neck cancer)

6.5.2 OTHER RESTRICTIONS AND PRECAUTIONS

Subjects with any active autoimmune disease or a history of recent known or suspected autoimmune disease or history of syndrome that required systemic corticosteroids or immunosuppressive medications, except for subjects with vitiligo or resolved childhood asthma/atopy or other syndromes that would not be expected to recur in the absence of an external trigger (e.g., drug-related serum sickness or post-streptococcal glomerulonephritis) are excluded from the study. Subjects with type 1 diabetes mellitus or hypothyroidism requiring thyroid hormone replacement are permitted to enroll.

6.5.3 PERMITTED THERAPY

Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids (e.g., prednisone ≤ 10 mg/day) are permitted. A brief course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DELAY OR DISCONTINUATION OF STUDY INTERVENTION

7.1.1 DOSE DELAY CRITERIA

Nivolumab administration should be delayed for the following AEs:

- Any Grade 2 non-skin, drug-related adverse event, except for fatigue and laboratory abnormalities
- Any Grade 3 drug-related laboratory abnormality (except lymphopenia, AST, ALT, or total bilirubin)
- Any 2-Grade drug-related shift from baseline in AST, ALT, or total bilirubin
    - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, dosing will be delayed for drug-related Grade 2 toxicity
    - If a subject has a baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, dosing will be delayed for drug-related Grade 3 toxicity
- Any Grade 3 skin drug-related AE
- Any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, warrants skipping the dose of study medication

In some cases, the natural history of immunotherapy-related AEs can differ and be more severe than AEs caused by other therapeutic classes. Early recognition and management may mitigate severe toxicity. Evaluation and Management Guidelines were developed to assist investigators and can be found in the Investigator Brochure:

- General Guideline
- Diarrhea and Colitis
- Endocrinopathies
- Hepatotoxicity (including asymptomatic elevated liver function tests [LFTs])

7.1.2 DOSE REDUCTIONS

Nivolumab dose reductions are not permitted in this study.

7.1.3 CRITERIA TO RESUME TREATMENT WITH NIVOLUMAB

Subjects may resume treatment with nivolumab when the drug-related AE(s) resolve(s) to Grade 1 or baseline value (except Grade 2 fatigue for which subjects are not required to delay treatment). Subjects with baseline AST/ALT or total bilirubin in the Grade 1 toxicity range 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 (Section 7.1.4) should have treatment permanently discontinued.

Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed.

In the case of endocrine-related AEs, hormone replacement therapy or glucose controlling agents may be utilized to restore physiologic function and to permit retreatment with nivolumab.

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled timepoint per protocol. However, if the treatment is delayed past the scheduled timepoint per protocol, the scheduled study treatment administration will be delayed, but not skipped, until dosing resumes. This is to ensure that subjects will receive 4 administrations of nivolumab treatment if toxicity allows.

If treatment is delayed > 4 weeks from the last dose, the subject must be permanently discontinued from study therapy.

7.1.4 DISCONTINUATION CRITERIA

Nivolumab administration should be discontinued if at least one of the following drug-related adverse event(s) occurs:

- Any ≥ Grade 2 eye pain or reduction of visual acuity 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 2 drug-related pneumonitis that that does not respond to delay of nivolumab and systemic corticosteroid treatment after 2 weeks
- Any ≥ Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the exception of laboratory abnormalities, drug-related bronchospasm, and hypersensitivity reactions
    - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except for Grade 3 febrile neutropenia > 1 day or Grade 3 thrombocytopenia ≥ 7 days or associated with bleeding
    - Grade 3 drug-related bronchospasm, hypersensitivity reaction, or infusion reaction of any duration
- Any liver function tests (LFTs) that meet the following criteria:
    - AST or ALT > 5 x ULN for > 2 weeks
    - AST or ALT > 10 x ULN
    - Total bilirubin > 5 x ULN
    - Concurrent AST or ALT > 3 x ULN AND total bilirubin > 2 x ULN
- Any drug-related Grade 4 laboratory abnormalities, except for the following which do not require discontinuation:
    - Grade 4 neutropenia ≤ 7 days
    - Grade 4 lymphopenia
    - 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
    - For Grade 4 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 (e.g., steroids, thyroid hormones) or glucose controlling agents, respectively, retreatment can be considered after discussion with the BMS Medical Monitor
- Any dosing interruption lasting > 4 weeks with the following exceptions:
    - Dosing 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 > 4 weeks, the BMS medical monitor must be consulted.
    - Dosing interruptions > 4 weeks that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 4 weeks, the BMS medical monitor must be consulted.
- Any adverse event, laboratory abnormality, or concurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

7.1.5 ADVERSE EVENT MANAGEMENT ALGORITHMS

Because of the potential for clinically meaningful nivolumab related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected pulmonary toxicity, GI toxicity, hepatotoxicity, endocrinopathy, skin toxicity, neurological toxicity, and nephrotoxicity. The algorithms recommended for utilization in this study are contained in Appendix 2.

7.1.6 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. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study medical monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 5.0) 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 acetaminophen 325 to 1000 mg at least 30 minutes before nivolumab 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, 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 acetaminophen 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid 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 CRF. The following prophylactic premedications are recommended for further infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms (severe reaction, Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]. Grade 4: life-threatening; pressor or ventilator support indicated): Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, and treat the subject as follows: 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 (e.g., appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine or corticosteroids).

7.1.7 STOPPING RULES FOR TOXICITY

A toxicity stopping rule will be implemented, and a 25% rate of serious adverse events will be considered unacceptable. If at least five of the first 18 subjects treated, or at least 11 of the 42 total patients enrolled, develop a non-skin-related Grade 3 or Grade 4 toxicity (attributable to nivolumab) that cannot be alleviated or controlled by appropriate care and/or steroid therapy within 14 days, accrual will be suspended until the investigators have reviewed the events and in consultation with BMS, determined whether to:

- continue accrual as planned;
- assess a lower dose of nivolumab; or
- discontinue further enrollment.

Subjects who received at least 1 dose of nivolumab will be evaluable for an analysis of toxicity.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Subjects MUST discontinue investigational product for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Protocol defined reasons for discontinuation (Section 7.1.4)

All subjects who discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this requirement is when a subject withdraws consent for all study procedures including follow-up or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). Subjects should notify the investigator of the decision to withdraw consent from future follow-up in writing, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up and entered on the appropriate CRF page. If study treatment is discontinued prior to the subject's completion of the study, the reason for discontinuation must be documented in the subject's medical records and entered on the appropriate CRF page.

