MSK PROTOCOL COVER SHEET

An Exploratory Study to Evaluate the Mediators of Sensitivity and Resistance to Nivolumab plus Ipilimumab in Patients with Advanced NSCLCs

Principal Investigator/Department: Adam Schoenfeld, MD / Medicine

Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, New York 10065

Table of Contents

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Title: An exploratory study to evaluate the mediators of sensitivity and resistance to nivolumab plus ipilimumab in patients with advanced NSCLC

Study Design: This is an open-label, single-center, single-arm, phase II exploratory study of nivolumab 3mg/kg q 2 weeks in combination with ipilimumab 1mg/kg q 6 weeks. The target population includes patients with advanced stage NSCLCs. This study aims to examine the factors that may contribute to sensitivity or resistance to nivolumab plus ipilimumab in patients with advanced NSCLCs. There are several objectives to this study, which are structured around a model of T-cell recognition of cancer.

Eligible patients must have at least one site of disease that is amenable to standard-of-care surgical resection or a core needle biopsy. For those undergoing standard of care resection, residual measurable disease following resection is required.

Eligible patients must have had no more than 2 prior regimens of chemotherapy and no prior immunotherapy. Patients with *EGFR* mutations or *ALK* re-arrangements must have had prior tyrosine kinase inhibitors. Those with auto-immune disease, concurrent treatment with alternative anti-cancer therapy or systemic immunosuppressants, or untreated brain metastases are excluded from study.

Patients will have a pre-treatment, standard-of-care tumor resection or tumor biopsy for fresh tissue collection. Patients will then start nivolumab 3mg/kg day 1 and continue this every 2 weeks during the study protocol. Patient will concurrently start ipilimumab 1mg/kg day 1 and continue this every 6 weeks during the study protocol. Tissue collection and correlative studies planned described below.

	Pre-Rx	C1D1	C2D1	C2D8	C3D1	C4D1 and each cycle thereafter
Nivolumab 3mg/kg		X	X		X	X
Ipilimumab 1 mg/kg		X				X and every 6 weeks thereafter
	Biospecimen collection for analysis					
Tumor resection or biopsy	X					
Tumor biopsy				X		
Isolation of TILs	X					
PBMCs	X	X	X	X	X	X and every 6 weeks thereafter
	Tumor-based analysis					

Mutation burden	X					
Candidate neoantigens	X					
Co-stimulatory receptors and ligands	X			X		X and every 6 weeks thereafter
	T cell analysis (TILs and/or PBLs)					
Identification of antigen-specific T-cells	X	X		X		X and every 6 weeks thereafter

Project	Methods
Mutation burden	Whole exome / transcriptome
Candidate neoantigens	Bioinformatics
Co-stim receptors and ligands	IHC
Antigen specific T-cells	MHC-multimer assays ICS assays

2.1 OBJECTIVES AND SCIENTIFIC AIMS

Nivolumab produces a response in ~15-20% in patients with advanced NSCLC and the combination of PD-1 blockade plus CTLA-4 blockade appears to have a response rate of ~30%(1). We have recently demonstrated that somatic mutation burden is associated with response to PD-1 blockade monotherapy in a retrospective study (2), but the predictors and mediators of response to nivolumab in combination with ipilimumab are not known. In this prospective study, we aim to examine mechanisms of sensitivity and resistance to nivolumab plus ipilimumab by dissecting the individual components that contribute to T-cell recognition of and response to a cancer cell.

A cornerstone of cancer immunotherapy is the ability of the adaptive immune system to recognize a cancer as foreign, i.e. non-self. One way that a cancer can appear foreign is by the accumulation of somatic mutations. Some of these mutations are oncogenic, while others are passengers. But irrespective of their oncogenic potential, each of these mutations has the potential to contribute to the immunogenicity of a cancer. The primary objective of this study is to explore how these somatic mutations in cancer mediate response or resistance to nivolumab plus ipilimumab. To fully contextualize the T-cell response to cancer, we will evaluate in parallel the other factors involved in T-cell and cancer cell interactions, including expression of co-stimulatory ligands on tumor cells and in the tumor microenvironment and expression of exhaustion/activation receptor on T-cells.

Primary objectives:

1) Explore the relationship between mutational burden and response to nivolumab plus ipilimumab therapy
2) Identify candidate neoantigens and explore their associations with response to nivolumab plus ipilimumab therapy

3) Identify neoantigen-specific T-cells using technology such as *in vitro* using MHC-multimer or intracellular cytokine staining.

Secondary objectives

1) Examine MHC and co-stimulatory receptor and ligand expression in tumor-microenvironment and explore their relationship with response to nivolumab plus ipilimumab.

3.0 BACKGROUND AND RATIONALE

INTRODUCTION TO LUNG CANCERS

Lung cancer is the most common cancer and leading cause of cancer related death worldwide, accounting for more than 1.6 million cases and 1.3 million deaths annually (3). For patients with advanced stage non-small cell lung cancer (NSCLCs), the most common form of lung cancer in the United States, cytotoxic chemotherapy improves outcomes (4, 5) but durable disease control is disappointingly rare – fewer than 5% of patients are alive 5 years later and median survival is ~10 months (6, 7). Histology-specific chemotherapy (8), maintenance chemotherapy (9-13), the addition of bevacizumab (14), and the identification of targetable driver oncogenes (15-20) have all improved outcomes, but there remains an urgent need for better treatment strategies for the majority of patients with advanced NSCLCs. T-cell checkpoint inhibitors, particularly those targeting PD1 and PDL1, have recently demonstrated promising activity in NSCLCs and represent a new paradigm for considering the treatment of patients with lung cancers.

T-CELL CHECKPOINT INHIBITION IN NSCLCs

T-cell checkpoint inhibitors targeting CTLA-4 (ipilimumab (21)), PD-1 (nivolumab, and other similar therapies in development (22-25)) and PDL1 (26, 27) have demonstrated effectiveness in advanced NSCLCs and validated the importance of cancer immunotherapy in the treatment of patients with NSCLCs.

PD-1 AND PD-L1

Programmed Cell Death-1 (PD-1; CD279) is a cell surface receptor on T-cells that is induced after T-cell activation. When PD-1 engages with its cognate ligands (PDL1, also known as B7-H1, or PD-L2, also known as B7-DC), it signals intracellularly in T-cells to inhibit effector T-cell function (28) via induction of effector T-cell apoptosis, suppression of effector T-cell proliferation or cytokine production (29-32). PDL1 and PD-L2, ligands of PD-1, are expressed not only by APCs but also by tumor cells and cells in the tumor microenvironment. An overexpression of PD-1 ligands by tumor cells and cells in its microenvironment leading to ineffective tumor infiltrating effector T-cells is postulated to be one important mechanism by which tumor cells prevent immune-mediated destruction (28, 33). Indeed, overexpression of the PD-L1 within solid tumors has been associated with poor prognosis and diminished tumor infiltrating effector T-cells (34-36), including NSCLCs (37, 38).

Aimed at reversing the immune inhibitory signals to restore effective tumor directed immune attack, multiple anti-PD-1 and anti-PDL1 monoclonal antibodies (mAb) are currently in development.

Nivolumab

Nivolumab (BMS-936558) is a fully human, IgG4 (kappa) isotype mAb that binds PD-1 on activated immune cells and disrupts engagement of the receptor with its ligands (PD-L1 and PD-L2), thereby abrogating inhibitory signals and augmenting the host antitumor response. In an early clinical trial, nivolumab demonstrated activity in several tumor types, including melanoma, renal cell cancer (RCC), and NSCLCs (22). Treatment was well tolerated, no dose-limiting toxicities were observed, three objective responses, including one complete response, were reported.

A second phase I study of 296 patients with advanced solid tumors treated with nivolumab given every two weeks in escalating dose cohorts has also been reported (24). 122 patients had NSCLCs. 55% had been treated with ≥ 3 prior regimens. Only 8% of those with NSCLCs experienced treatment related grade 3-4 toxicity (fatigue, pneumonitis, transaminitis being most common), although two patients with NSCLCs died of treatment-related pneumonitis. Of all NSCLC patients evaluable for clinical activity [i.e. all doses], 17% has an objective response; in those who received 3 or 10mg/kg (the recommended phase II doses), the response rate was 22% (21/96). Impressively, the 24-week PFS rate among all NSCLCs patients treated at 3mg/kg was 42-45% (23, 39). These results are similar to the ORR and median PFS from achieved with first-line platinum-based chemotherapy (ORR ~30%, median PFS ~5 months (8, 14)) and appear numerically superior to standard second-line treatment options (including erlotinib, docetaxel, or pemetrexed; ORR 3-8%, median PFS 6-8 weeks (40, 41)).

Since then, nivolumab has since been studied in several studies include two phase 3 studies of nivolumab versus docetaxel in patients with advanced NSCLCs previously treated with one line of therapy. In both studies, nivolumab significantly improved response rate and overall survival compared to docetaxel. As a result, nivolumab has recently been approved by the FDA for patients with previously treated squamous cell lung cancers. NCCN has also suggested that nivolumab is reasonable therapy for patients with previously treated lung adenocarcinomas, though this has not been FDA approved yet. In this context, the recent successes of PD1/PDL1 directed therapy offer perhaps the most encouraging results for the treatment of NSCLCs in years.

Nivolumab plus ipilimumab

Although both CTLA-4 and PD-1 function as inhibitory co-receptors expressed on T cells, their ligands and function are distinct. When localized to the T cell surface after antigen-driven TCR-mediated T cell activation(42), CTLA-4 binds to CD80 and CD86(43) and prevents effector T cell activation and proliferation(44-46) by competitively preventing binding of B7 ligands to the costimulatory receptor CD-28(47-50) and inhibition of intracellular signaling pathways(51-53). As above, PD-1 is similarly shuttled to the surface of effector T cell upon activation(54), where PD-1 can bind to ligands PD-L1(28, 55) and PD-L2(56) and inhibit proliferation(57), cytokine production(58, 59), and survival(60, 61), characteristic of T cell exhaustion.(62, 63) In this context, CTLA-4 and PD-1 can produce differing effects on effector T cells, including inhibition of early activation and differentiation by CTLA-4 and modulation of effector function by PD-1

Confirming the potential for syngery with these therapies, the combination of nivolumab and ipilimumab has produced truly transformative responses for patients with melanoma. Building upon an initial phase I dose-escalation study of this combination [Wolchok NEJM 2013], reports of randomized Phase II and Phase III studies have recently been reported. The Phase II study was a double-blind, randomized study of nivolumab plus ipilimumab compared to ipilimumab in patients with advanced melanoma (Postow NEJM 2015). The objective response rate to nivolumab plus ipilimumab was 59%, compared to 11% with ipilimumab alone. Among those treated with combination therapy, the median change in tumor volume was a 68% decrease and 22% of patients achieved a complete response.

Most recently, a double-blind, phase III, randomized study of nivolumab plus ipilimumab versus nivolumab versus ipilimumab was performed in patients with treatment-naïve advanced melanoma (Larkin NEJM 2015). Again, the response rate with combination therapy was 57.6%, compared to 43.7% in the nivolumab monotherapy arm and 19% in the ipilimumab monotherapy group. Progression-free survival also favored combination therapy, with hazard ratio of 0.57 (95% CI 0.43-0.76) compared to ipilimumab and 0.74 (95% CI 0.60-0.92) compared to nivolumab. Overall, with responses exceeding 50% of the population and median PFS reaching nearly a year, it is clear that combination therapy has reshaped the treatment landscape of advanced melanoma and profoundly improved the outcomes for these patients.

Building upon the remarkable activity seen in patients with melanoma, several studies have begun to explore this combination in NSCLCs as well. In an initial study of nivolumab and ipilimumab, patients with NSCLC were initially treated with two dosing schedules (Nivo1/Ipi3 or Nivo3/Ipi1 every three weeks for four doses, followed by Nivo3 every two weeks) (Antonia, ASCO 2014). A total of 49 patients were treated and frequent toxicity was seen in both groups, with 49% patients experiencing a treatment-related grade 3-4 toxicity and 35% of patients discontinuing therapy due to treatment-related events. Some responses were seen, but efficacy was difficult to interpret in the setting of the rate of toxicity. Subsequently, the study was amended to examine several additional treatment regimens, including giving lower doses of both nivolumab and ipilimumab (1mg/kg each) or increasing the interval between ipilimumab administration (every 6 or 12 weeks). These data have demonstrated the response rate to be ~20-30% across arms and safety to be much better tolerated. Nivo 3mg/kg every two weeks plus Ipi 1mg/kg every six weeks has emerged as an optimal dose and schedule and will be assessed further in a Phase 3 study of nivolumab plus ipilimumab versus nivolumab monotherapy versus chemotherapy has been recently begun .(NCT02477826).

Additionally, and with similar result, a dose-escalation study of anti-PD-L1 inhibitor MEDI4736 in combination with the CTLA-4 inhibitor tremelimumab in patients with NSCLC was also recently reported (Antonia ASCO 2015). 102 patients were treated across 10 dose-escalation cohorts. MEDI4736 given at 10mg/kg every two weeks or 3, 10, 15, 20mg/kg every four weeks and tremelimumab was given at 1, 3, or 10mg/kg every four weeks. In cohorts of tremelimumab 3 or 10mg/kg, the rate of treatment-related grade 3-4 toxicity was 50-80% and 34-45% lead to treatment discontinuation; therefore these doses were felt to be unacceptable for development. Toxicity was more modest in cohorts of tremelimumab 1mg/kg, with grade 3-4 toxicity occurring in 29% of patients, and only 7% resulting in discontinuation of therapy. In addition to manageable toxicity

with lower doses of tremelimumab, initial efficacy was also promising with objective responses seen in 33% of patients and 52% were progression-free 16 weeks after beginning therapy. Phase 3 studies of MEDI4736 plus tremelimumab versus MEDI4736 versus chemotherapy in untreated, advanced NSCLC are planned to begin this year (NCT02453282).

Overall, early efficacy with combination of CTLA-4 + PD-1/PD-L1 blockade is promising with response rates of ~30% that numerically exceeds (nearly double) what has been reported with anti-PD-1/PD-L1 monotherapy in NSCLC. However, as it remains a minority of patients who respond to either therapy, it remains critical that we examine the determinants of response to combination therapy in order to optimize therapy for patients.

Predictors of response to PD-1 blockade

Although robust responses to PD-1 blockade have been seen across many tumor types, it is a fraction of patients treated who ultimately respond. Significant recent effort has been dedicated to finding predictors of response to anti-PD-1/PD-L1 therapies. Expression of PD-L1 in the tumor microenvironment appears to enrich for response, but is neither sensitive nor specific (24, 64-66).

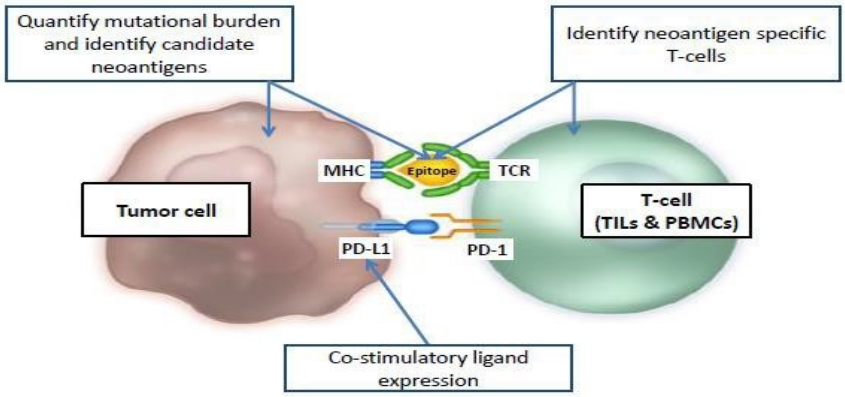
Our group has largely focused on the genomic predictors of response to PD-1 blockade and recently reported the results of whole exome sequencing of paired tumor/normal tissue from 34 patients with NSCLC who were treated with pembrolizumab as part of a phase I study. Similar to previous series of NSCLCs that have been examined with exome sequencing, we found a substantial range in the mutation burden of samples, with some tumors harboring as few as 11 somatic non-synonymous mutations and others with as many as 1192 mutations. Importantly, somatic mutation burden substantially correlated with clinical benefit to treatment with pembrolizumab. Patients with durable benefit lasting >6 months (termed "durable clinical benefit," DCB) had significantly higher mutation burden compared to those with no durable benefit (NDB) (median 299 vs 127 mutations, p=0.0008). Additionally, the rate of objective response, DCB, and progression-free survival were all significantly greater in patients with an elevated mutation burden (59% vs 12%, p=0.01; 79% vs 18%, p=0.001; HR 0.19, 95% CI 0.08-0.47, respectively).

We hypothesized that neoantigens, cancer-specific mutated peptides formed as a consequence of somatic mutations, may underlie the association between mutation burden and response to T cell checkpoint blockade. We applied a computational pipeline recently developed to identify candidate neoantigens from cancer exome data (Snyder et al, NEJM 2014) to examine the neoantigen landscape of one patient with NSCLC who had an excellent response to pembrolizumab. In collaboration with Ton Schumacher's lab, candidate neoantigens from this patient were synthesized and neoantigen-specific T cell reactivity was screen used prospectively collected autologous peripheral blood lymphocytes. A neoantigen-specific T cell response to a neoantigen resulting from a *HERC1* P3278S mutation was detected in the peripheral blood and the increase in neoantigen-specific reactivity mirrored the clinical response to pembrolizumab. The T cell response was only detectable after starting therapy, increased rapidly initially, and then plateaued at levels just above background as tumor regression was maintained over the next year. This is the first neoantigen-specific T cell response identified in the peripheral blood of a patient treated with PD-1 blockade.

This data has demonstrated clear differences in response to PD-1 blockade monotherapy based on mutation burden and a suggestion that neoantigens may be a fundamental component of directing an effective anti-tumor immune response during treatment. However, it is unknown whether a similar result will be seen in patients treated with combination PD-1 plus CTLA-4 blockade. There is

suggestion from combination studies that there may be a distinct molecular profile of responders to combination therapy. For example, in one study of NSCLCs treated with PD-L1 plus CTLA-4 blockade, there was no difference in response rate by PD-L1 expression in this study(69). However, the study of ipilimumab plus nivolumab in NSCLC did show a persistent enrichment of response among patients whose tumors expressed PD-L1(1). Ultimately larger sample sizes from the ongoing Phase 3 studies will be needed to fully examine the impact of PD-L1 on response to combination immunotherapy in patients with NSCLC.

Still, it remains unknown whether mutation or neoantigen burden associate with response to combination therapy. More broadly, and most importantly, there are currently no predictive markers of response to combination PD-1 plus CTLA-4 blockade.



The goal of this study is to evaluate in parallel the individual components that are involved in T-cell recognition of lung cancers in order to comprehensively explore the mediators of sensitivity or resistance to nivolumab plus ipilimumab in patients with NSCLCs. Due to the multiple planned exploratory analyses, this trial is tissue-intensive and will focus on a specific set of patients from whom sufficient pre-treatment tissue can be feasibly obtained. Overall, our goals are to examine in parallel some of the individual components that are involved in T-cell recognition of lung cancers in order to more fully identify the potential mediators of sensitivity or resistance to combination therapy in patients with NSCLCs.

Primary Objectives

1) Mutational burden:

As above, in patients with lung cancers we have previously demonstrated that response to PD-1 blockade monotherapy is greatest in patients with elevated somatic mutation burden. The examination of mutation burden in PD-1 treated patients was initially spurred by the observation that responders to nivolumab were almost exclusively former smokers, whose tumors are characterized by substantially greater mutational burden compared to never smokers (76, 77). For example, using provisional data available from The Cancer Genomic Atlas project (TCGA) (www.cbioportal.org), we found that smoking-related lung adenocarcinomas have on average 370 mutations/sample compared to never smokers with 86 mutations/sample ($p<0.0001$). In contrast, initial results of patients with NSCLCs treated with PD-1/PD-L1 plus CTLA-4 blockade suggests that smoking status is not associated with response to combination therapy. It remains an open question whether or how the molecular landscape of NSCLCs will determine response to combination immunotherapy.

We aim to prospectively evaluate the response rate to nivolumab plus ipilimumab in patients whose tumors are characterized by either high or low mutation burden. We will also compare the molecular landscape of patients treated with combination therapy to our previously generated data of the molecular features of patients treated with PD-1 blockade monotherapy.

2) Identification of candidate neoantigens:

Beyond a general increased mutational burden, there may be specific mutations that direct a T-cell response to cancer. In particular, non-synonymous somatic missense mutations have the potential to give rise to "neoantigens," which are uniquely expressed in tumor tissue and may direct anti-tumor T-cell recognition.

Neoantigens are tumor-specific antigens and should be differentiated from tumor-associated antigens, such as cancer-testis (CT) antigens, which are self-antigens that are expressed particularly but not exclusively on cancer cells (78). Although CT-antigen based therapies have been attractive targets for cancer immunotherapies (79, 80), none have yet demonstrated significant clinical activity in lung cancer (25). This lack of efficacy may be related to the fact that these antigens were subjected to thymic tolerance during early development which may restrain the degree to which an effective immunologic response can be mounted. By contrast, neoantigens are truly cancer-specific (81), are not subject to thymic tolerance, and have the potential to invoke a more significant T-cell response (82).

MSKCC has pioneered the development of bioinformatic methods to identify candidate neoantigens using DNA sequencing of tumors. Segal et al (83) evaluated a set of 1152 somatic mutations found in 11 colon and 11 breast cancers and used *in silico* modeling of the predicted binding affinity of MHC I to peptide strings containing each mutation. Peptides with high affinity MHC I binding are considered effective epitopes for generating a T-cell response and may be important neoantigens. This study revealed an average of 7–10 mutated peptides/tumor that were predicted to be effective neoantigens. Additionally, this study demonstrated that it was possible to use cancer genomics to identify mutations that are predicted to be immunologically relevant and that the identity and spectrum of neoantigens may be unique in each tumor.

Building on this initial study, several recent pre-clinical studies have highlighted the importance of neoantigens and neoantigen-specific T-cells in cancers (84-87). Of note, DuPage et al (85) demonstrated in a murine model of lung cancer that neoantigen-specific T-cells quickly infiltrated tumors, but the quantity and function of these T-cells waned quickly over time. These functionally incompetent antigen-specific T-cells appeared to have an exhausted phenotype, characterized by increased expression of PD-1. This result may recapitulate the experience in human lung cancers and highlights how T-cell checkpoint blockade may be precisely what is needed to re-establish an effective tumor-directed T-cell response.

In humans, the Schumacher lab at NKI has recently provided proof-of-concept that cancer genomic sequencing can be used to identify clinically relevant neoantigens (88). Using tumor (and matched normal) tissue from a patient with melanoma who had a durable response to ipilimumab, the authors performed whole exome sequencing to identify somatic mutations and found 1075 non-

synonymous mutations. This exome data was then combined with RNA expression data to focus only on expressed mutations. They then modeled the MHC I binding affinity of each predicted mutant protein. Those with high affinity were consider candidate neoantigens and were further studied in *in vitro* studies. Candidate neoantigens were synthesized to generate a large library of peptide-MHC multimers. Using combinatorial coding, autologous T-cells were exposed to the peptide-MHC multimers to evaluate reactive T-cell populations. Two neoantigen-specific T-cell responses were identified, including a dominant response (3.3% of CD8+ T cells) against a neoantigen derived from the *ATR* DNA damage response gene. Cultured TILs exposed to the wild-type version of ATR had no reactivity, but the addition of the mutant $ATR_{S>L}$ peptide resulted in a significant increase in T-cell reactivity. Additionally, analysis of peripheral blood samples pre- and post- treatment with ipilimumab showed a five-fold increase in the frequency of mutant $ATR_{S>L}$ specific CD8+ T cells upon treatment. Intriguingly, it is possible (but not proven) that this specific T-cell clone may have mediated the tumor regression seen in this patient after treatment with ipilimumab.

These studies have highlighted the importance of neoantigens and neoantigen-specific T-cells in mediating T-cell recognition and response to cancers. But these studies also demonstrate the complexity of identifying candidate neoantigens and neoantigen-specific T-cells, especially from human samples. We have developed a cross-disciplinary, cross-institutional collaboration to bring together the technical expertise needed to perform this study. Collectively, the ability to identify candidate neoantigens and neoantigen-specific T-cells may represent significant a breakthrough in the ability to model the interactions between the adaptive immune system and cancer and in the development of more effective (and more personalized) immunotherapies in the future.

3) Identification of neoantigen-specific T-cells

Neoantigens may represent to precise targets of the tumor-specific T-cells which are responsible for response to nivolumab. To complement and validate the *in silico* identification of candidate neoantigens, we will evaluate the presence of neoantigen-specific T-cells. The Schumacher Lab at NKI has developed *in vitro* methods for identifying neoantigen-specific T-cells using clinically relevant tissue materials (88). These methods, termed combinatorial coding, permit examination of T-cell reactivity to multiple candidate peptides in parallel. This system builds upon a peptide exchange model that uses a conditional peptide ligand that is cleaved in the presence of UV light to permit the generation of multiple different peptide-MHC complexes (89-91) and further includes fluorochrome-labeled MHC-peptide multimers such that each neoantigen of interest is coded by a unique set of fluorochromes (92, 93).

To evaluate the presence of neoantigen-specific T-cells, candidate neoantigens identified from the whole exome/transcriptome analysis above will be synthesized and used to analyze autologous intratumoral T-cells and peripheral blood lymphocytes. Autologous TILs and PBMCs isolated from the pre- and on-treatment (if feasible) as well as serial peripheral blood specimens which will be analyzed.

Secondary Objectives

4) MHC and co-stimulatory receptor/ligand expression

The validity of tumor expression of PD-L1 as a predictive biomarker of response to anti-PD1 mAb is a topic of current debate. Tumors expressing PD-L1 contain tumor-infiltrating lymphocytes (TILs) that typically express PD-1 (37, 67, 94) but are dysfunctional (32, 95-98). These data support

the hypothesis that expression of PD-L1 on tumor cells or cells in the tumor microenvironment may be an adaptive mechanism of immune escape by binding to PD-1 on TILs and quieting a tumor-directed immune attack.
In this context, it is further hypothesized that PD-L1 expression is needed for response to anti-PD1 mAb, while tumors lacking PD-L1 are insensitive to anti-PD1 mAb and evade immune surveillance using alternate mechanisms (99). Currently available data suggest PD-L1 expression may enrich for response, but is neither necessary nor sufficient (24). We will integrate an evaluation of PD-L1 expression, MHC expression, as well as other co-stimulatory ligands, in patients treated with nivolumab plus ipilimumab using IHC, flow cytometry, or other methods if become available.

Study Therapy Summary: Nivolumab plus Ipilimumab

Preclinical data indicate that the combination of PD-1 and CTLA-4 receptor blockade may improve antitumor activity. In vitro combinations of nivolumab plus ipilimumab increase IFN- □ production 2- to 7-fold over either agent alone in a mixed lymphocyte reaction. Increased antitumor activity of the combination was also observed in 3 of 5 syngeneic murine cancer models. In a murine melanoma vaccine model, blockade with either CTLA-4 or PD-1 antibodies increased the proportion of CTLA-4 and PD-1-expressing CD4/CD8 tumor infiltrating T effector cells, and dual blockade increased tumor infiltration of T effector cells and decreased intratumoral T regulatory cells, as compared to either agent alone.

The combination of nivolumab and ipilimumab was evaluated in CA209004 (MDX1106-04), a Phase 1b multiple ascending dose study in subjects with treatment-naive and previously treated advanced melanoma. Results showed promising activity, with higher, but tolerable toxicity than ipilimumab alone.16 Based on these data, CA209069, a phase 2 study, compared the combination to ipilimumab alone in treatment-naïve patients with advanced melanoma: nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks x4 followed by nivolumab 3 mg/kg every 2 weeks versus ipilimumab 3 mg/kg every 3 weeks x 4.12 In patients with BRAF wild type tumors, the ORR was 61% (44/72), including 22% (16/72) complete responses (CR) in the group treated with the combination, compared to 11% (4/37) with 0 CRs in those treated with ipilimumab alone. The median PFS was not reached in the combination versus 4.4 months for ipilimumab alone (HR=0.4). It should be noted that in the combination group, the ORR was independent of PD-L1 expression. In this group, ORR was 58% among patients with PD-L1+ tumors and 55% among those with PD-L1- tumors. In contrast, in the ipilimumab alone group, the ORR was numerically higher among patients with PD-L1+ tumors (18%) compared to those with PD-L1- tumors (4%).

Grade 3-4 treatment-related AEs were reported in 54% of patients receiving the combination compared to 24% for ipilimumab alone. Ipilimumab has been shown to have activity in lung cancer. A Phase 2 study (CA184041) in subjects with NSCLC or small cell lung cancer (SCLC) investigated the addition of ipilimumab to carboplatin and paclitaxel using 2 different schedules (concurrent and phased). The phased schedule demonstrated a significant improvement of immune-related progression-free survival as well as progression-free survival by modified WHO criteria compared to chemotherapy alone, in both NSCLC and SCLC.

Based on the initial data in melanoma, and the activity observed with nivolumab and ipilimumab in lung cancer, the nivolumab plus ipilimumab combination has been also evaluated as first-line therapy in patients with advanced NSCLC. In CA209012, early combination cohorts evaluated 2 dosing schedules that were studied in the CA209004 study in melanoma:

- nivolumab 1 mg/kg + ipilimumab 3 mg/kg, q 3 weeks x4, followed by nivolumab 3 mg/kg q 2 weeks (arms G and H, n=24);

- nivolumab 3 mg/kg + ipilimumab 1 mg/kg, q 3 weeks x4, followed by nivolumab 3 mg/kg q 2 weeks (arms I and J, n=25)

These regimens resulted in significant toxicity, with 39% of patients discontinuing treatment due to a treatment-related adverse event.