7.3 LOST TO FOLLOW-UP

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 SCHEDULE OF ACTIVITIES (SOA)

	Pre Screening	Pre-treatment	Dose 1 (Week 0)	Dose 2 (Week 2)	Dose 3 (Week 4)	Dose 4 (Week 6)	Week 8	Month 3	Month 6	Month 9	Month 12	FU***
PHYSICAL												
History and Physical		X	X	X	X	X	X	X	X	X	X	X
Height/Weight		X	X	X	X	X	X	X	X	X	X	X
Smoking History		X	X	X	X	X	X	X	X	X	X	
Performance Status		X	X	X	X	X	X	X	X	X	X	X
Toxicity Assessment			X	X	X	X	X	X	X	X	X	X
LABORATORY VALUES												
CBC		X						X	X	X	X	X
Complete metabolic profile		X	X	X	X	X	X	X	X	X	X	X
Thyroid function tests		X						X	X	X	X	X
Research blood		X					X		X			
Pregnancy Test		X*			X*		X*	X*	X*	X*	X*	
MISC. PROCEDURE												
Bronchoscopy/ Biopsies/BAL		X					X		X			
Sputum	X****	X					X		X			
CT chest		X							X*	X*	X*	X*
Urine**		X					X		X			
TREATMENT												
Nivolumab			X	X	X	X						

* If indicated

** Urine for banking

*** Follow up: patients who have developed drug-related toxicities will have follow-up clinic visits monthly until the toxicity resolves, and then contacted yearly by telephone for 5 years. Patients who experience no toxicities will be followed yearly by telephone for 5 years. The telephone survey is attached (Appendix 3).

**** **Subjects who are current or ex-smokers with a > 30 pack year history of smoking will be offered a pre-consent consent form to collect sputum to determine if they are eligible for the trial.**

8.2 EFFICACY ASSESSMENTS

All bronchoscopies will be performed at the RMR VAMC Screening/baseline bronchoscopy should be performed within 30 days prior to first dose of nivolumab.

For this trial, each endobronchial biopsy will be scored using the histologic scale in Section 3.2.1, and a summary measure calculated which will be used as the histologic endpoint. The primary endpoint will be the change (follow-up – baseline) in the summary measure of worst (i.e. maximum) histology after 8 weeks of nivolumab and at 6 months (to determine whether responses persist after discontinuation of nivolumab). The data from which these scores will be calculated are sets of all matched pairs of biopsies.

Study procedures mandated to answer the primary endpoint include:

1. Bronchoscopy (Baseline, Week 8, Month 6)
    - Study subjects will undergo a screening bronchoscopy with white-light bronchoscopy and either LIFE (laser-induced fluorescence endoscopy) or narrow-band imaging (NBI) after fasting for a minimum of six hours
    - The patient will be monitored with continuous electrocardiographic, respiratory, and oximetric monitoring, and with intermittent blood pressure monitoring
    - A complete endobronchial inspection will be performed and suspicious areas identified under fluorescence, narrow-band imaging, or white light will be biopsied
    - A Bronchoscopy Patient Communication Log Form is attached (Appendix 3) to follow-up with patients after the bronchoscopy is performed. Patients are called 24 hours and 72 hours after the bronchoscopy and are instructed to call within 30 days if they develop fever, increased sputum production, increased shortness of breath, or any perceived deterioration of respiratory condition.
2. Endobronchial biopsies (Baseline, Week 8, Month 6)
    - Biopsies will be taken from six predetermined sites (left and right upper lobe orifices, left and right superior segment orifices, carina between left upper lobe division and lingular orifices, and right middle lobe orifice). In addition, biopsies will be taken from any sites that appear suspicious under white light, fluorescence, or narrow-band imaging.
    - On follow-up bronchoscopies, all sites from the original bronchoscopy will be re-biopsied, along with any new abnormal appearing areas under white light, fluorescence, or narrow-band imaging.
    - Biopsies will be formalin-fixed and paraffin-embedded for hematoxylin and eosin staining, as well as for immunohistochemical staining.
    - One or more biopsies may be cultured or snap frozen for protein, RNA or DNA analysis.
    - Depending on patient tolerance and operator discretion, endobronchial biopsies may be terminated at any time. However, an attempt will be made to biopsy between 6 and 12 sites on each patient during each bronchoscopy. Additional sites may be biopsied if deemed clinically indicated but more than 12 endobronchial biopsies will not be routinely taken.

All research samples will be stored at the SPORE Tissue Bank located within the Biorepository Core Facility on the University of Colorado Anschutz Medical Campus.

8.3 SAFETY ASSESSMENTS

At baseline, a medical history will be obtained to capture relevant underlying conditions. The baseline examinations should be performed within 14 days prior to first dose and should include signs and symptoms, weight, height, ECOG Performance Status, blood pressure, heart rate, temperature, and oxygen saturation by pulse oximetry at rest. Smoking history and concomitant medications will also be collected from within 14 days prior to first dose and through the study period (See Schedule of Activities Table in Section 8.1).

Subjects will be evaluated for safety and toxicity assessments will be continuous during the treatment phase. During the follow-up phase, toxicity assessments should be done in person.

Adverse events and laboratory values will be graded according to the NCI-CTCAE version 4.0.

Vital signs, body weight, and ECOG performance status should be assessed at each on study visit prior to nivolumab dosing. Vital signs should also be taken as per institutional standard of care prior to, during and after nivolumab dosing. Oxygen saturation by pulse oximetry at rest should be assessed at each on study visit prior to nivolumab dosing. The start and stop time of the study drug infusion should be documented. Physical examinations are to be performed as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse event page.

Baseline laboratory assessments should be done within 14 days prior to the first dose and include: complete blood count (CBC) with differential, comprehensive metabolic panel (CMP: sodium, potassium, bicarbonate, BUN, creatinine, glucose, calcium, total protein, albumin, total bilirubin, AST, ALT, alkaline phosphatase), TSH (thyroid-stimulating hormone), free T4, and total T3 levels. Pregnancy testing for WOCBP must be performed within 72 hours prior to the initial administration of study drug at baseline, then every 4 weeks during the treatment phase (week 0 – week 8), and then at the follow-up visits (months 3, 6, 9, and 12). CMP should be drawn within 72 hours prior to each subsequent scheduled cycle and then at the follow-up visits. CBC with differential, TSH, free T4, and total T3 levels should be drawn every 3 months. Additional measures including non-study required laboratory tests should be performed as clinically indicated.

Laboratory toxicities (e.g., suspected drug induced liver enzyme elevations) will be monitored during the follow-up phase until all study drug related toxicities resolve, return to baseline, or are deemed irreversible.