Thus, additional combination cohorts were initiated, using lower doses of both nivolumab and ipilimumab, or less frequent dosing of ipilimumab. Data from these cohorts demonstrate that both nivolumab 1 mg/kg + ipilimumab 1 mg/kg q 3 weeks with nivolumab maintenance 3 mg/kg q2w (arm N in study CA209012), as well as ipilimumab at 1 mg/kg q6w is tolerable, when given with nivolumab 3 mg/kg q2w (arm Q in study CA209012).

Overall, the safety data are not dissimilar to what has been observed in the nivolumab monotherapy arm (arm F in CA209012). Of particular note, the rate of discontinuation due to drug-related AEs was 13% in arm N and 11% in arm Q compared to 10% in the nivolumab monotherapy arm (arm F).

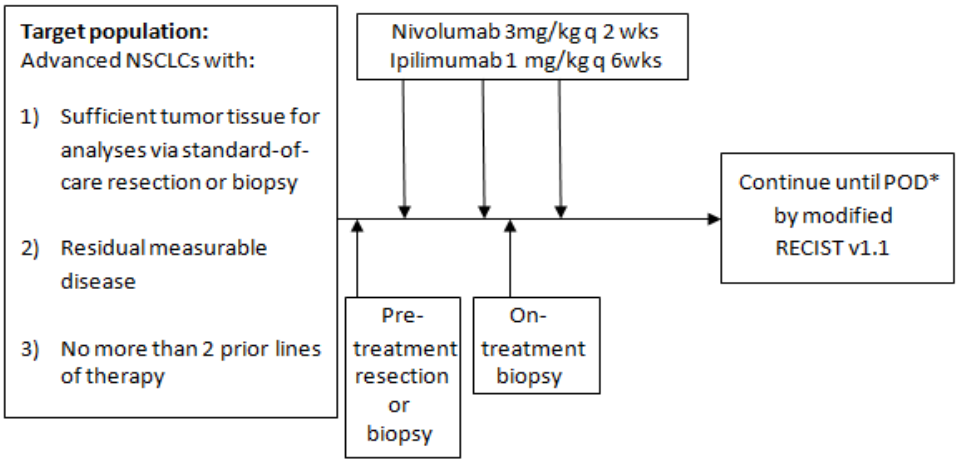
Arm	Treatment	N subjects/ arm	Follow-up time (median, wks)	N subjects still on treatment	N subjects with drug-related AEs	N subjects with grade 3-4 drug-related AEs	N subjects d/c due to drug-related AEs
N	Nivo 1mg/kg plus Ipi 1mg/kg every three weeks x 4, followed by nivo 3mg/kg every two weeks)	31	57	9 (29%)	23 (74%)	9 (29%	4 (13%)
Q	Nivo 3mg/kg every two weeks plus Ipi 1mg/kg every 6 weeks	37	18	19 (51%)	20 (54%)	9 (24%)	4 (11%)
F	Nivo 3mg/kg every two weeks	52	62	5 (10%)	37 (71%)	10 (19%)	5 (10%)

Based on these data, the following schedule will be evaluated in this study:

- Nivolumab (3 mg/kg every 2 weeks, i.e. the FDA approved dose in pretreated squamous NSCLC) with the highest dose and frequency of ipilimumab feasible (1 mg/kg every 6 weeks).

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design



This will be a single-arm, single-institution, open-label, exploratory trial of combination therapy with nivolumab plus ipilimumab in patients with advanced NSCLCs. This is an analyses-intensive trial with multiple exploratory aims. Due to the tissue required to perform these analyses, eligible patients must have advanced NSCLCs and require a pre-treatment tumor resection as standard of care. However, if pre-treatment tumor resection is not clinically indicated as standard of care, patient may instead have a pre-treatment tumor biopsy. For those patients undergoing pretreatment resection, patients must also have residual measurable disease following resection.

The objectives of this exploratory trial are descriptive in nature.

Primary objectives:

1) Quantify mutational burden and identify candidate neoantigens:
    a. We will describe the response rate to nivolumab plus ipilimumab in patients with "high" and "low" somatic mutational burden (stratified about a median of mutations/sample)
2) We will then identify candidate neoantigens by assessing the antigenicity of each expressed somatic mutation using an established bioinformatics platform. We will describe the association between the presence of candidate neoantigens and response to combination therapy.
3) Identify neoantigen-specific T-cells: We will describe the ability to identify neoantigen-specific T-cells *in vitro* using MHC-multimer assays or similar technology.

Secondary objectives

1) Examine MHC and co-stimulatory receptor and ligand expression in tumor-microenvironment: We will describe the impact of the tumor expression of MHC, PD-L1, and other co-stimulatory ligands and receptors on response to nivolumab.

4.3 Intervention

Patients who are eligible and provide study consent will undergo screening procedures and evaluation by thoracic surgery (or other appropriate surgical/interventional radiological specialty) to discuss and plan standard-of-care surgical resection or biopsy (the biopsy is research non-billable unless performed for a standard-of-care reason).

In those patients undergoing a resection, the CT scan of the chest (+/- abdomen/pelvis depending on sites of known disease) which will serve as the baseline for this protocol must be obtained after surgical procedure or biopsy has taken place. For those undergoing biopsy, the CT scan be performed before or after the biopsy but must be completed during the screening period. Additional screening procedures (including blood tests and EKG) may take place before or after surgical procedure or biopsy so long as they occur during the screening window. All screening procedures (including biopsies if performed) and scans must be done within 28 days of beginning study therapy with the exception of those undergoing tumor resections which may be performed within 12 weeks (84 days) before beginning study therapy so long as there has been no intervening systemic anti-cancer therapy.

Following resection/biopsy and screening procedures, patients will begin treatment with nivolumab IV 3mg/kg and ipilimumab 1mg/kg. Treatment with nivolumab will continue every 2 weeks (+/- 3 days) thereafter and treatment with ipilimumab will continue every 6 weeks (+/- 3 days) thereafter. Each treatment cycle will be defined as below:

- C1D1: Nivolumab 3mg/kg + Ipilimumab 1mg/kg
- C2D1 (+/- 3 days): Nivolumab 3mg/kg
- C3D1 (+/-3 days): Nivolumab 3mg/kg
- C4D1 (+/- 3 days): Nivolumab 3mg/kg + Ipilimumab 1mg/kg

Treatment will continue until protocol-defined toxicity, confirmed progression of disease*, withdrawal of consent, or death.

*Patients who experience initial progressive disease may continue therapy if they are experiencing clinical benefit. A CT scan should be repeated no earlier than 4 weeks after the first documentation of progressive disease. If there is more than10% additional progression compared to baseline (e.g. first scan showed 24% growth relative to baseline, second scan shows 36% growth relative to baseline), then study therapy should be discontinued. If, instead, <10% further progression is seen, the patient may continue study therapy until confirmed progression of disease so long as there is continued clinical benefit (detailed in Section 9.0).

Protocol-related research blood draws will occur during screening, before treatment on C1D1 (+/- 1 day), C2D1 (+/- 3 days), C2D8 (+/- 1 day from date of on-treatment biopsy), C3D1 (+/-3 days), C4D1 (+/- 3 days), C5D1 (+/- 3 days), and at the end-of-study visit.

In addition to the baseline CT scan, which will occur after pre-treatment surgical resection or biopsy, tumor assessments will be performed with CT scans of the chest (+/- abdomen/pelvis depending on sites of known disease) every 6 weeks (+/- 1 week) while on treatment for up to 48 weeks. After 48 weeks, CT scans will be performed every 12 weeks (+/- 1 week). CT scans should occur every 6 (or 12) weeks throughout the patient's time on study irrespective of treatment interruptions or delays.

In addition to pre-treatment standard-of-care surgical resection or biopsy, a protocol-mandated tumor biopsy will be required at C2D8 (+/- 1 week) for all patients who remain on study at that time. The tumor biopsy should be optimally performed on a non-target lesion, if feasible.

Study Size

30 patients will be treated on this study. Patients who enroll on study but withdrawal study consent or for any other reason never receive study therapy will be considered a screen failure and will be replaced. Additionally, in order to be considered eligible for the primary and secondary objectives described in this study, patients must receive (1) at least one dose of study therapy and remain on study until at least the first radiographic tumor assessment (week 6) or (2) at least one dose of study therapy and have clear clinical or radiographic progression prior to the planned first radiographic tumor assessment at week 6. Patients who come off study for reasons other than clinical/radiographic progression prior to the first radiographic tumor assessment will be replaced.

4.3 Rationale for dosage of nivolumab plus ipilimumab

The dose and schedule of nivolumab in combination with ipilimumab in this proposed study is nivolumab 3 mg/kg every 2 weeks and ipilimumab 1mg/kg every 6 weeks. This dose and schedule selection was based on results of safety, efficacy, and exposure-response analyses obtained from the CA209-012 study (MSKCC IRB # 11-189).

4.5 Pre-treatment tumor resection or pre-treatment biopsy

Pre-treatment tumor tissue will be obtained via surgical resection or biopsy from all patients enrolled on study. Tumor resections may be performed within 12 weeks (84 days) before beginning study therapy so long as there has been no intervening systemic anti-cancer therapy. Biopsies will be performed within the 28 day screening window.

Tumor resections will be standard-of-care. Possible indications may include a painful skin or lymph node metastasis or pleural effusions with pleural metastases which require resection and pleurodesis. However, if a standard-of-care tumor resection is not clinically indicated, patient may still fulfill pre-treatment tumor tissue requirements by having a biopsy which will be considered research non-billable unless otherwise indicated.

Initial processing of tissue from resection: In the case of those patients undergoing pre-treatment tumor resections, a portion of resected tumor tissue will be sent to pathology for diagnostic

confirmation of NSCLC and any other testing with may be required. A separate portion of tumor tissue (at least 1 x 1 x 1cm in aggregate size) will be collected from the OR or procedure room by a dedicated research assistant.

Resected tumor tissue will be delivered directly to the Wolchok Lab in ZRC15 and partitioned into at least three parts:

- One portion will be snap frozen for future DNA and RNA extraction.
- One portion will be processed as single-cell suspensions of tumor and infiltrating immune cells and then snap frozen for future T-cell assays.
- One portion will be processed as formalin-fixed tissue and will be embedded in paraffin for future IHC assays.

And if sufficient tissue is available:

- One portion will be processed fresh and infiltrating T-cells will also be isolated.

Initial processing of tissue from biopsy: In the case of those patients undergoing pre-treatment biopsies, image-guided core needle tumor biopsies are recommended.

Patient will undergo up to 5 core biopsies, if can be performed safely:

- Core #1 and #3 will be snap frozen for future DNA and RNA extraction.
- Core #2 will be placed in formalin, fixed, and embedded in paraffin.
- Core #4 and #5 (or more) will be processed either as snap frozen or as single-cell suspensions of tumor and infiltrating immune cells and then snap frozen for future antigen-specific T-cell assays.

If it is only possible to safely obtain fewer than five cores, priority will be given as numbered above.

A research assistant or investigator will be present at the time of the either resection or core biopsy to assess with material handling and processing.

Sufficient material must be collected to permit at least (1) frozen material for DNA/RNA extraction, and (2) FFPE material for IHC. Within 5 business days of each collected case, the adequacy of material collected with be reviewed and determination made regarding eligibility.

4.6 On-treatment tumor biopsy

On-treatment tumor tissue will be obtained from all patients enrolled on study on C2D8 (+/- 1 week).

Image-guided core needle tumor biopsies are recommended and the biopsied lesion is preferred not to be a target lesion.

Patients will undergo up to 5 core biopsies, if can be performed safely:

- Core #1 and #3 will be snap frozen for future DNA and RNA extraction.
- Core #2 will be placed in formalin, fixed, and embedded in paraffin.

- Core #4 and #5 (or more) will be processed either as snap frozen or as single-cell suspensions of tumor and infiltrating immune cells and then snap frozen for future antigen-specific T-cell assays.

If it is only possible to safely obtain fewer than five cores, priority will be given as numbered above.

A research assistant or investigator will be present at the time of the core biopsy to assess with material handling and processing.

4.7 Tumor-based studies

Tumor (and matched normal) whole exome and transcriptome sequencing for evaluation of mutational burden:

Tumor DNA, matched normal DNA, and tumor RNA will be extracted for whole exome and transcriptome analysis. Once DNA has been obtained and extracted, we will perform massively parallel sequencing of the whole exome of the tumor tissue and the available normal tissue. Genomic DNA will be captured via solution-based hybrid selection and sequenced on the Illumina HiSeq platform. Matched normal DNA will also be collected from whole blood and sequenced in conjunction with somatic tumor DNA. This is necessary to make variant calls in next-generation sequencing assays. It is not the intent of this analysis to utilize these samples to identify germline susceptibility mutations. However, in the course of investigating somatic sequence variations, germline susceptibility variants may be suggested by comparative germline sequencing. In addition, some somatic mutations are themselves directly suggestive of a germline predisposition (e.g. *BRCA1*).

The following plan will be followed by MSKCC investigators who identify a potentially actionable incidental finding in the course of research conducted on samples collected under this protocol:

> In the event an investigator's research identifies a finding that he or she believes should be communicated to the subject (and/or family designee), the investigator shall communicate this to the OCR-IRB. The finding will be reviewed by a group convened by the IRB to determine whether the incidental finding should be discussed with the subject. In the event that group convened by the IRB determines that the finding should be discussed with the subject, and the subject has consented to be re-contacted, then the treating/consenting physician shall be contacted by the OCR-IRB representative and asked to refer the subject to the Clinical Genetics Service for further discussion of th research finding. After appropriate counseling and consent, the Clinical Genetics Service will request permission to confirm the result in a New York DOH-approved laboratory prior to communication of the specific result. If the patient is not available (e.g. deceased), then the surrogate designated on the consent will be contacted and the above will occur.

Germline BAM files will not be separately analyzed in the future without additional informed consent (such as responded YES to question 4 on the IRB# 06-107 consent form or consenting to IRB #12-245), anonymization, and/or human subjects review by this committee or the IRB.

The somatic sequencing data will be analyzed for base mutations, insertions, fusions, deletions, copy number alterations and in all target genes. Exon capture will be performed using the SureSelect

Human All Exon 50MB kit (Agilent). Enriched exome libraries will be sequenced on the HiSeq 2000 platform (Illumina) to >100X coverage. Raw sequencing data will be mapped to the human reference genome using the BurrowsWheeler Aligner (BWA). All filtered candidates will be annotated and manually reviewed (103) using the Integrated Genomic Viewer (IGV) (104). Mutations will be annotated using SnpEffect (105). In order to improve quality of calls in these FFPE samples, mutations will be analyzed using four callers: Somatic Sniper (106), VarScan (107), Strelka (108) and MuTect (109) then filtered by allelic frequency of each alteration in tumor (>10%) and normal (<3%), depth of coverage (≥7X) and call quality. Calls made by only one caller will be manually reviewed using IGV (104).

Whole transcriptome tumor mRNA will be sequenced using next-generation sequencing. Briefly, after ribogreen quantification and quality control of Agilent BioAnalyzer (RIN>7), poly(A) RNA will be isolated using Dynabeads® mRNA DIRECT™ Micro Kit(Life Technologies) from 1ug of total RNA. mRNA is then fragmentated using RNaseIII and purified. The Fragmented Samples quality and yield are evaluated using Agilent BioAnalyzer. Subsequently, the fragmented material will undergo Whole transcriptome Library preparation according to the Ion Total RNA-Seq Kit v2 protocol (Life Technologies), with 12 to 16 cycles of PCR. Samples will be barcoded, template-positive Ion PI™ Ion Sphere™ Particles (ISPs) will be prepared using the ion one touch system II and Ion PI™Template OT2 200kit v2 Kit (Life Technologies). Enriched particles will be sequenced on a Proton sequencing system using 200bp version 2 chemistry. An average of 70 to 80 million reads will be generated per samples.

Bioinformatic Analysis - identification of candidate neoantigens:

We have developed a bioinformatic pipeline to use whole exome sequencing to identify candidate neoantigens. Neoantigens are modeled *in silico* by examining the components of antigen presentation on MHC (*antigenicity)* (110). Expressed somatic missense mutations are translated into pairs of short peptide strings: one including the mutation and one corresponding to the wild-type sequence. Next, *in silico* analysis is performed using NetMHC (http://www.cbs.dtu.dk/services/NetMHC-3.2/ (111, 112)) or similar algorithm to predict the binding affinity of a given peptide for patient-specific MHC I. IEDB (http://www.iedb.org (84)) can also used to predict the induction of a T-cell response to a given amino acid peptide sequences or that have sequence homology to known antigens. Candidate neoantigens of particular interest will be identified by having predicted class I MHC binding affinity to patient-specific HLA alleles of at least 500nM.

The binding affinity of a given candidate neoantigen is dependant in part on the specific MHC I and II alleles that are presenting the antigen. Although initial studies restricted analysis to the predicted binding affinity to HLA-A*02:01 (83), the most common allele in Caucasians, NetMHC 3.2 is now able to predict the nanomolar peptide binding affinity of nearly any human HLA allele (113). Exome sequencing done above may not provide sufficient coverage to accurately determine the patient-specific HLA allele, so HLA typing may be performed separately using normal DNA.

Co-stimulatory receptor and ligand expression:

FFPE tumor tissue collected from pre-treatment tumor resection and on-treatment biopsy will be examined for expression of PD-L1 on tumor and microenvironment cells by immunohistochemical (IHC) staining with the 28-8 antibody, and/or alternative method(s) if available. 3rd party vendors

have also developed IHC stains which may be used. In addition to PD-L1, there are other surface markers that may mediate immunogenicity and selective sensitivity to different immunotherapy approaches. These include, but are not limited to, MHC I, MHC II, PD-1, LAG-3, TIM-3 which can be examined by IHC, immunofluorescence, and/or flow cytometry.

4.8 Peripheral blood-based studies

Identification of neoantigen-specific TILs and PBMCs:

To evaluate the presence of neoantigen-specific T-cells from TILs and/or PBMCs, candidate neoantigens identified from the whole exome/transcriptome analysis above will be synthesized and used to analyze autologous T-cells. Autologous T-cells will be collected in the form of either single cell suspensions of T-cells and/or as CD3/CD4/CD8+ selected cells isolated fresh from resected, digested tumor tissue and/or PBMCs.

Isolated T-cells will be frozen and examined at MSKCC or in collaboration with outside investigators with relevant expertise (MTA will be obtained). All biospecimens will be anonymized and labeled with a unique study ID prior to analysis. Coding linking the identifiers with the unique study ID will be retained by the listed investigators at MSKCC, but will not be shared outside of the institution.

To identify neoantigen-specific T-cells, the Schumacher lab has developed a technology called combinatorial coding (89, 93) that permits high-throughput detection of antigen-specific T-cells to multiple potential antigens in parallel. Briefly, using synthesized peptides from candidate neoantigens, large quantities of fluorochome-labeled peptide-MHC complexes are generated such that each neoantigen is coded by a unique fluorochrome combination. Then, using conditional MHC ligands that are cleaved upon exposure to UV-light, empty, peptide-reactive MHC molecules are then be exposed autologous T-cells and reactivity of TILs to peptide-MHC complexes will be assessed and quantified by flow cytometry. Neoantigen-specific T-cells will be isolated and may be expanded and used for future experiments, including treatment of autologous PDX models.

In addition to these methods, the Wolchok lab has also developed methods for identifying antigen-specific T-cell responses by IFN-gamma ELISpot assay, tetramer staining, and ICS assay. These assays had been well validated at Immune Monitoring Core at MSKCC (114).

For the ELISpot assay, multi-screen IP plates will be coated with 10 ug/ml anti-human IFN- gamma T cells will be re-stimulated with neoantigen derived peptides, then IFN-gamma production detected by addition of biotinylated mouse-anti-human IFN-gamma Ab using the AEC substrate Vector ABC kit (Vector Laboratories, Burlingame, CA) and analyzed with an Automated CTL ImmunoSpot Analyzers (C.T.L., Shaker Heights, OH). For tetramer staining, HLA-class I-PE labeled tetramers will be loaded with neoantigen peptides (Tetramer Core, Lausanne Branch, Ludwig Cancer Research). 5×10^5 cells are incubated with 0.5 µl of peptide-loaded tetramer, followed by incubation with antibodies to surface markers (PE-Cy7-CD3, APC-CD27, PerCPCy5.5-CD28 [BD, Pharmingen, San Jose, CA], APC-

AF750-CD8 [eBioscience, San Diego, CA], ECD-CD45RA [Beckman Coulter Inc., Fullerton, CA] and FITC-CCR7 [R&D Systems, Minneapolis]). Cells are acquired using a CYAN flow cytometer (Dako Cytomation California Inc., Carpinteria, CA) and analyzed using FlowJo software (version10.1; TreeStar, Inc.). Intracellular cytokine staining: Two million cultured autologous patient T cells (PBMC or TILs) are incubated with PE-Cy5-CD107a then stimulated with the addition of neoantigen peptides followed by Brefeldin A and monensin (BD Bioscience). After staining with pacific blue-CD3, APC-AF750-CD8 (Ebioscience) and ECD-CD4 (Beckman Coulter), washing and permeabilizing, the cells are stained with FITC-IFN-gamma PE-Cy7-TNF-alpha and APC-IL-2 (BD Pharmingen) and analyzed by flow cytometry as described above.

As improvements in technology and scalability permit, alternative strategies for identifying neoantigen-specific T cells in treated patients may be explored.

5.1 THERAPEUTIC/DIAGNOSTIC AGENTS

Product description - Nivolumab					
Description	Potency	Primary packaging(volume)/label type	Secondary packaging(qty)/label type	Appearance	Storage conditions (per label)
"BMS-936558-01 Solution for Injection" Injection drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL	100mg (10mg/mL)	10 mL per vial/Open-label	10 vials per carton/Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles.	2 to 8 degrees Celsius. Protect from light and freezing.
Ipilimumab Solution for Injection	200 mg (5 mg/ml)	40 ml vial	4 vials per carton/Open-label	Clear, colorless to pale yellow liquid. May contain particles	2 to 8 degrees Celsius. Protect from light and freezing.

Ordering of Nivolumab and Ipilimumab

Following submission and approval of the required regulatory documents, a supply of nivolumab and ipilimumab may be ordered from by completing a Drug Request Form. The first request may take place upon screening of the first patient.

Nivolumab vials (10 mL) are shipped in quantities of ten. The initial order should be limited to 20 vials (2 cartons of 10 vials each). Ipilimumab vials (40 mL) are shipped in quantities of four. Allow 5 business days for shipment of drug from BMS receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. All drug product will be shipped by courier in a temperature-controlled container. It is possible that sites may have more than one nivolumab clinical study ongoing at the same time. It is imperative that only drug product designated for this protocol number be used for this study.

Drug re-supply request form should be submitted electronically business days before the expected delivery date. Deliveries will be made Tuesday through Friday.

When assessing need for resupply, institutions should keep in mind the number of vials used per treatment dose, and that shipments may take 14 business days from receipt of request. Drug is not patient-specific. Be sure to check with your pharmacy regarding existing investigational stock to assure optimal use of drug on hand.

Storage of Nivolumab and Ipilimumab

Nivolumab and Ipilimumab should be stored in a secure area according to local regulations. Temperature monitoring of the storage area must be performed by site as per local practice and any temperature deviations reported to Sponsor. The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as described in the Investigator's Brochures. Nivolumab and Ipilimumab vials must be stored at a temperature between 2°C and 8°C and should be protected from light and freezing. These products do not contain anti-microbial preservative nor bacteriostatic agent so care must be taken to assure drug sterility.

After nivolumab has been prepared for administration, the total storage time (combination of refrigeration and room temperature) is not to exceed 24 hours. IV bags containing undiluted and diluted solutions of nivolumab injection prepared for dosing may be stored up to 20 hours in a refrigerator at 2°-8°C (36°-46°F) and used within 4 hours at room temperature and under room light. The maximum 4-hour period under room temperature and room light conditions for undiluted and diluted solutions of Nivolumab injection in the IV bag should be inclusive of the product administration period. Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between nivolumab and polyolefin bags have been observed.
After ipilimumab has been prepared for administration, the total storage time (combination of refrigeration and room temperature) is not to exceed 24 hours. IV bags containing undiluted and diluted solutions of ipilimumab injection prepared for dosing may be stored up to 24 hours in a refrigerator at 2°C to 8°C or at room temperature/room light. The maximum 24 hour period under room temperature and room light conditions for undiluted and diluted solutions of ipilimumab injection in the IV bag should be inclusive of the product administration period.

Detailed instructions on prepared drug storage and use can be found in the Investigator Brouchures, under "Recommended Storage and Use Conditions."

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as described in the Investigator's Brochure.

Dispensing of Nivolumab and Ipilimumab

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.

Nivolumab and ipilimumab product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage,

administration and, as applicable, storage temperatures, reconstitution, and use of required processes (e.g., required diluents, administration sets).

Nivolumab and Ipilimumab Dosing

Patients will receive treatment with nivolumab as a 30 minute infusion 3 mg/kg every 2 weeks and ipilimumab as a 30 minute infusion 1 mg/kg every 6 weeks, starting on Day 1, until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

When nivolumab and ipilimumab are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The second infusion will always be ipilimumab and will start no sooner than 30 minutes after completion of the nivolumab infusion.

Nivolumab and ipilimumab may be diluted in 0.9% Sodium Chloride Solution or 5% Dextrose solution.

Dosing calculations should be based on the body weight assessed during screening. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the prior dose, the dose must be recalculated. All doses should be rounded per local standards for rounding.

There will be no dose modifications allowed.

Subjects may be dosed with nivolumab no less than 12 days from the previous dose.

There are no premedications recommended.

Subjects should be carefully monitored for infusion reactions during nivolumab and/or ipilimumab administration. If an acute infusion reaction is noted, subjects should be managed according to Section 11.4.

Doses of nivolumab and/or ipilimumab may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment. See Sections 11.5-11.7 for more details regarding dose delays, retreatment, and discontinuations.

Destruction of Nivolumab and Ipilimumab

Study drugs supplied by BMS such as partially used study drug containers, vials and syringes may be destroyed on site and their disposition should be recorded on an investigational drug accountability form according to the institution's SOP.

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 BMS to review throughout the clinical trial period.

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.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

Describe the characteristics of the patient/subject population.

6.2 Subject Inclusion Criteria

1. Patient must be capable, willing, and able to provide written, informed consent.
2. ≥ 18 years old.
3. Advanced stage NSCLC
4. Previously treated with no more than two lines of prior systemic therapy for advanced stage lung cancer.
    a. Patients who previously received neoadjuvant, concurrent, or adjuvant chemotherapy for localized NSCLC and then recurred within 6 months of completing chemotherapy may be considered as having received one line of prior therapy
    b. Maintenance therapy does not count as a separate line of therapy
5. Patients must:
    a. Be scheduled to undergo a standard-of-care resection of tumor tissue as part of treatment plan prior to beginning study therapy OR have pre-treatment biopsy. Patients may not have intervening systemic anti-cancer therapy between the time of resection/biopsy and treatment with nivolumab.
    b. Have collection of adequate pre-treatment tissue for correlative analysis defined as sufficient material for 1) frozen tissue for DNA/RNA extraction, 2) FFPE material for IHC. Adequacy of collected material will be determined within 5 business days of each collected case.
    c. Have measurable by RECIST v1.1 (those undergoing pre-treatment resection must have imaging assessment after resection to determine measurability)
        i. Previously irradiated sites of tumor may be considered measurable if there is radiographic progression at that site subsequent to the time of completing radiation.

d. Have a safely biopsiable tumor lesion

6. ECOG performance status of 0-1.
7. Adequate hematologic, renal, and/or hepatic function (following criteria must be met within 28 days of C1D1):
    a. WBC ≥ 2,000/ul
    b. ANC ≥ 1,500/ul
    c. Hemoglobin ≥ 9.0 g/dl
    d. Platelet count ≥ 100,000/ul
    e. Total bilirubin ≤ 1.5 x ULN (unless evidence of Gilbert's syndrome, in which case, direct bilirubin must be ≤ 1.0 x ULN)
    f. AST and ALT ≤ 3 x UNL (unless elevated transaminases are felt to be directly related to metastatic disease involving the liver, in which case AST and ALT must be ≤ 5x ULN)
    g. Serum creatinine ≤ 1.5 x ULN or estimated creatinine clearance of ≥ 40 mL/min calculated using the formula of Cockcroft and Gault: (140-Age) • Mass (kg)/(72 • creatinine mg/dL); multiply by 0.85 if female
8. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 3 days prior to the start of study drug.
9. Effective contraception:
    h. Women of childbearing potential must agree to practice 2 effective methods of contraception from the time of signing the informed consent form through 23 weeks (5 half-lives plus 30 days, the duration of an ovulatory cycle) after the last dose of nivolumab, or agree to completely abstain from heterosexual intercourse.
    i. Male subjects, even if surgically sterilized (i.e., status post vasectomy) must agree to 1 of the following: practice effective barrier contraception during the entire study treatment period and through 31 weeks (5 half-lives plus 90 days, the duration of sperm turnover) after the last dose of study drug, or completely abstain from heterosexual intercourse.

6.3 Subject Exclusion Criteria

10. Patients who are pregnant or lactating.
11. Presence of activating *EGFR* mutations or *ALK* re-arrangement unless previously treated with standard TKI therapy. All patients with adenocarcinoma histology must be tested for *EGFR* and *ALK* status.
12. History of allergy to study drug components or history of severe hypersensitivity reaction of any monoclonal antibody.
13. Prior treatment with immune checkpoint inhibitor, including (but not limited to) those targeting PD-1, PD-L1, PD-L2, CTLA-4, CD137, GITR, TIM3, LAG3, or OX40
14. Any systemic anti-cancer therapy within 3 weeks prior to C1D1 of study therapy

j. Exception is made for patients with *EGFR* or *ALK* re-arrangements who must have stopped TKI therapy at least 7 days prior to C1D1

15. Patients who have not previously been treated with platinum-based based doublet chemotherapy and who, in the judgment of the investigator, have rapidly progressive disease such that serious complications may arise from disease progression within the next 12 weeks will be excluded
16. Non-CNS radiotherapy within 1 week prior to C1D1 of study therapy
17. Active infection requiring therapy
18. Prior or current systemic immunosuppressive therapy (> 10 mg/day prednisone equivalents) within 1 week prior to C1D1 of study therapy. Inhaled, ocular, intra-articular, intranasal, and topical corticosteroids are permitted in absence of active autoimmune disease.

    k. Adrenal replacement doses are permitted in the absence of active autoimmune disease.