Pulse oximetry should be obtained prior to each dose of nivolumab and at any time a subject has any new or worsening respiratory symptoms. A reading at rest and on exertion should be obtained at each time point. The extent of the exertion should be based on the judgment of the investigator, but should remain consistent for each individual subject throughout the study. If the patient's status changes, the investigator can alter the extent of exertion based on their medical judgment. If a subject shows changes on pulse oximetry or other pulmonary-related signs (hypoxia, fever) or symptoms (e.g., dyspnea, cough, fever) consistent with possible pulmonary adverse events, the patient should be immediately evaluated to rule out pulmonary toxicity. An algorithm for the management of suspected pulmonary toxicity can be found in Appendix 2.

Safety assessments will be performed at the site of enrollment/nivolumab infusion (*i.e.*, research subjects enrolled at UCHealth will undergo physical examinations, medical histories, and laboratory

assessments at UCHealth; research subjects enrolled at the RMR VAMC will undergo physical examinations, medical histories, and laboratory assessments at the RMR VAMC).

8.4 EXPLORATORY ASSESSMENTS

An important aspect of this trial is to identify novel prognostic and predictive markers present at the time of diagnosis. As such, sputum, CT chest, endobronchial biopsies, endobronchial brushings, bronchoalveolar lavages, and peripheral blood will also be collected throughout the study period. The markers to be assessed will be determined according to the best scientific knowledge and technology available. Correlative studies will be interpreted as hypothesis-generating data, to be validated in subsequent trials.

All research samples from both institutions (including bronchoscopy specimens; research urine, blood, and sputum) will be stored at the SPORE Tissue Bank located within the Biorepository Core Facility on the University of Colorado Anschutz Medical Campus.

8.4.1.1 SPUTUM INFLAMMATORY CELL ANALYSIS

For subjects without prior history of lung cancer or prior history of head and neck cancer, sputum cytology will be obtained **if a specimen has not been obtained within 3 months of study entry. Subjects who are current or ex-smokers with a > 30 pack year history of smoking will be offered a pre-consent form to collect sputum to determine if they are eligible for the trial.** Subjects will be asked to perform an early morning sputum collection over a six day period (Appendix 4). The sputum will be collected in a container containing a mild, methanol-based Carnoy's fixative that will preserve antigen epitopes in an unaltered state. Sputum samples will be collected by research subjects at home and mailed directly to the SPORE Tissue Bank. Incoming sputum specimens will be processed by a cytotechnologist using the Saccomanno two slide pull technique. Two slides will be stained by the Papanicolaou method and screened by both a cytotechnologist and by the study pathologist.

In addition to determining whether subjects should undergo screening bronchoscopy to evaluate for bronchial dysplasia, sputa collected during this study provide an excellent resource to assess the potential value of using these specimens for non-invasive predictive testing. Initial analyses will focus on comparing the features of the inflammatory cells with those seen in the biopsy tissue to determine how closely the inflammatory cells in sputa represent the findings seen in the bronchial dysplastic lesions. Secondary analyses will focus on identifying a signature in sputa that predicts response to nivolumab.

8.4.1.2 RADIOLOGIC MARKERS

In subjects without prior history of lung cancer or prior history of head and neck cancer, but with ≥ 30 pack-year smoking history and sputum atypia, CT scanning of the chest will be performed as standard of care to evaluate for evidence of lung cancer. In subjects who have undergone curative-intent surgical resection of lung cancer or of head and neck cancer, CT scanning of the chest will be performed as standard of care for follow-up and surveillance. CT scans will be obtained at the site of enrollment (*i.e.*, research subjects enrolled at UCHealth will undero CT scans at UCHealth, and research subjects enrolled at the RMR VAMCwill undergo CT scans at the RMR VAMC).

Participants found to have no nodules and definitely benign nodules (Lung-RADS category 1), nodules with benign appearance (Lung-RADS category 2), or nodules that are probably benign (Lung-RADS

category 3) are eligible for this trial. CT scans for subjects in this trial may be used in future efforts to utilize advanced segmentation and quantitative analysis beyond size criteria for better discrimination of pulmonary nodules.

Participants with findings on CT chest suspicious for lung cancer (Lung-RADS category 4) will be referred for additional evaluation designed to confirm the presence of the finding and the likelihood of lung cancer by documenting growth characteristics and morphology. Participants with suspected malignancy will not be allowed to enroll in this trial and undergo treatment with nivolumab until they have undergone additional evaluation. The intention of all subsequent management will be to confirm the presence of malignancy, establish clinical stage, and to attempt curative resection or optimal treatment. These efforts will be under the direction of the participant's treating physicianand may involve percutaneous lung (or other organ) needle aspiration biopsy, bronchoscopic sampling, thoracoscopic-directed or open biopsy, or nodal sampling with endobronchial ultrasound, transcervical mediastinoscopy, or thoracotomy.

Participants found to have abnormalities of clinical significance unrelated to lung cancer will be referred to their physician according to standard practices. Sites may or may not provide recommendations for further evaluation depending upon their local practice. The management of these participants is beyond the scope of this trial.

8.4.1.3 SAMPLES OBTAINED DURING BRONCHOSCOPY

8.4.1.3.1 ENDOBRONCHIAL BIOPSY-BASED BIOMARKER MEASURES

Expression of PD-L1 and PD-1, characterization of inflammatory infiltrates, and total mutational burden analysis of bronchial dysplastic lesions will be performed on endobronchial biopsies as described in Section 3.2.3.

8.4.1.3.2 ENDOBRONCHIAL BRUSHINGS

A cytology brush will be placed in a microcentrifuge tube containing 0.5 mL Trizol reagent, labeled with a non-identifiable subject ID and time-point (baseline, Week 8, or Month 6), snap-frozen in liquid nitrogen and stored at < -70°C.

A second cytology brush, if available, will be placed in a microcentrifuge tube containing 0.5 mL cell lysis reagent (RIPA buffer supplemented with protease inhibitors), labeled with a non-identifiable subject ID and time-point (enrollment, immediately post-treatment, or 6 months), frozen and stored at < -70°C.

Samples should be maintained at < -70°C until a sufficient number has been collected for a batch shipment.

Additional brush biopsies, one normal and one suspicious, will be obtained under direct visualization. Brushes will be placed in Saccomanno's fixative. An aliquot will be removed for cytological examination and differential.

8.4.1.3.3 BRONCHOALVEOLAR LAVAGE

Depending on patient tolerance and operator discretion, after biopsies are completed, the bronchoscope will be wedged in the right middle lobe or lingular orifice. Aliquots of 30 mL sterile saline will be sequentially instilled and retrieved by gentle suction, pooled, and placed on ice for later analysis and storage. Percent recovery will be recorded.

8.4.1.3.4 BRONCHIAL SECRETIONS

During the bronchoscopy procedure, bronchial secretions will be suctioned, collected, and saved for cytological and biomarker analyses.