19. Patients with known or suspected history of autoimmune disease. Subjects with type I diabetes melitis, hypothyroidism only requiring hormone replacement, resolved childhood asthma/atopy, patients with asthma requiring intermittent bronchodilator therapy, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
20. Other active malignancy requiring concurrent intervention.
21. Patients with previous malignancies (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, cervical/dysplasia, melanoma, or breast) are excluded unless definitive therapy has been completed at least 1 year prior to study entry and the patient is now without evidence of disease from that malignancy and no additional therapy is required or anticipated to be required during the study period.
22. Known untreated brain or leptomeningeal metastasis.

    l. Patients with brain metastases are eligible if metastases have been adequately treated and neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least two weeks prior to C1D1.

23. Patients with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.
24. Any positive test for HIV
25. Any positive test for HCV RNA or HBsAg.

7.0 RECRUITMENT PLAN

A member of the patient's treatment team, the protocol investigator or research team at Memorial Sloan-Kettering Cancer Center will identify potential research participants. If the investigator is a part of the treatment team, s/he will screen the patient as to eligibility, and will discuss the study and the possibility of enrollment in the research study with the patient. The preliminary screen of eligibility will be confirmation of the diagnosis of NSCLC, ascertaining the exact stage of the disease, and confirmation of the presence of appropriate need for pre-treatment tumor resection.

Potential subjects that meet these basic criteria may be referred by their treating physician to the investigator/research staff of the study. Minorities and women are well represented in the thoracic oncology clinics, and we expect that they will be well represented in the trial accrual. The principal investigator will be available to all patients for further questions and information through a contact number which will be provided on the consent form itself.

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 MSKCC in order to further assess eligibility. 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.

8.1 PRETREATMENT EVALUATION

All aspects of the screening evaluation should be completed within four weeks of starting treatment unless otherwise noted.

- Documented (or suspected) histologic/pathologic diagnosis of NSCLCs and radiographic/pathologic evidence of advanced stage disease
    - Patients who are highly suspected to have advanced stage NSCLCs and who are planned for a standard-of-care diagnostic tumor resection or biopsy may also be enrolled. Patients who are confirmed to have advanced stage NSCLCs will be eligible to continue with screening procedures. Those who are found after surgery/biopsy to not have advanced stage NSCLCs will not be eligible continue with screening procedures and may not receive study therapy.
- Standard-of-care tumor resection or pre-treatment biopsy (resection within 12 weeks of beginning nivolumab plus ipilimumab, biopsy within screening period) and successful collection of sufficient pre-treatment tumor tissue for planned correlative studies. If patient is a candidate for a standard-of-care tumor resection, patient will be consented to a separate screening consent to permit collection of tissue at the time of the procedure, in addition to tissue that will be collected for routine pathology evaluation.
- Full medical history.
- Physical examination, complete vital signs (pulse, blood pressure, temperature, respiratory rate, oxygen saturation), as well as weight and height.
- 12-lead electrocardiogram (EKG) recorded at MSKCC at any point in the last 3 months.
- Performance status by ECOG.
- Baseline tumor assessment with CT scans at least of the chest (+/- abdomen/pelvis depending on sites of known disease) but should also include all known non-CNS sites of disease. Tumor burden must be measurable using RECIST 1.1. IV and PO contrast is preferred but not required.
    - For those undergoing resection, the screening CT scan which will be used for the baseline tumor measurements during this protocol should be obtained after the patient has completed the pre-treatment tumor resection. Other screening

assessments may be completed prior to or after tumor resection, so long as they occur during the screening period.

- Serum or urine pregnancy test for women of childbearing potential must be performed within 3 days prior to the initial administration of study therapy.
- Complete blood count with differential.
- Comprehensive metabolic panel (glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate, calcium, total protein, albumin, bilirubin, alkaline phosphatase, ALT, AST), magnesium, LDH, amylase, lipase
- HIV antibody, Hepatitis B surface antigen, Hepatitis C antibody (with RNA if antibody is positive)
- Thyroid function test (TSH, with reflexive free T4/T3 if TSH is abnormal).
- Research blood:
    - Germline DNA
    - PBMCs

9.1 TREATMENT/INTERVENTION PLAN

This protocol is an open-label, single-arm, phase 2 trial of nivolumab plus ipilimumab patients with advanced NSCLCs.

Nivolumab and Ipilimumab

Patients will receive treatment with nivolumab at a dose of 3 mg/kg as a 30-minute IV infusion, on Day 1 of each treatment cycle every 2 weeks. Patient will receive treatment with ipilimumab at a dose of 1 mg/kg as a 30 minute infusion every 6 weeks. The second infusion on combination treatment days will always be ipilimumab and will start approximately 30 minutes after completion of the nivolumab infusion. This treatment schedule will continue until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

Dosing calculations should be based on the body weight at time of screening visit. It is not necessary to re-calculate the dose if the patient's weight is within 10% of baseline weight or prior dose weight. All doses should be rounded to the nearest milligram.

There will be no dose escalations or reductions of nivolumab or ipilimumab allowed. Patients may be dosed no less than 12 days from the previous dose. There are no premedications recommended for nivolumab on the first cycle.

Patients should be carefully monitored for infusion reactions during nivolumab and ipilimumab administration. If an acute infusion reaction is noted, subjects should be managed according to Section 11.4.

Doses of nivolumab or ipilimumab may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment. See Sections 11.5-11.7 for more details regarding dose delays, retreatment, and discontinuations.

Cycle 1 Day 1: Initiation of nivolumab plus ipilimumab

At each study visit, performance status, vital signs (including oxygen saturation), a physical exam, toxicity evaluation, review of current medications and blood tests will be performed. Blood tests must be performed on the day of the study visit.

Nivolumab 3mg/kg IV and ipilimumab 1mg/kg will be initiated on cycle 1, day 1.

Cycle 2 Day 1 (+/- 3 days) – Treatment visit, blood collection, toxicity visit

At each drug-administration visit, performance status, vital signs (including oxygen saturation), a physical exam, toxicity evaluation, review of current medications and blood tests will be performed. Blood tests must be performed on the day of the study visit or within the 2 days prior to the study visit.

Patient will be treated with Nivolumab 3mg/kg IV alone on Cycle 2 Day 1.

Cycle 2 Day 8 (should be same day as C2D8 biopsy, +/- 1 day from date of biopsy) – Research blood collection

Patients will have research blood collection on C2D8.

Cycle 2 Day 8 (+/- 1 week) – On-treatment tumor biopsy

An on-treatment tumor biopsy of (ideally) a non-target lesion will occur on C2D8 (+/- 1 week, i.e. during week 3-4 of study treatment). Acceptable samples include core needle biopsies for tumor tissue or lymph nodes or excisional, incisional, punch, or forceps biopsies for cutaneous or subcutaneous lesions. The safest and most feasible tissue biopsy is preferred and will be at the discretion of the treating physician. For core needle biopsies, five cores are preferred but at least three cores should be obtained; 1 will be fixed in formalin, 3 will be immediately frozen and then stored, and 1 will be processed fresh to isolate CD4/CD8+ cells prior to freezing.

Cycle 3 Day 1 (+/- 3 days) – Treatment visit, toxicity visit

At each drug-administration visit, performance status, vital signs (including oxygen saturation), a physical exam, toxicity evaluation, review of current medications and safety blood tests will be performed. Blood tests must be performed on the day of the study visit or within the 2 days prior to the study visit. Research bloods will be collected at C3D1 visit.

Patient will be treated with Nivolumab 3mg/kg alone on C3D1.

Cycle 4 Day 1 (+/- 3 days) – Treatment visit, toxicity visit

At each drug-administration visit, performance status, vital signs (including oxygen saturation), a physical exam, toxicity evaluation, review of current medications and safety blood tests will be performed. Blood tests must be performed on the day of the study visit or within the 2 days prior to the study visit. Research bloods will be collected at C4D1 visit.

Patient will be treated with both Nivolumab 3mg/kg and Ipilimumab 1mg/kg on C4D1.

Subsequent study visits

Patients will return for nivolumab administration, blood collection, and toxicity visit every two weeks (+/- 3 days) thereafter. Patient will be treated with both nivolumab and ipilimumab on Day 1 of every third cycle (i.e. every six weeks, +/- 3 days). Performance status, vital signs (including oxygen saturation), a physical exam, toxicity evaluation, review of current medications, and blood tests will be performed at each visit. Research bloods will be collected at C5D1 and at end-of-treatment visit. Blood tests must be performed on the day of the study visit or within the 2 days prior to the study visit.

Tumor assessment with CT scan – Beginning Week 6 (+/- 1 week)

Tumor assessments must include at least CT scans of the chest (+/- abdomen/pelvis depending on sites of known disease). IV (and PO, if abdomen/pelvic CT obtained) contrast is preferred but not required. Bone or PET scans are not adequate for assessment of RECIST 1.1 response in target lesions. The same radiographic procedure should be used to assess disease sites at screening should be used throughout the study (e.g. the same contrast protocol for CT scans). All known sites of disease must be documents at screening and re-assessed at each subsequent tumor evaluation (with exception of CNS lesions which do not need to be examined at each assessment). Scans should be performed and response assessed by RECIST v1.1 prior to patient's next study visit to determine if treatment should be continued.

Tumor assessments will be performed after 6 weeks (+/- 1 week) and subsequently every six week (+/- 1 week) while on study until week 48. After week 48, tumor assessments will be conducted every 12 weeks (+/- 1 week). Additional tumor assessments may be performed at the discretion of the treating physician.

Toxicity monitoring and adverse events

Patients should be assessed for toxicity at least every 2 weeks so long as patient remains on study. Safety blood tests must be performed on the day of the study visit or within the 2 days *prior* to the study visit.

Toxicity will be evaluated in this study through the monitoring of all serious and non-serious AEs, defined and graded according to NCI CTCAE v4.0.

Follow-up Assessments Prior to Progression of Disease

Patients who discontinue study treatment early for reasons other than disease progression (e.g. toxicity) should continue to undergo scheduled tumor assessments per protocol until the patient experiences confirmed progression, starts new anti-cancer treatment, withdraws consent, or dies, whichever occurs first.

Treatment beyond Disease Progression:

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD (115). Subjects treated with nivolumab plus ipilimumab will be permitted to continue nivolumab plus ipilimumab treatment beyond initial RECIST 1.1 defined PD, assessed by the investigator, as long as they meet the following criteria:

- Investigator-assessed clinical benefit, and do not have rapid disease progression.
- Tolerance of study drug
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases)
- Subject provides written informed consent prior to receiving additional nivolumab treatment acknowledging the possibility of any reasonably foreseeable risks or discomforts, as well as the possibility of alternative treatment options.

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

If the investigator feels that the nivolumab plus ipilimumab subject continues to achieve clinical benefit by continuing treatment, the subject should remain on the trial and continue to receive monitoring according to the Study Calendar in Section 10.0. A radiographic assessment/CT scan should be performed no earlier than 4 weeks after original PD to determine whether there has been a decrease in the tumor size or continued PD.

For the subjects who continue nivolumab plus ipilimumab study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden compared to baseline above the degree of progression determined at the time of initial PD (e.g. if progression of disease is determined with 24% growth from baseline and a subsequent confirmatory scan shows 33% growth compared to baseline (but 9% growth compared to initial PD) patient an continue on therapy. However, if there is 36% growth compared to baseline (and 12% growth compared to initial PD, patient should be discontinued from study treatment). This includes an increase in the sum of diameters of all target lesions and/or the development of new measurable lesions.

New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measureable at the time of initial progression may become measureable and therefore included in the tumor burden volume if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm).

Nivolumab/ipilimumab treatment should be discontinued permanently upon documentation of further progression.

Palliative Local Therapy

Palliative local therapy, including palliative (limited-field) radiation therapy and palliative surgical resection, is permitted prior to discontinuation of study treatment if the following criteria are met:

1) The subject is considered to have clinically or radiographically progressed at the time of palliative local therapy and meets criteria to continue with treatment beyond progression in the section above.
2) The lesion planned for palliative local radiation is not a target lesion used for assessing radiographic response
3) The case is discussed with the PI-Sponsor prior to the initiation of palliative local therapy. Palliative therapy must be clearly documented as such in the study record.

The potential for overlapping toxicities with radiotherapy and nivolumab plus ipilimumab currently is not known. If palliative radiotherapy is required for a tumor lesion, study therapy should be withheld for at least 1 week before, during, and 1 week after radiation. Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs should resolve to Grade ≤ 1 prior to resuming nivolumab or ipilimumab.

Follow-up Assessments after Last Dose of Study Treatment

Patients will be followed for safety for 100 days following their last dose of study treatment. Patients who have an ongoing study-treatment related adverse event at the time of study completion or at discontinuation from the study will be followed until one of the following occurs: the event has resolved to baseline grade, the event is assessed by the study doctor as stable, new anti-cancer treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that the study treatment or participation was not the cause of the AE.

All patients will be followed for survival and subsequent anti-cancer therapy approximately every 3 months until death, loss to follow-up, or study termination.

End of Study

The end of study is defined as the date of the last follow-up visit of the last patient enrolled and is expected to occur approximately 4 months after the last patient enters the study.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

	Screening	C1D1	C2D1	C2D8	C3D1	Each cycle thereafter Day 1	Final visit[14]
	Within 28 days of C1D1 unless otherwise noted		+/- 3 days	See note below[13]	+/- 3 days	+/- 3 days	100 days after last dose of study therapy (+/- 2 weeks)
Informed screening consent[1]	X						
Informed treatment consent	X						
History[2], Physical [3,4,5]	X	X	X		X	X	X

Pregnancy test for WOCBP[6]	X[6]						
Comprehensive metabolic panel, Mg, LDH, amylase, lipase[7]	X	X	X		X	X	X
Complete blood count[7]	X	X	X		X	X	X
Thyroid function test[8]	X	X				Every third cycle	X
Hepatitis B, C, HIV	X						
EKG	X						
Adverse event assessment and attribution[9]	X	X	X		X	X	X
Radiographic tumor assessment[10]	X					Every 6 (or 12) weeks[10]	X
Research blood tests	X[11]	X[12]	X[12]	X[13]	X[12]	C4D1, C5D1[12]	X[12]
Pre-treatment tumor resection or biopsy	X (resection permitted within 12 weeks)						
Biopsy				X[13]			
Nivolumab 3mg/kg q 2 weeks		X	X		X	X	
Ipilimumab 1 mg/kg q 6 weeks		C1D1 and every 6 weeks (+/- 3 days)					

[1] Patients will be consented separately for screening consent by either medical oncologist or thoracic surgeon.

[2] Medical history includes baseline symptoms as well as detailed history of prior cancer therapies including start and stop dates, disease progression during or after therapy, as well as discontinuations due to intolerability or any other serious illness

[3] Body height to be measured at screening only

[4] Vital signs include weight, temperature, pulse, blood pressure, and oxygen saturation

[5] Full physical exam for baseline and end of study visit. Other study visit physical exams may be symptom directed.

[6] Applicable for women of childbearing potential. Serum or urine beta-HCG test within 3 days before the first dose of study drug.

[7] Screening safety blood tests (CBC and CMP) must be done within 28 days of C1D1. Subsequent safety blood tests may be performed the day of the study visit or within 2 days *prior* to the study visit.

[8] Thyroid function tests (TSH, reflexive free T4/free T3 if TSH is abnormal) should be performed at baseline, C4D1, and then D1 of every third cycle thereafter.

[9] Adverse events will be graded and attributed using CTCAE 4.0

[10] Tumor assessments will be performed with CT scan of the chest (+/- abdomen/pelvis depending on sites of known disease) but should also include all known sites of cancer (with exception of previously treated CNS lesions which do not need to be examined at each assessment). Scheduled on-treatment tumor assessments should begin 6 weeks after beginning nivolumab and continue thereafter every 6 weeks irrespective of dose interruptions or delays during the first 48 weeks of treatment, and every 12 weeks thereafter. Tumor assessments have a window of +/- 1 week from scheduled day. If an appropriate imaging study is done for an unrelated reason, it can be used for disease assessment.
[11] At screening, research bloods will be drawn for a) germline sequencing as a companion to somatic tumor DNA sequencing (1 blue top tube), b) T-cell subsets (4 CTP tubes)
[12] At C1D1, C2D1, C2D8, C3D1, C4D1, C5D1 and end-of-treatment, research bloods will be drawn for T-cell subsets (4 CTP tubes).
[13] The window for the on-treatment biopsy will be +/- 1 week from the date of C2D8. The corresponding research blood draw should be the same day of the on-treatment biopsy, +/- 1 day from the date of the biopsy [The +/- 1 day window should be applied to the date of the biopsy, not the date of C2D8].
[14]All patients will be followed for survival and subsequent anti-cancer therapy approximately every 3 months until death, loss to follow-up, or study termination.

11.0 TOXICITIES/SIDE EFFECTS

11.1 Nivolumab and Ipilimumab toxicity overview

Nivolumab and Ipilimumab are currently in clinical development and both have been FDA-approved for use as monotherapies respectively. The entire safety profile of nivolumab plus ipilimumab is not known at this time. Measures will be taken to ensure the safety of the patients participating in this trial, including the use of stringent inclusion and exclusion criteria and close monitoring. Toxicity grading will be performed in accordance with NCI CTCAE 4.0. If toxicities are encountered, adjustments will be made to the study treatment as detailed in the sections below. All AEs and SAEs will be recorded during the trial and for up to 100 days after the last dose of study treatment.

11.2 Risks associated with nivolumab

Likely

- Fatigue
- Skin changes including: rash, itching, hives, dry skin, or redness
- Diarrhea
- Nausea
- Abdominal pain
- Decreased appetite
- Low red blood cells
- Joint pain or stiffness

Less Likely

- Bowel inflammation
- Liver function blood test abnormalities
- Loss of color (pigment) from areas of skin
- Dry mouth
- Vomiting
- Weight loss
- Thyroid gland abnormalities
- Blood chemistry abnormalities, including low blood phosphate, magnesium, and potassium levels.
- High blood uric acid level
- Lung inflammation
- Cough
- Dizziness
- Headache
- Low white blood cell
- Chills
- Muscle soreness, weakness, stiffness, spasms, or paralysis
- Pain in arms or legs
- Tingling, burning, or numbness in hands and feet
- Shortness of breath
- Abnormal taste
- Flushing
- High or low blood pressure
- Allergic reaction during or between study drug infusions
- Increased sensitivity of skin to sunlight
- Constipation
- Difficulty swallowing
- Heartburn
- Low blood platelets (may increase risk of bleeding)

Rare but serious

- Low blood oxygen level
- Acute lung injury or failure
- Collection of fluid around the lungs
- Inflammation of the appendix
- Increase in inflammatory blood proteins (e.g., lipase)
- Adrenal gland abnormalities
- Pituitary gland inflammation
- Changes in vision, inflammation of the eye (or optic nerve), or bleeding into the eye
- Swelling of the optic disc
- Liver inflammation
- Acute kidney injury or failure

- Inflammation of the mouth and lining of the digestive tract
- Swelling of the face, arms, or legs
- Inflammation of the pancreas
- Back pain
- Autoimmune disorders, including Guillain-Barre syndrome (associated with progressive muscle weakness or paralysis)
- Chest discomfort
- Heart palpitations
- Inflammation of the heart or its lining
- Collection of fluid around the heart
- Increased blood sugar
- Dehydration
- Infections: including sepsis, lung infections, and skin infections
- Decreased movement of the intestines
- Confusion
- Inflammation of the optic nerve
- Inflammation or loss of the lining of the brain and spinal cord
- Abnormal brain function due to brain inflammation
- Drug reaction with rash, blood cell abnormalities, enlarged lymph nodes, and internal organ involvement (including liver, kidney, and lung)
- Myasthenia gravis, a nerve disease that may cause weakness of eye, face, breathing, and swallowing muscles
- Muscle breakdown or inflammation in the muscle
- Toxic epidermal necrolysis, a potentially fatal disease characterized by blistering and peeling of the top layer of the skin resembling a severe burn, has occurred in patients who received nivolumab treatment
- Rhabdomyolysis (muscle fiber released into the blood stream which could damage your kidney) and polymyolsis (chronic inflammation with muscle weakness) has been reported in one patient
- Lung inflammation (pneumonitis)
- Death

11.2 Risks associated with ipilimumab

Likely

- Fever
- Nausea and/or vomiting
- Rash
- Diarrhea
- Inflammation of the colon
- Increased liver enzymes
- Fatigue

- Skin itchiness
- Decreased appetite
- Abdominal pain
- Headache
- Constipation
- Adrenal gland abnormalities
- Pituitary gland abnormalities
- Colitis

Most of the side effects are mild and may be treated with common medications.

Less Likely

- Chills
- Weakness
- Muscle pain
- Redness of skin

Rare but Serious

- Decrease in hormones of pituitary gland
- Allergic reactions
- Inflammation of the liver
- Inflammation of the pituitary gland
- Decreased red blood cells
- Loss of color from areas of skin
- Decreased or blurry vision, or inflammation of the eye
- Numbness or tingling
- Inflammation of the membrane surrounding the spinal cord and brain
- Inflammation of the kidneys
- Joint pain
- Death

11.3 Risks associated with Nivolumab and Ipilimumab Combined Therapy

Likely, Some May Be Serious

- Fatigue
- Fever and/or chills
- Flu-like feeling
- Skin changes including dryness, rash, or itching
- Vitiligo (loss of pigment or color in the skin)
- Diarrhea
- Nausea and/or vomiting
- Abdominal Pain

- Bowel Inflammation
- Dry Mouth
- Liver function blood test abnormalities
- Cough
- Shortness of breath
- Headache
- Dizziness
- Lung inflammation (pneumonitis)
- Joint pain or stiffness
- Decreased appetite
- Lowe blood pressure
- Inflammation of the thyroid
- Muscle soreness, weakness, stiffness, or spasms
- Increase in inflammatory blood proteins (e.g. lipase)

Lung Inflammation: It is possible that nivolumab may cause inflammation of the tissues of the lung. This adverse effect has been reported in approximately 3% of patients treated with nivolumab. Although many patients are have no symptoms from this lung inflammation, some patients have developed mild to severe symptoms and 2 patients have died as a result of their lung inflammation. Symptoms of lung inflammation may include difficulty breathing, fever, or fatigue. Your doctor and nurse will watch you closely for signs that might show you are developing lung inflammation.

Please inform your doctor or nurse at once if you experience any of the following:

- Any new or increased shortness of breath
- Any new or increased chest pain
- Any new or increased cough or any significant change in your type of cough
- Any increase in the amount of supplemental oxygen you require
- Any fever, fatigue, or other symptoms that occur at the same time as changes to your breathing or other lung symptoms.

If you start to develop symptoms concerning for lung inflammation, your doctor will ask you to return to clinic to perform regular tests including physical exams, measurement of oxygen levels, pulmonary function tests, blood tests, bronchoscopy, and/or CT scans. This may require treatment with steroids or other immune suppressive medicines as well as holding nivolumab. You may even require hospitalization.

Kidney inflammation: It is possible that nivolumab may cause kidney damage due to inflammation in the kidneys. This is very rare. You should let your doctor know if you notice any decreased amount of urine, difficulty urinating, sudden weight gain, increased tiredness, increased thirst or inability to tolerate liquids. This may require treatment with steroids and holding nivolumab.

Reproductive risks

Patients should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study.

11.3 Management Algorithms for Unique Nivolumab/Ipilimumab-Related Toxicities

Nivolumab and Ipilimumab are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management Algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological

The above algorithms are found in appendix 1-7 or in the current Investigator Brochure.

11.4 Management of Nivolumab or Ipilimumab-Related Infusion Reactions

Since nivolumab and ipilimumab contain 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, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions.

Infusion reactions should be graded according to NCI CTCAE (Version 4.0) guidelines.

Treatment recommendations are provided below and may be modified 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/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.

- For **Grade 2** symptoms: (moderate reaction required therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, non-steroidal anti- inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids); prophylactic medications indicated for ≤ 24 hours):
    - Stop infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as

appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF).

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

- For **Grade 3 or 4** symptoms: (severe reaction, Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates). Grade 4: Life-threatening; pressor or ventilatory support indicated):
  - Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. The study drug that is associated with infusion reaction will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.
  - In case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine or corticosteroids).

11.5 Dose Delay Criteria

Dose delay criteria apply for all drug-related events (regardless of whether or not the event is attributed to nivolumab, ipilimumab or both).

Nivolumab and ipilimumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay.
- Any Grade 3 skin, drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, AST, ALT, or total bilirubin or asymptomatic amylase or lipase:
  - Grade 3 lymphopenia does not require dose delay

  - If a subject has a baseline AST, ALT or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity
  - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity
  - Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Patients who require delay of nivolumab or ipilimumab should be re-evaluated weekly or more frequently if clinically indicated. Both drugs should be delayed until re-treatment criteria are met (per Section 11.7).

Nivolumab may be delayed until the next planned ipilimumab dose if the next ipilimumab dose is scheduled within the next 12 days. This will permit periodic ipilimumab dosing to be synchronized with nivolumab dosing.

Ipilimumab should be dosed at the specified interval regardless of any delays in intervening nivolumab doses. However, in order to maintain periodic synchronized dosing of ipilimumab and nivolumab, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted +/- 5 day window, as long as consecutive nivolumab doses are given at least 12 days apart. Ipilimumab may be delayed beyond the 5 day window if needed to synchronize with the next nivolumab dose.

If an ipilimumab dose is delayed beyond 6 weeks from the prior ipilimumab dose, then subsequent ipilimumab doses should rescheduled to maintain the 6 week interval between consecutive ipilimumab doses.

Dose delay of nivolumab which results in treatment interruption of > 6 weeks or ipilimumab for > 12 weeks require treatment discontinuation, with exceptions as noted in Section 13.0

11.6 Dose Reduction Criteria

There will be no dose reductions for nivolumab or ipilimumab.

11.7 Criteria to resume treatment

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

- Patients may resume treatment in the presence of Grade 2 fatigue
- Patients who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Patients with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin
- Patients with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 13.0) should have treatment permanently discontinued

- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment
- Subjects who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone □ 10 mg/day.
- Ipilimumab may not be resumed sooner than 6 weeks (+/- 5days) after the prior ipilimumab dose.
- In general, subjects who meet criteria to resume ipilimumab will also have met criteria to resume nivolumab, so it should be feasible to synchronize dosing of both drugs when resuming ipilimumab. In order to facilitate this, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted +/- 5 day window, as long as consecutive nivolumab doses are given at least 12 days apart.
- In instances in which toxicity if felt to be exclusively related to ipilimumab, treatment with nivolumab alone may be resumed after retreatment criteria are met and after discussion with PI-Sponsor.

11.8 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product during the course of a study and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the medicinal product.

Disease signs, symptoms, and/or laboratory abnormalities already existing prior to the use of the product are not considered AEs after administration of the study product unless they reoccur after the patient has recovered from the pre-existing condition or they represent an exacerbation in intensity or frequency.

11.9 Laboratory AEs

For this protocol, an abnormal laboratory value will not be assessed as an AE unless:

- The laboratory test result is clinically significant or meets the definition of an SAE
- The laboratory test result leads interruption or discontinuation in study treatment
- Any laboratory test result requires a specific correlative therapy/therapeutic intervention.

Laboratory AEs will be reported by the clinical term rather than the laboratory term (e.g. anemia, rather than low hemoglobin).

11.10 Adverse Event Documentation

Adverse events will use the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE). This study will utilize the CTCAE Version 4.0 for adverse event reporting.

Documentation of each adverse event must be supported by an entry in the patient's file. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product as judged by the Investigator, action taken and outcome.

11.11 Causality of AEs

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.

11.12 Serious Adverse Event

Reporting of SAEs is detailed in Section 17.2.

Clarification should be made between the terms *serious* and *severe* because they are not the same. The term *severe* is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is not the same as *serious*, which is based on the patient/event outcome or an action criterion described above, and is usually associated with events that pose a threat to a patient's life or functioning. A severe AE does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but may not be considered an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Following the patient's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy). All SAEs should be followed to resolution or stabilization.

A **Serious** Adverse Event or Reaction is any AE occurring at any dose that:

- Results in death

- Is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization EXCEPT as noted below
- Results in persistent or significant disability/incapacity (defined as substantial disruption of a person's ability to conduct normal life's functions).
- Results in a congenital anomaly / birth defect
- Results in anaphylaxis related to study drug
- Results in an important medical event that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above (example: intensive treatment in an emergency room or at home for bronchospasm, convulsions that do not result in hospitalization). Medical and scientific judgment should be exercised in deciding whether some events should be considered as serious because their quick reporting to the sponsor may be of interest for the overall conduct of the study. 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, or drug-induced liver injury.
- Results in suspected transmission of an infectious agent (pathologic or nonpathologic) via the study drug

Hospitalization: Any adverse event leading to hospitalization or prolongation of hospitalization will be considered an SAE, UNLESS at least one of the following exceptions is/are met:

- 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 for a planned medical/surgical procedure as part of the study protocol
- Routine health assessment requiring admission for baseline/trending of health status (e.g. 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).

It should be noted that invasive treatment during any hospitalization may fulfil the criteria of 'medically important' and as such may be reportable as a serious adverse event dependant

on clinical judgement. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

Pregnancies occurring in study patients/sexual partner(s) will be treated procedurally as SAEs and patient is required to immediately discontinue the trial medication. **Overdoses** and **Potential Drug Induced Liver Injury (DILI)** should also be reported as an SAE.