8.4.1.4 PERIPHERAL BLOOD MARKERS

In this study, we will collect and store approximately 30 mL of peripheral blood for future potential biomarker analysis. A variety of factors that could potentially predict clinical response to nivolumab will be investigated in peripheral blood from subjects as described in Section 3.2.3. Candidate markers to be evaluated may include (depending on specimen availability and resources):

1. Exploratory serum biomarkers
2. Characterization and immunophenotyping of immune cell populations in peripheral blood by mass cytometry
3. Peripheral T cell repertoire analysis

8.4.1.5 URINE

Urine will be collected and adjusted to a final concentration of 2N glacial acetic acid and stored at –70°C for future biomarker testing.

8.5 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.5.1 ADVERSE EVENTS (AE)

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

8.5.2 CLASSIFICATION OF AN ADVERSE EVENT

8.5.2.1 SEVERITY OF EVENT

Adverse events (AEs) will be assessed by the clinician using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (*https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf* [Accessed on: December 21, 2016])

For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.5.2.2 RELATIONSHIP TO STUDY INTERVENTION

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.

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

8.5.3 SERIOUS ADVERSE EVENTS (SAE)

8.5.3.1 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A ***Serious Adverse Event (SAE)*** is any untoward medical occurrence that:

- results in death
- is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include,

but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.

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

The following hospitalizations are not considered SAEs:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

8.5.3.2 SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 100 days of discontinuation of dosing must be reported to BMS Worldwide Safety, whether related or not related to study drug. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these aforementioned time periods, which is believed to be related to study drug or protocol-specified procedure.

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

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

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies must be reported on a Pregnancy Surveillance Form.

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: +1 609-818-3804

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

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

All SAEs should be followed to resolution or stabilization.

8.5.4 NON-SERIOUS ADVERSE EVENTS

8.5.4.1 DEFINITION OF NON-SERIOUS ADVERSE EVENTS

A ***non-serious adverse event*** is an AE not classified as serious.

8.5.4.2 NON-SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

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

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

8.5.5 LABORATORY TEST ABNORMALITIES

All laboratory test results captured as part of the study should be recorded on the nonserious AE CRF page or SAE Report Form. 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 participant to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy.

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

8.5.6 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:

1) ALT or AST elevation > 3 times upper limit of normal (ULN)

AND

2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

AND

3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

8.5.7 PREGNANCY

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued.

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

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

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

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

8.5.8 OVERDOSE

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

8.5.9 OTHER SAFETY CONSIDERATIONS

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

9 STATISTICAL CONSIDERATIONS

The primary endpoint of this single-arm phase II trial is the dichotomous endpoint of whether or not a subject responds to treatment. Response to treatment will be based on the 6-month change (difference between 6-month score and baseline score) in worst (i.e. maximum) histologic classification score, using the 2004 WHO classification scale for endobronchial dysplasia. The data from which these scores will be calculated are sets of all matched pairs of biopsies. A positive treatment response will be defined as improvement in bronchial dysplasia by ≥1.0 histology unit.

We have analyzed histology endpoints from two completed SPORE chemoprevention trials, in which patients with a 30 pack-year or more smoking history and sputum atypia were randomized to receive study drug or placebo for 6 months. Patients underwent a baseline bronchoscopy followed by a bronchoscopy at 6 months. Results from the two completed chemoprevention trials (oral iloprost and oral pioglitazone) were used to estimate the response rate in un-treated subjects (i.e., the null response rate, p_0). Of 71 subjects treated with placebo who had baseline histology scores ≥ 4.0, 21 subjects had improvement in their bronchial dysplasia by ≥1.0 histology unit. Thus, we estimate that the null response rate (p_0) is 0.30 (21/71).

Simon's two-stage design will be used. The null hypothesis that the true response rate is 0.30 will be tested against a 1-sided alternative. In the first stage 18 subjects will be enrolled. If there are 6 or fewer responses in these 18 subjects, the study will be stopped. Otherwise, if there are 7 or more responses among the first 18 subjects, 24 additional subjects will be enrolled for a total of 42 subjects. The trial will continue to the total of 42 subjects as soon as the 7^{th} response is observed, so there will not be a delay when proceeding to the 2^{nd} cohort of the trial if the 7^{th} response occurs prior to the 18^{th} subject. If 17 or fewer subjects are responders at the end of the trial, no further investigation of the drug is warranted. The null hypothesis will be rejected if 18 or more responses are observed in the 42 total subjects. This design has 80.2% power to reject the null hypothesis when the true response rate is 0.50, controlling the type I error rate at 0.05 (actual α=0.044). Based on our experience with other chemoprevention trials (13 cis-retinoic acid, pioglitazone, and iloprost), there is typically a 10% drop out rate. To account for subjects who drop out, we expect to enroll six additional subjects (48 total) to obtain 42 evaluable subjects. This trial plans to enroll half of the subjects (24) with $\geq$ 30 pack-year history of smoking and sputum cytologic atypia, and the other half of the subjects with history of early stage lung or early stage head and neck cancer.

The expected accrual rate for this study is approximately 1-2 patients every month with an estimated study length of approximately 3 years.

Subjects will be eligible for an analysis of nivolumab efficacy (change in bronchial dysplasia) if they meet the following criteria: (1) underwent baseline bronchoscopy and endobronchial biopsies, (2) received at least one dose of nivolumab, and (3) underwent one protocol-defined follow up bronchoscopic examination to evaluate response to therapy. Subjects who do not meet these criteria or who do not have a 6-month bronchoscopy will be replaced and will not count towards the Simon two-stage design, because change in histology score at 6 months is the primary endpoint.

The analysis population for efficacy is the full analysis set. Subjects who complete 4 doses of nivolumab will also be analyzed separately. Subset analyses according to history of cancer and smoking status are also planned.

Safety analyses will be performed in all subjects who receive nivolumab. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All on-study AEs, Grade 3-4 AEs, treatment-related AEs, Grade 3-4 treatment-related AEs, SAEs, treatment-related SAEs, and AEs leading to discontinuation will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function, and renal function, and Grade 3-4 Lab Abnormalities will be summarized using worst grade NCI CTCAE v 4.0 criteria.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 ETHICAL CONSIDERATIONS

10.1.1 GOOD CLINICAL PRACTICE

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive IRB/IEC approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s).

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

10.1.2 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects. The investigator or sponsor should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects, and any updates.

The investigator or sponsor should provide the IRB/IEC with reports, updates, and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institutional procedures.

10.1.3 INFORMED CONSENT

Investigators must ensure that subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representatives, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

BMS will provide the investigator with an appropriate (i.e., Global or Local) sample informed consent form which will include all elements required by ICH, GCP, and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helskinki.