11.13 Pregnancy

If, following initiation of nivolumab or ipilimumab, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half lives after product administration, nivolumab and ipilimumab will both be permanently discontinued.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify Worldwide Safety @BMS of this event via the Pregnancy Surveillance Form in accordance with SAE reporting procedures described in Section 17.2.1.

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.

11.14 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 (see Section 17.2.1 for reporting details.).

11.15 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 17.2.1 for reporting details).

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

11.16 Events NOT to be reported as SAEs

For this study, the following are **not** classified as serious adverse events

- Progression or deterioration of the malignancy under study (including new metastatic lesions) or death due to disease progression.
- Hospitalization for the performance of protocol-required procedures or administration of study treatment, including any hospitalization required for pre-treatment tumor resection. However, hospitalization or a prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Hospitalization or procedures planned prior to start of study therapy, including any hospitalization required for pre-treatment tumor resection. A pre-planned procedure must be documented in the source documents. However, hospitalization or prolonged hospitalization for a complication remains to be reported as an SAE.
- An elective hospitalization for a pre-existing condition unrelated to the studied indication.
- Hospital admission that is not associated with an adverse event (e.g. social hospitalization for purpose of respite care).
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusions remains to be reported as an SAE.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

12.1 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Best overall response rate (confirmed partial + complete response) will be assessed as part of this study. Tumor response will be assessed using RECIST 1.1. All responses must be confirmed on subsequent scan to be considered a true response.

The same CT method with the same technique (i.e. with or without contrast) should be used to characterize each identified and reported lesion at baseline and every 6 weeks (+/- 1 week) thereafter while on study until week 48. After week 48, tumor assessments will be conducted every 12 weeks (+/- 1 week). Tumor assessments should be scheduled irrespective of dose delays/treatment interruptions. Designated radiologists/physician will be responsible for interpretation of the study imaging according to RECIST 1.1.

A CT scan of the chest or CT chest (+/- abdomen/pelvis depending on sites of known disease) with or without contrast will be performed to demonstrate all known areas of measurable disease. The baseline study will occur no more than 4 weeks prior to first study drug administration. An alternative imaging test, including MRI, can also be used in patients with contraindications to radiographic contrast media used in CT scans. PET scans or bone scans are not adequate for assessment of RECIST 1.1 response in target lesions. All patients must have at least one measurable disease lesion by CT or MRI.

Target Lesions:

All measurable lesions, up to a maximum of 5 lesions total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size, should be representative of all involved organs, and should lend themselves to reproducible repeat measurements. All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline as well. All baseline evaluations should be performed as close as possible to the start of treatment and never more than 28 days prior to beginning treatment.

All measurements should be recorded in millimeters. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-Target Lesions:

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should be also recorded at baseline. Measurements are not required and these lesions should be followed as “present,” “absent,” or in rare cases “unequivocal progression.” In addition, it is possible to record multiple non-target lesions involving the same organ as a single item (e.g. “multiple enlarged pelvic lymph nodes”).

Tumor Response Evaluation:

Definitions of response in target and non-target lesions are described in Table 12.1 and 12.2 below. Table 12.3 provides overall responses for all possible combinations of tumor responses in target and non-target lesions.

Table 12.1: Evaluation of target lesions	
Complete Response (CR):	Disappearance of all target lesions
Partial response (PR)	At least a 30% decrease in the sum of the diameters of the target lesions
Progressive disease (PD):	At least a 20% increase in the sum of the diameter of the target lesions or the appearance of one or more new lesions
Stable disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD

Table 12.2: Evaluation of non-target lesions	
Complete Response (CR):	Disappearance of all non-target lesions
Incomplete response/Stable disease (SD):	Persistence of one or more non-target lesions
Progressive disease (PD):	Appearance of one or more new lesion and/or unequivocal progression of existing non-target lesion

Table 12.3: Combinations of responses			
Target lesions	**Non-target lesions**	**New lesions**	**Overall response**
CR	CR	No	CR
CR	Incomplete/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Evaluation of Non-Target Lesions:

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

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

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

Progressive Disease (PD): Unequivocal progression of existing non-target lesions (Note: the appearance of one or more new lesions is also considered progression). To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

Confirmation of Scans

Verification of Response: Initial observations of response will be confirmed by repeat scans which should be performed no earlier than 4 weeks after the original observation to ensure that responses identified are not the result of measurement error. After an initial PR or CR is noted, the subsequent protocol-specified tumor assessment may serve as the confirmation.

Verification of Progression: Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date

of the initial scan. If repeat scans do not confirm PD, then the subject is considered not to have progressive disease per RECIST 1.1.

Best Overall Response:

The best overall response is determined once all the data for a subject is known. It is defined as the best response designation recorded between the date of first treatment and the date of objectively documented progression per RECIST v1.1 or the date of initiating subsequent therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment. The subjects best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Modifications to RECIST v1.1: Immune-related Response Criteria

Immune-related response criteria using uni-dimensional measurements are used to describe tumor shrinkage following RECIST-defined disease progression. The methodology is the same as described above for RECIST except:

1. New lesions do not automatically denote disease progression
2. The measurements of longest diameter of new measureable lesions are included in the sum of the measurements of the original target lesions.

Best immune-related responses, for subjects who have progression followed by tumor shrinkage are classified as irCR (disappearance of all lesions) or irPR (>/= 30% reduction from baseline).

Continuation of treatment despite radiographic progressive disease

Patients who experience initial progressive disease may continue therapy if they are experiencing clinical benefit. The date of progression for calculation of PFS will remain the first CT scan that demonstrates progression (if it is confirmed on subsequent scan, as above).

For the subjects who continue nivolumab and ipilimumab study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden volume (relative to baseline) above the degree of progression identified at the time of initial PD. This includes an increase in the sum of diameters of all target lesions and/or the development of new measurable lesions.

New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measureable at the time of initial progression may become measureable and therefore included in the tumor burden volume if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm).

Discontinuation of treatment in absence of objective progression of disease

Early death is defined as having no repeat tumor assessments following initiation of study therapy resulting from death of the patient due to disease or treatment. Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression will be recorded as "symptomatic deterioration." This is a reason for stopping therapy, but is NOT objective progressive disease. Every effort will be made to document objective progression even after discontinuation of treatment.

Special Considerations regarding lesion measurability:

Bone lesions:

- Bone scan, PET scan, or plain fils are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described by RECIST v1.1.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- "Cystic lesions" though to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described by RECIST v1.1. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other local-regional therapy, may be considered measurable ONLY if there is documented progression in that lesion.

Clinical lesions:

- Clinical lesions (e.g. biopsy confirmed skin metastasis) will only be considered measurable when they are superficial and larger than 10mm in longest diameter. For the case of skin lesions, documentation by serial color photography using a ruler to measure the size of the lesion is suggested. However, if non-clinical lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions that spit or coalesce on treatment:

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

Lesions which become too small to measure:

- If the radiologist is able to provide an actual measurement, that should be recorded, even if below 5 mm.
- However, when a lesion becomes difficult to assign an exact measurement, then:
    - If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0.
    - If the lesion (including lymph nodes) is believed to be present and is faintly seen, but too small to characterize, a default value of 5mm should be assigned.

Non-measurable lesions:

- The following are considered non-measurable lesions:
    - Small lesions with longest diameter <10mm or pathologic lymph nodes with ≥ 10 to < 15 mm short axis
    - Leptomeningeal disease
    - Ascites
    - Pleural or pericardial effusion
    - Lymphangitic involvement of skin or lung
    - Abdominal masses/organomegaly identified by physical exam that is not measurable by reproducible imaging techniques

<u>Special Considerations for New Lesions:</u>

The appearance of new malignant lesions denotes disease progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). New lesions may be defined by any modality (i.e. CT, PET, MRI, clinical exam). The finding of a new lesion should be unequivocal (i.e. not attributable to differences in scanning technique, change in imaging modality, or findings thought to possibly represent something other than tumor [e.g. pneumonitis or a "new" bone lesion that may simply be healing or flare or a pre-existing lesion]). This is particularly important when the patient's baseline lesions show partial or complete response.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered to be a new lesion and will constitute progression.

If a new lesion is equivocal, for example because of small size or indeterminate etiology, therapy may be continued and follow-up examination will clarify if it represents new disease. If repeat scans confirm that the new lesion represented malignant disease, the progression should be declared using the date of the initial scan.

Special Considerations for Pleural/Pericardial Effusions and Ascites:

As above, pleural/pericardial effusions and ascites are considered non-measureable lesions. The appearance of new or worsening pleural/pericardial effusions or ascites does not necessarily constitute unequivocal progression unless cytologically proven to be of malignant origin since some effusions may be a therapy-related toxicity or related to other medical conditions.

If a new or worsening pleural/pericardial effusion or ascites is determined to be unequivocally related to progressive disease (e.g. cytopathologic confirmation of new effusion or change from "trace" to "large" effusion), then this is consistent with progression and treatment would be discontinued.

If a new or worsening pleural/pericardial effusion or ascites is equivocal, for example because of small size or indeterminate etiology, therapy may be continued and follow-up examination or cytopathologic analysis will clarify if it represents new disease. If repeat scans or procedures confirm that the new lesion represented malignant disease, the progression should be declared using the date of the initial scan.

Definitions

Evaluation of best overall response: The best overall response is the best response recorded from the start of treatment until disease progression, as defined in Table 12.3.

Evaluable for toxicity: All patients who receive at least one dose of study therapy will be evaluable for toxicity which will be assessed according to CTCAE v4.0 as well as by documentation of dose delay/adjustments that are required.

Evaluable for objective response: All patients who receive at least one dose of study therapy will be included in the modified intent-to-treat analysis of efficacy. Patients who come off study for any reason prior to the first radiographic tumor assessment will be treated as having progressive disease.

Evaluable for primary/secondary objectives: In order to be considered eligible for the primary and secondary objectives described in this study, patients must receive (1) at least one dose of study therapy and remain on study until at least the first radiographic tumor assessment (week 6) or (2) at least one dose of study therapy and have clear clinical or radiographic progression prior to the planned first radiographic tumor assessment at week 6. Patients who come off study for reasons other than clinical/radiographic progression prior to the first radiographic tumor assessment will be replaced.

Progression free survival (PFS) is defined as the duration of time from beginning study therapy (C1D1) to time of progression or death, whichever occurs first. Clinical deterioration consistent with progressive disease in absence of radiographic evidence of progression ("clinical progression") will be considered progression for purposes of determining PFS. In patients who continue on study therapy after an initial scan demonstrates progressive disease, if repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject will not be considered to have progression at the initial scan. Patients who enroll but do not receive any study therapy will not be included in the PFS analysis. Patients who started a

subsequent anti-cancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the subsequent anti-cancer therapy. Patients who discontinue from therapy and withdraw consent for follow-up without a prior reported progression will also be censored at the last evaluable tumor assessment prior to withdrawal of consent.

Overall survival (OS) is defined as the duration of time from beginning study therapy (C1D1) to time of death. Patients who enroll but do not receive any study therapy will not be included in the OS analysis.

13.0 CRITERIAFOR REMOVAL FROM STUDY

Nivolumab and ipilimumab treatment should be permanently discontinued for the following reasons and the specific reasons for removal from study will be documented:

- Patient withdrawal of consent at any time
    - Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented. However, patients will not be followed for any reason after consent has been withdrawn.
- Termination of the study by MSKCC or BMS for any reason
- Radiographic progression: Confirmed disease progression per RECIST v1.1.
    - Patients who experience initial progressive disease may continue therapy if they are experiencing clinical benefit. A CT scan should be repeated no more than 6 weeks after the first documentation of progressive disease. If there is at least 10% more progression (e.g. first scan showed 24% growth relative to baseline, second scan shows 36% growth relative to baseline), then study therapy should be discontinued. If, instead, <10% further progression is seen, the patient may continue study therapy until confirmed progression of disease so long as there is continued clinical benefit.
- Clinical progression: Symptomatic deterioration attributed to disease progression as determined by the investigator after integrated assessment of radiographic data, biopsy results, and clinical status.
- Other conditions: Any medical condition that may jeopardize the patient's safety if he or she continues on study treatment.
- Pregnancy
- New therapies: Use of another systemic anti-cancer therapy.
    - Cases in which patients experience a mixed response requiring local therapy (e.g. surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) for control of tumor growth or symptoms may still be eligible to continue study treatment so long

as such therapy is not directed at a target lesion used for assessment of radiographic progression per RECIST v1.1 Such cases must be discussed with and approved by the Sponsor-PI.

Certain toxicities, specific to each drug: The assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of ipilimumab. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for ipilimumab but not for nivolumab, treatment with nivolumab may continue if ipilimumab is discontinued. If a subject in any of the nivolumab/ipilimumab combination arms meets criteria for discontinuation and investigator is unable to determine whether the event is related to both or one study drug, the subject should discontinue both nivolumab and ipilimumab and be taken off the treatment phase of the study.

Nivolumab dose discontinuation:

- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria requires discontinuation:
      - AST or ALT > 10x ULN
      - AST or ALT > 5-10x for > 2 weeks
      - Total bilirubin > 5x ULN
      - Concurrent AST or ALT > 3x ULN and total bilirubin > 2x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia
  - Isolated Grade 4 amylase or lipase abnormalities that is not associated with symptoms or clinical manifestations of pancreatitis.
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation

- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Tumor assessments should continue as per protocol even if dosing is delayed.
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-study-drug-related reasons may be allowed. Tumor assessments should continue as per protocol even if dosing is delayed.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

Ipilimumab dose discontinuation:

- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade ≥ 3 bronchospasm or other hypersensitivity reaction
- Any Grade 3 non-skin, drug-related adverse event with the following exceptions for laboratory abnormalities, grade 3 nausea and/or vomiting, grade 3 neutropenia or thrombocytopenia, and symptomatic endocrinopathies which resolved (with or without hormone substitution)
- Any drug-related liver function test (LFT) abnormality that meets the following criteria requires discontinuation:
  - AST or ALT > 8x ULN
  - Total bilirubin > 5x ULN
  - Concurrent AST or ALT > 3x ULN and total bilirubin > 2x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia
  - Isolated Grade 4 amylase or lipase abnormalities that is not associated with symptoms or clinical manifestations of pancreatitis.
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Tumor assessments should continue as per protocol even if dosing is delayed.

- Dosing delays lasting > 6 weeks from the previous dose that occur for non-study-drug-related reasons may be allowed. Tumor assessments should continue as per protocol even if dosing is delayed.

Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

14.0 BIOSTATISTICS

This study will enroll thirty patients with advanced NSCLCs, who will receive nivolumab plus ipilimumab therapy following standard-of-care resection of tumor tissue. In order to be considered eligible for the primary and secondary objectives described in this study, patients must receive (1) at least one dose of study therapy and remain on study until at least the first radiographic tumor assessment (week 6) or (2) at least one dose of study therapy and have clear clinical or radiographic progression prior to the planned first radiographic tumor assessment at week 6. Patients who come off study for reasons other than clinical/radiographic progression prior to the first radiographic tumor assessment will be replaced.