Investigators must:

1. Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2. Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3. Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4. Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5. If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating their informed consent during the study, then consent must additionally be obtained from the subject.
6. Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

Subjects unable to give their written consent (e.g., stroke patients, or subjects with severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with the subjects' understanding, and should they become capable, personally sign and date the consent form as soon as possible. The explicit wish of a subject unable to give his or her written consent, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

10.2 STUDY MANAGEMENT

10.2.1 COMPLIANCE

10.2.1.1 COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, Bristol-Myers Squibb (BMS). The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- Bristol-Myers Squibb
- Regulatory authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is an administrative letter, investigators must inform their IRB(s)/IEC(s).

10.2.1.2 MONITORING AND OVERSIGHT

The sponsor investigator will be responsible for monitoring the trial per the trial monitoring plan, in addition to overseeing the safety and efficacy of the trial including any specimens collected, executing the data and safety monitoring (DSM) plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and study participant safety for all clinical studies at the CU Cancer Center, which is the coordinating institution of this trial. A summary of the DSMC's activities is as follows:

• Conduct of internal audits

• Ongoing review of all serious adverse events (SAEs) and unanticipated problems (UAPs)

• May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, SAEs and UAPs are reported to the DSMC, IRB and the sponsor investigator per protocol. All SAEs and UAPs are to be reported to the DSMC within 7 (for fatal or life-threatening events) or 15 (non-life-threatening events) calendar days of the sponsor investigator receiving notification of the occurrence.

Each subject's treatment outcomes will be discussed by the site PI and appropriate staff at regularly scheduled meetings. Data regarding number of subjects, significant toxicities, dose modifications, and treatment responses will be discussed and documented in the meeting's minutes.

The sponsor investigator will provide a DSM progress report to the CU Cancer Center DSMC on a recurring basis (either every six or twelve months based on DSMC vote). The DSM report will include a protocol summary, current enrollment numbers, summary of toxicity data to include specific SAEs, UAPs and AEs, any dose modifications, all protocol deviations, and protocol amendments. The DSM progress report submitted to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted. Results and recommendations from the review of this progress report by the DSMC will then be provided to the sponsor investigator in a DSMC review letter. The sponsor investigator is then responsible for ensuring this letter is submitted to the site's IRB of record at the time of IRB continuing review.

10.2.1.3 QUALITY CONTROL AND QUALITY ASSURANCE

Site monitoring visits will be performed by the sponsor investigator's authorized representative on a regular basis, pursuant to the Monitoring Plan. During these visits, information recorded on the CRFs will be verified against source documents. Additional computer programs that identify selected protocol deviations, out-of-range data, and other data errors within the electronic data entry may also be used to help monitor the study. As necessary, requests for data clarification or correction will be sent to the appropriate site PI.

Independent auditors from the sponsor investigator's authorized representative will be allowed by the site's PI to audit. In addition, audits may be conducted at any time by appropriate regulatory authorities and/or the IRB.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and very that the facilities remain acceptable

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

10.2.2 RECORDS

10.2.2.1 RECORDS RETENTION

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IRB). Notice of such transfer will be given in writing to BMS.

10.2.2.2 STUDY DRUG RECORDS

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by BMS) is maintained at each study site where study drug is inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area
- Amount currently in storage area
- Label identification number or batch number
- Amount dispensed to and returned by each subject, including unique subject identifiers
- Amount transferred to another area/site for dispensing or storage
- Nonstudy disposition (e.g., lost, wasted)
- Amount destroyed at study site, if applicable
- Amount returned to BMS
- Retain samples for bioavailability/bioequivalence, if applicable
- Dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form

BMS will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

10.2.2.3 CASE REPORT FORMS

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated in the investigation. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by the sponsor.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by a qualified physician who is an investigator or subinvestigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by the sponsor. User accounts are not to be shared or reassigned to other individuals.

10.2.3 PUBLICATIONS

The data collected during this study are confidential and proprietary to the sponsor. Any publications or abstracts arising from this study require approval by the sponsor prior to publication or presentation and must adhere to the sponsor's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to the sponsor at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. Sponsor shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and delay publication for up to 60 days for purposes of filing a patent application.

11 ABBREVIATIONS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).

AE	Adverse Event
ANCOVA	Analysis of Covariance
BD	Bronchial Dysplasia
BMS	Bristol-Myers Squibb
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form

CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CTLA4	Cytotoxic T-Lymphocyte Associated Protein 4
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DILI	Drug Induced Liver Injury
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
DSM	Data and Safety Monitoring
DSMC	Data and Safety Monitoring Committee
DVAMC	Denver Veterans Affairs Medical Center
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
IF	Immunofluorescence
IND	Investigational New Drug Application
irAEs	Immune Related Adverse Events
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
IUD	Intrauterine Device
LFTs	Liver Function Tests
LIFE	Laser Induced Fluorescence Endoscopy
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NAC	N-Acetylcysteine
NBI	Narrow-band imaging
NCI	National Cancer Institute
NCT	National Clinical Trial
NIH	National Institutes of Health

NIH IC	NIH Institute or Center
NSCLC	Non-Small Cell Lung Cancer
OHRP	Office for Human Research Protections
ORR	Objective Response Rate
OS	Overall Survival
PD-1	Programmed Death Receptor 1
PFS	Progression Free Survival
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
Th1	T-Helper 1
Th2	T-Helper 2
TIL	Tumor-Infiltrating Lymphocyte
TME	Tumor Microenvironment
TSH	Thyroid-Stimulating Hormone
ULN	Upper Limit of Normal
UP	Unanticipated Problem
US	United States
WHO	World Health Organization
WOBCP	Women of Childbearing Potential

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13 APPENDICES

13.1 APPENDIX 1 – ECOG PERFORMANCE STATUS

Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair.*

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

13.2 APPENDIX 2 – ADVERSE EVENT MANAGEMENT ALGORITHMS

GI Adverse Event Management Algorithm

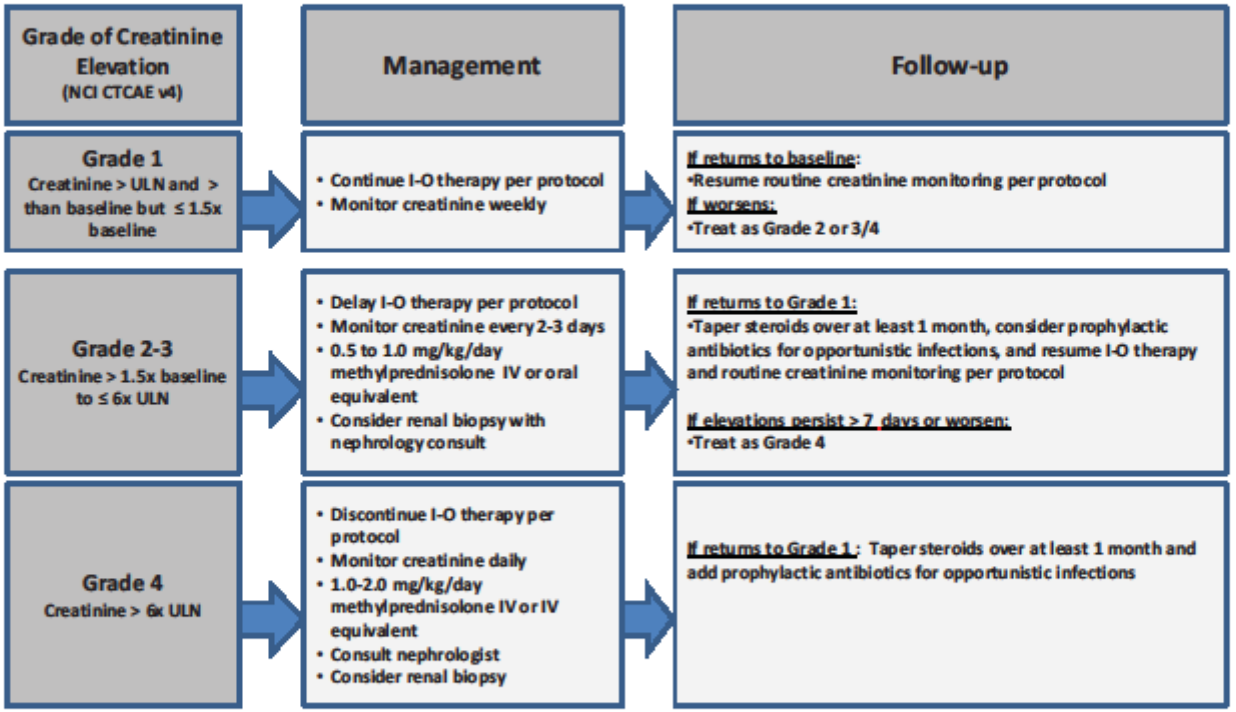
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea: < 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

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

Renal Adverse Event Management Algorithm

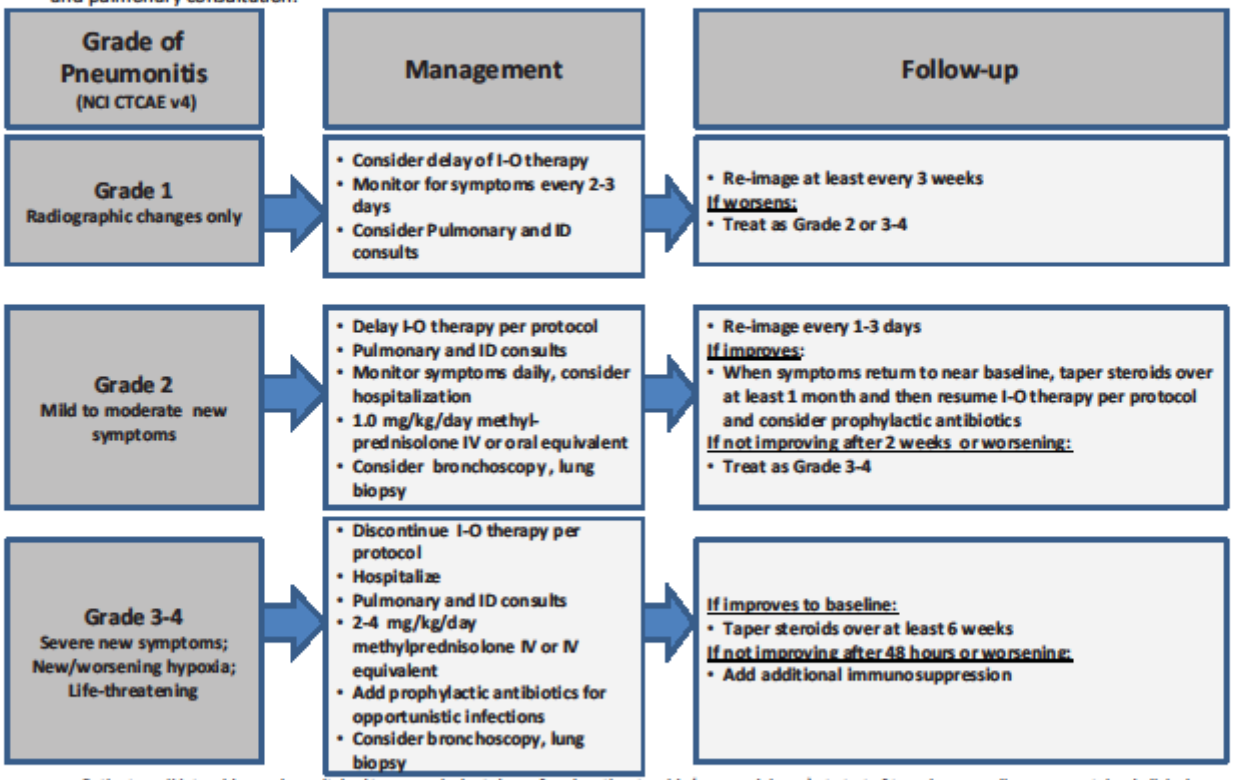
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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.

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.



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.

Hepatic Adverse Event Management Algorithm

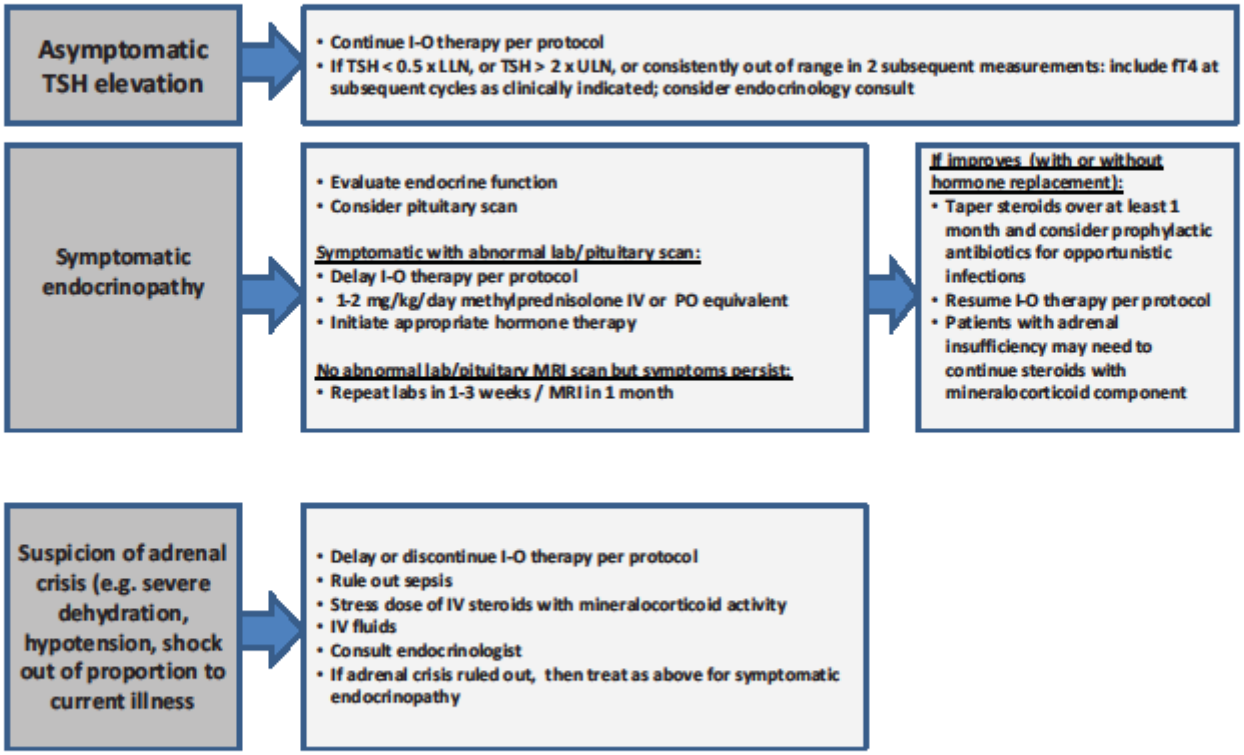
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN -2.5 x ULN and/or T. bili > ULN - 1.5 x ULN	• Continue I-O therapy per protocol	• Continue LFT monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 2.5 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen : • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent** • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1 g BID • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

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

Endocrinopathy Management Algorithm

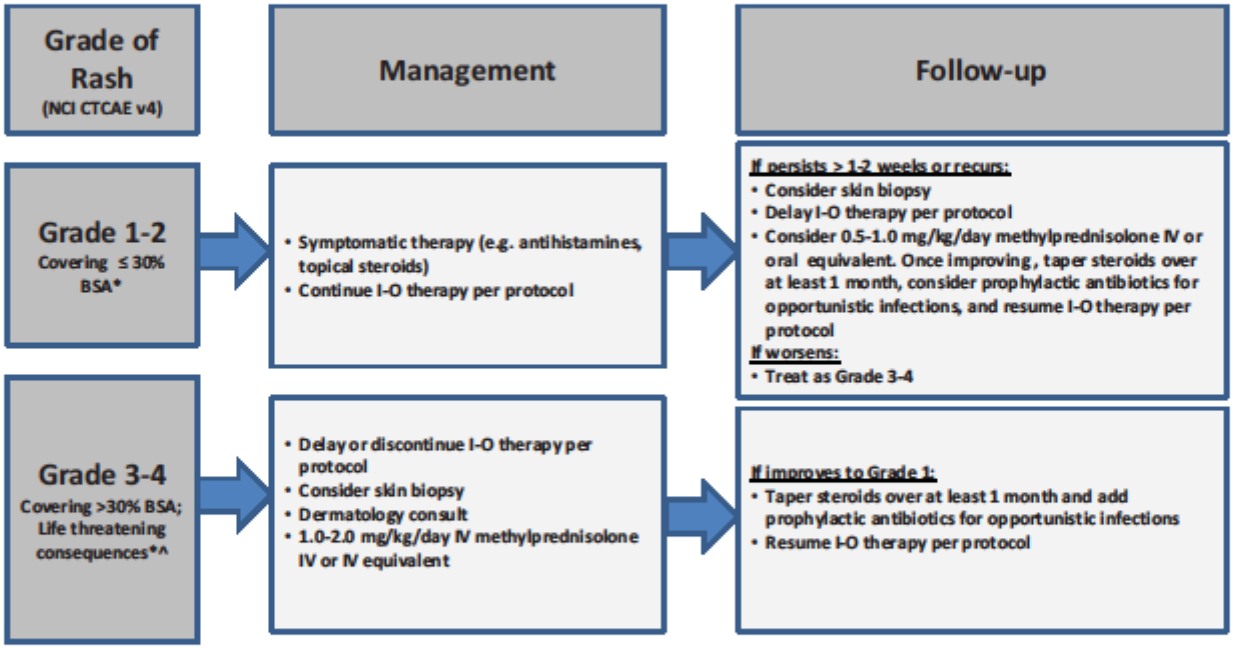
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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

Skin Adverse Event Management Algorithm

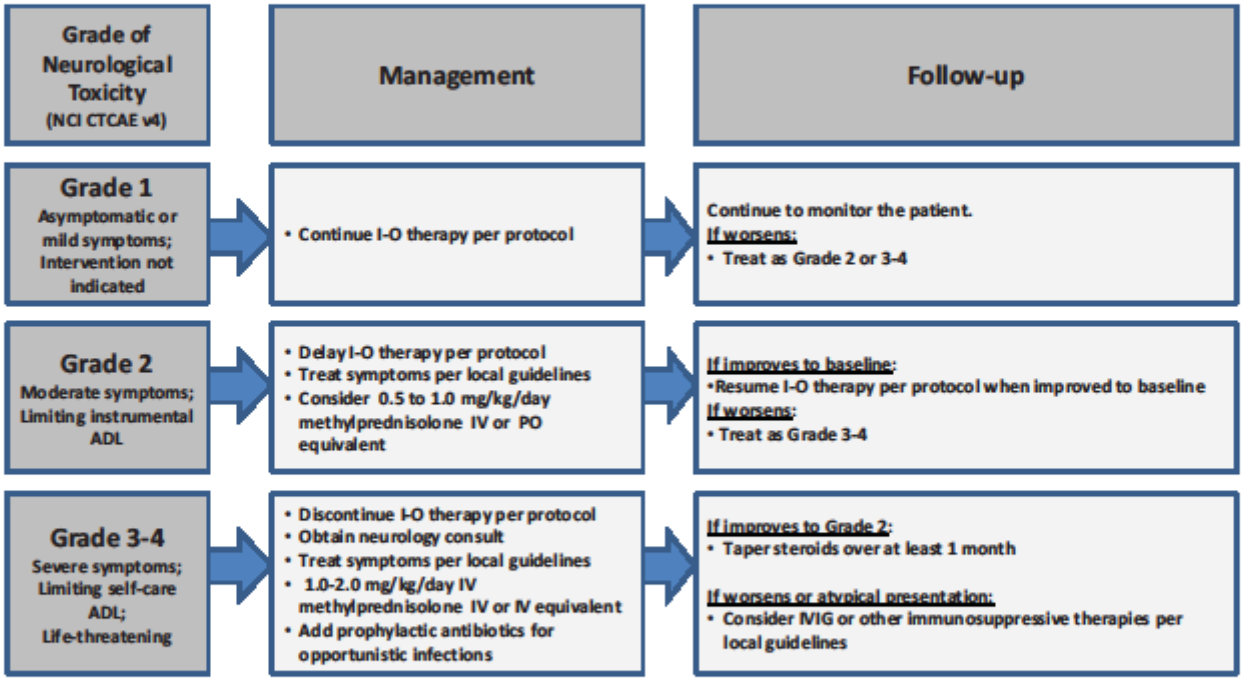
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

Neurological Adverse Event Management Algorithm

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



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

13.3 APPENDIX 3 – BRONCHOSCOPY PATIENT COMMUNICATION LOG

Protocol: Nivolumab
Source Document :

Patient Name:_____ Phone:_____
SPORE #_____

Pre-Case Communication:
Date of Consent: _____ (The patient verbalized understanding of the consent, and a copy of the signed consent was provided to the patient.)

_____
_____
_____
_____
_____
_____
_____
_____

SIGNATURE:_____ DATE:_____

Procedure Date:

Date:_____ Time:_____

Physician:_____ Notified:_____

24-Hour Follow-up:

Date:_____
Comments:
_____
_____
_____

SIGNATURE:_____

72-Hour Follow-up:

Date:_____
Comments:
_____
_____
_____

The patient was instructed to call within 30 days if febrile or with increased sputum production, increasing shortness of breath, or any perceived deterioration of respiratory condition:
Yes:_____ No:_____
Signature:_____

13.4 APPENDIX 4 – SPUTUM COLLECTION PATIENT INSTRUCTION SHEET

INSTRUCTIONS FOR OPENING AND CLOSING CONTAINERS

- How to open containers: To open container, unscrew the top of the first canister and slide out second metal canister. Unscrew the lid on the second canister. Inside this canister are two small containers. When you open these small containers, do so slowly so that the liquid inside does not spill.

  BLUE DOT CONTAINER: You must use the small clear container with the blue dot for the first three-day collection of sputum.

  RED DOT CONTAINER: You must use the small clear container with the red dot for the second three-day collection of sputum.

PROCEDURES FOR PERFORMING THE EARLY MORNING SPONTANEOUS COUGH TECHNIQUE

- When you wake up in the morning, clear your throat and mouth of any food and debris which may have accumulated overnight and spit it out.
- Next, rinse your mouth out with water and spit the water into the sink, not into the sputum container.
- Begin coughing deep from your diaphragm. We need sputum from the lungs. Spit sputum into the small clear container and close container.
- Do this procedure within the first hour you are awake for six mornings in a row. (Note: If you do not produce sputum in the first hour you are awake, you are permitted to use the first sputum you cough up that day, regardless of the time of day.)
- Collect the first three days of coughed up sputum in the blue dotted container.
- Collect the second three days of sputum in the red dotted container.

After you have collected sputum for six days, individually place the two small clear containers inside each biohazard bag (in case there is leakage during shipping). Put them inside the steel canister and then place the steel canister inside the larger postage paid container that has our address on the outside. **Please make sure all lids are on tightly**. Drop the mailing container in the any U.S. mailbox or at the U.S. post office. If you have any questions, please contact either:

Mary Jackson: 303-724-1650

Brandi Bagwell: 303-724-1657

YOUR PARTICIPATION IS GREATLY APPRECIATED. YOUR PHYSICIAN WILL RECEIVE THE RESULTS OF YOUR SPUTUM EXAMINATION.

13.5 APPENDIX 5 – NIVOLUMAB FOLLOW-UP SCRIPT

1. *Hello. This is _{your_name}__ calling on behalf of the Rocky Mountain Regional VA Medical Center and the University of Colorado Cancer Center. May I please speak with __{participant}____?_*

☐ Unavailable	→ **7a** [Reschedule, page 2]
☐ Not home	→ **7a** [Reschedule, page 2]
☐ Not a good time	→ **7a** [Reschedule, page 2]
☐ Deceased	→ **9a** [Cause of death, page 3]
☐ Respondent refuses	→ **8** [Refusal exit, page 2]
☐ Household refuses	→ **7a** [Reschedule, page 2]
☐ Yes	→ **2**

2. *Hello _{participant}_. I am calling in regards to your participation in the Nivolumab study at the Rocky Mountain Regional VA Medical Centerand University of Colorado Cancer Center. We would like to follow up on your health status. Do you have a few moments to help me with that?*

☐ Yes	→ **3**
☐ No	→ **7a** [Reschedule, page 2]

3. *First, I need to verify your current mailing address. Are you still residing at (give most recent address)?* (If no, obtain current address.) → **4**

4. *Is this the best telephone number for us to reach you?* (If not, obtain current phone number) → **5a**

5a. *Have you been diagnosed with cancer since you completed the Nivolumab study?*

☐ Yes	→ **5b**
☐ No	

5b. *What was your diagnosis?*

_____

5c. *What was the date of the diagnosis?*

(_ _/_ _/_ _)
MM/DD/YY

CLOSING

Thank you very much for talking with me today. Do you have any questions you would like to ask?

Thank you very much for your time. Take care!

---END CALL---

SCHEDULING A BETTER TIME TO REACH PARTICIPANT

7a. *What would be a good day and time to call back within the next couple of weeks to reach you/him/her?*

Date:_____ Time:_____

7b. *At what phone number should I try to reach you/him/her?*

† Home:_____
† Work:_____
† Other:_____

REFUSAL EXIT AND CLOSING

8. *That's no problem. You certainly don't need to feel any obligation to complete this follow-up. May we contact you again next year?*

☐ Yes → *Thank you for your time and have a nice day.*
☐ No

Note: If the respondent says, "I don't know" or is reluctant check "YES."

CAUSE OF DEATH

9a. **If patient is deceased:** (Apologize and give condolences, ask for the name of the person with whom you are speaking so that you may keep the conversation more personal by referring to them by name). *I'm sorry to hear about your loss. Would you be willing to share the causes of death with me?*

† Yes → **9a1**
† No → *Thank you for taking the time to talk with me today. Good bye.*

9a1. *What were the causes?*

9b. *What was the date of his/her death?*

(_ _/_ _/_ _) or unknown
MM/DD/YY

9c. *Was __{participant}_ ever diagnosed with lung cancer?*

†Yes → **9d**
† No → *Thank you for taking the time to talk with me today.*

Good bye. ***{END CALL}***

9d. *What was the date of his/ her diagnosis?*

(_ _/_ _/_ _) or approximate MM/DD/YY → *Thank you for taking the time to talk with me today. Good bye.* ***{END CALL}***