The sample size is based on feasibility and budgetary considerations, as well as generating sufficient preliminary data to more specifically inform a larger study of sufficient power. In the thoracic surgery service, there is an average of 1-3 cases per week of patients with advanced stage disease who undergo intervention or resection of a metastatic site of disease and who may be eligible for this trial. We would expect that 20-40% of such patients would be willing to participate in this study and therefore anticipate an accrual rate of 1-2 patients per month, or 20 patients/year. We therefore expect to complete accrual in 18 months. Due to the limited sample size and to the heterogeneity of the patient population (both smokers and never smokers permitted, no restriction related to PD-L1 expression), we will not be able to draw definitive conclusions regarding the effect of specific factors and mechanisms. The nature of this study is descriptive and exploratory. Any hypotheses generated will need to be further confirmed. Response to nivolumab will be evaluated using RECIST criteria and patients will be classified as either responders (CR or PR at any time during nivolumab treatment) or non-responders.

Primary objective 1: In each tumor sample, we will quantify the mutational burden (number of somatic, non-synonymous mutations detected through whole exome sequencing) and investigate graphically its relationship with response to nivolumab plus ipilimumab. We will describe the burden of mutations for responders and non-responders using summary statistics, and compare it (in an exploratory analysis) using Wilcoxon rank sum test. Depending on the number of responses, we may also perform logistic regression with mutational burden as a covariate and/or use Cox regression to analyze PFS and OS with mutational burden as a covariate. We expect that higher burden of somatic mutations will show an indication of positive association with response to nivolumab plus ipilimumab. Patients will be stratified into mutation “high” and “low” groups based on the median number of non-synonymous mutations/sample in patients with NSCLCs, and we will report objective response rate along with exact 95% confidence intervals in the low and high burden groups, respectively. Because this is not an established categorization, we will graphically

investigate whether other types of functional relationship between the burden of mutation and response might be more appropriate.

Primary Objectives 2: Identification of candidate neoantigens

Candidate neoantigens will be broadly defined as those mutations that generate peptides that have <500nM binding affinity to patient specific MHC class I alleles. Analysis may be further refined by IEDB or in vitro methods to identify relevant neoantigens that are predicted to elicit T-cell response. Using these methods, a list of candidate neoantigens will be generated and we will use non-parametric Wilcoxon tests to compare responders vs non-responders with respect to the quantity of putative neoantigens. Those neoantigens significantly associated with response status (controlling for a false-discovery rate of 5%) will be validated in further studies. Data will be compared to TCGA data to see if there are mutated sequences enriched in either the responder or non-responder group.

Primary Objective 3: Identification of neoantigen-specific T-cells.

The presence of neoantigen-specific peripheral blood and (if possible) intratumoral T-cells will be quantified in pre- and on-treatment specimens. We will present these data graphically and summarize them for responders and non-responders. We are interested in observing whether neoantigen-specific T-cells exhibit patterns of change between the two evaluations that are different between responders and non-responders. The presence of neoantigen-specific lymphocytes will be quantified in samples collected at baseline and serially while on treatment. Their trajectory will be presented graphically, summarized separately for responders and non-responders, and compared using mixed-effects models for longitudinal data.

Secondary objectives: Tumor expression of co-stimulatory ligands and receptors and MHC expression will be analyzed and quantified in pre-treatment and on-treatment tissue samples. All measures, as well as percent changes between values pre- and during treatment, will be summarized separately for responders versus non-responders. Association between pre-treatment values and response will be explored using Wilcoxon rank sum test in order to investigate the predictive potential.

Exploratory analyses: Additional post-hoc, exploratory assessments are expected and may be performed. Much such as, but not limited to, logistic regression and graphical summaries may be used to assess associations between various potential biomarker measures and clinical efficacy.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for

ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.3 Randomization

N/A

16.1 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team. The data collected for this study will be entered into a secure database (Clinical Research Database (CRDB). Source documentation will be available to support the computerized patient record. The principal investigator will maintain ultimate responsibility for the clinical trial.

16.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, or more frequently if indicated.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at:
http://www.cancer.gov/clinicaltrials/patientsafety/dsm -guidelines /page1

The DSM Plans at MSKCC were established and are monitored by the Clinical Research Administration. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at:
http://smskpsps9/dept/ocr/OCR%20Website%20Documents/Clinical%20Research%20Quality%20Assurance%20(CRQA)/MSKCC%20Data%20and%20Safety%20Monitoring%20Plan.pdf

There are several different mechanisms by which clinical trials are monitored for data safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The

committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level or risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industry sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.1 PROTECTION OF HUMAN SUBJECTS

Prior to the enrollment of each patient, the risks, benefits and objectives of the study will be reviewed with the participant, including a discussion of the possible toxicities and side effects. Alternative, non-protocol, treatment options will be discussed with the patient. It will be reviewed that participation in this clinical trial is voluntary and that the patient may withdraw consent at any time. The study is designed with careful safety monitoring for toxicity including physician visits. Specific guidelines for symptom management are in place to protect the study participant.

Human Subjects Involvement and Characteristics: All patients at MSKCC who meet the all of the inclusion and none of the exclusion criteria will be eligible. At least 30 patients will will be enrolled. Patients eligible will be 18 years of age or older with a ECOG performance status ≤ 1. Both men and women and members of all ethnic groups are eligible for this trial. Pregnant and breast-feeding women are excluded from this study. This protocol does not include children because the number of children is expected to be limited for the patient population expected to be accrued onto this study. Also, the majority of children are already accessed by a nationwide pediatric cancer research network. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

Consent process: All patients at MSKCC who meet the inclusion criteria will be eligible. Participation in the trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to IRB guidelines. The informed consent procedure is described in Section 18.0.

Possible Toxicities/Side-Effects: There are risks associated with treatment as described in Section 11.0; however, patients screened for enrollment will be deemed appropriate for treatment independent of this study.

Benefits: Based on data from a Phase I trial, nivolumab plus ipilimumab appears to benefit some patients with lung cancers. At present, it is unknown what the predictors of that response are. The goal of this study is to evaluate the potential somatic genetic predictors of objective response to nivolumab plus ipilimumab in patients with lung cancer.

Costs: Patients will be charged for physician visits, routine laboratory tests, and radiologic studies required for monitoring their condition. Pre-treatment tumor resections will be performed as standard-of-care.

The cost of research-only biopsies, nivolumab, as well as tumor tissue based- and blood based-exploratory correlatives will be covered by research funds.

Alternatives: For patients considering this trial as second-line therapy, docetaxel or erlotinib could be alternative standard options. Nivolumab would also be a standard option for patients with squamous cell lung cancer. For patients considering this trial as third-line therapy or beyond, there are no standard treatment alternatives.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patients' names and any other identifying information will not be used in reports or publications resulting from this study. Other authorized agencies and appropriate internal personnel (e.g. qualified monitors from MSKCC) and external personnel (e.g. qualified monitors from BMS (the manufacturer of nivolumab and ipilimumab), its authorized agents, the FDA, and/or other governmental agencies) may review patient records as required.

Future Contact: Participants will not be routinely told of the results from research assays (e.g. DNA sequencing). With their permission, the participant and/or family members may be contacted in the future to ask if they are interested in learning about potential findings of inherited risks for cancer that may have been an outcome of the research assay testing of their samples.

Patient safety: Patients are monitored by physicians and oncology nurses who are very familiar with clinical trials. In the case of an adverse reaction, immediate medical attention is available. In the evenings and weekends, we have a 24-hour urgent care facility for outpatients. The PI or co-PI will also be available at all times to organize any necessary intervention.

Monitoring of data to ensure safety: This study is to be monitored by the institutional IRB. This incorporates an independent data and safety monitoring board established by arrangement with the National Cancer Institute. The analysis of safety will include all patients. Adverse events, including all toxic effects of treatment, will be tabulated individually, and summarized by severity and causality.

17.2 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.3 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number

- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
    - If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB AE report should be completed as above and the FDA assigned IND/IDE number written at the top of the report. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

17.2.1 Procedures for Reporting Serious Adverse Events (SAEs) to Drug Sponsor

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. Adverse events (AEs) may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures must be reported to BMS (or designee). AEs which are serious must be reported to BMS (or designee) from study enrollment up to and including 100 days after administration of the last dose of nivolumab. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. Any SAE that occurs at any time after completion of nivolumab treatment or after the designated follow-up period that the investigator and/or sub-investigator consider to be related to any study drug must be reported to the BMS Worldwide Safety (or designee). The investigator should report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

This is an investigator-initiated study. The principal investigator Adam Schoenfeld, MD, who may also sometimes be referred to as the sponsor-investigator, is conducting the study and acting as the sponsor. Therefore, the legal/ethical obligations of the principal investigator include both those of a sponsor and those of an investigator.

For studies conducted under an Investigator IND, any event that is both serious and unexpected must be reported to the Food and Drug Administration (FDA) as soon as possible **and no later than 7 days**

(for a death or life-threatening event) **or 15 days** (for all other SAEs) **after the investigator's or institution's initial receipt of the information.** BMS will be provided with a simultaneous copy of all adverse events filed with the FDA.

SAEs should be reported on MedWatch Form 3500A or similar form. It MUST include the institutional **AND** BMS study ID [per study Agreement]

MedWatch SAE forms should be sent to the FDA at:

MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)
http://www.accessdata.fda.gov/scripts/medwatch/

All SAEs should simultaneously be faxed or e-mailed to BMS at:

Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
SAE Fax Number: 609-818-3804
SAE Email Address: Worldwide.Safety@BMS.com

The study period during which adverse events will be reported is from the initiation of study procedures to the end of the study treatment follow-up, defined as 100 days following the last administration of nivolumab treatment.

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 to BMS using the same procedure used for transmitting the initial SAE report.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent forms indicating their consent to participate.

These consent forms meet the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent forms will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.

5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

This study will have two consents: one for screening prior to surgical resection of tumor tissue. This consent form will discuss that the surgical procedure will be performed as standard-of-care, but that tumor tissue will be collected for research. If sufficient tissue can be collected, the patient will be invited to participate in the main treatment part of this study and, if they agree and sign the second treatment consent, will begin screening procedures for the treatment part of this study.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consents, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCES

1. Rizvi NA, Gettinger SN, Goldman JW, Hellmann MD, Chow LQ, Juergens R, et al. Safety and Efficacy of First-Line Nivolumab (NIVO; Anti-Programmed Death-1 [PD-1]) and Ipilimumab in Non-Small Cell Lung Cancer (NSCLC). Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2015:Abstract #786.
2. Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science. 2015;348(6230):124-8.
3. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. International journal of cancer Journal international du cancer. 2010;127(12):2893-917.
4. Spiro SG, Rudd RM, Souhami RL, Brown J, Fairlamb DJ, Gower NH, et al. Chemotherapy versus supportive care in advanced non-small cell lung cancer: improved survival without detriment to quality of life. Thorax. 2004;59(10):828-36.
5. NSCLC_Meta-Analyses_Collaborative_Group. Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: a systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. J Clin Oncol. 2008;26(28):4617-25.
6. Postmus PE, Brambilla E, Chansky K, Crowley J, Goldstraw P, Patz EF, Jr., et al. The IASLC Lung Cancer Staging Project: proposals for revision of the M descriptors in the forthcoming (seventh) edition of the TNM classification of lung cancer. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2007;2(8):686-93.
7. Detterbeck FC, Boffa DJ, Tanoue LT. The new lung cancer staging system. Chest. 2009;136(1):260-71.
8. Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol. 2008;26(21):3543-51.
9. Ciuleanu T, Brodowicz T, Zielinski C, Kim JH, Krzakowski M, Laack E, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet. 2009;374(9699):1432-40.

10. Belani CP, Brodowicz T, Ciuleanu TE, Krzakowski M, Yang SH, Franke F, et al. Quality of life in patients with advanced non-small-cell lung cancer given maintenance treatment with pemetrexed versus placebo (H3E-MC-JMEN): results from a randomised, double-blind, phase 3 study. The lancet oncology. 2012;13(3):292-9.
11. Paz-Ares L, de Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. The lancet oncology. 2012;13(3):247-55.
12. Fidias PM, Dakhil SR, Lyss AP, Loesch DM, Waterhouse DM, Bromund JL, et al. Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer. J Clin Oncol. 2009;27(4):591-8.
13. Perol M, Chouaid C, Perol D, Barlesi F, Gervais R, Westeel V, et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol. 2012;30(28):3516-24.
14. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. The New England journal of medicine. 2006;355(24):2542-50.
15. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. The New England journal of medicine. 2004;350(21):2129-39.
16. Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science. 2004;304(5676):1497-500.
17. Pao W, Miller V, Zakowski M, Doherty J, Politi K, Sarkaria I, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. Proceedings of the National Academy of Sciences of the United States of America. 2004;101(36):13306-11.
18. Kris MG, Johnson BE, Kwiatkowski DJ, Iafrate AJ, Wistuba II, Aronson SL, et al. Identification of driver mutations in tumor specimens from 1,000 patients with lung adenocarcinoma: The NCI's Lung Cancer Mutation Consortium (LCMC). J Clin Oncol 2011;29:suppl; abstr CRA7506.
19. Pao W, Hutchinson KE. Chipping away at the lung cancer genome. Nature medicine. 2012;18(3):349-51.
20. Shaw AT, Kim DW, Nakagawa K, Seto T, Crino L, Ahn MJ, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. The New England journal of medicine. 2013;368(25):2385-94.
21. Lynch TJ, Bondarenko I, Luft A, Serwatowski P, Barlesi F, Chacko R, et al. Ipilimumab in Combination With Paclitaxel and Carboplatin As First-Line Treatment in Stage IIIB/IV Non-Small-Cell Lung Cancer: Results From a Randomized, Double-Blind, Multicenter Phase II Study. J Clin Oncol. 2012;30(17):2046-54.
22. Brahmer JR, Drake CG, Wollner I, Powderly JD, Picus J, Sharfman WH, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol. 2010;28(19):3167-75.
23. Brahmer JR, Horn L, Antonia S, Spigel DR, Gandhi L, Sequist LV, et al. Clinical activity and safety of anti-PD1 (BMS-936558, MDX-1106) in patients with advanced non-small-cell lung cancer (NSCLC). J Clin Oncol. 2012(30):suppl; abstr 7509.
24. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. The New England journal of medicine. 2012;366(26):2443-54.
25. Brahmer JR. Harnessing the immune system for the treatment of non-small-cell lung cancer. J Clin Oncol. 2013;31(8):1021-8.

26. Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. The New England journal of medicine. 2012;366(26):2455-65.
27. Spigel DR, Gettinger SN, Horn L, Herbst RS, Gandhi L, Gordon MS, et al. Clinical activity, safety, and biomarkers of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC). J Clin Oncol. 2013;31:suppl; abstr 8008.
28. Freeman GJ, Long AJ, Iwai Y, Bourque K, Chernova T, Nishimura H, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. The Journal of experimental medicine. 2000;192(7):1027-34.
29. Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nature medicine. 2002;8(8):793-800.
30. Azuma T, Yao S, Zhu G, Flies AS, Flies SJ, Chen L. B7-H1 is a ubiquitous antiapoptotic receptor on cancer cells. Blood. 2008;111(7):3635-43.
31. Postow MA, Harding J, Wolchok JD. Targeting immune checkpoints: releasing the restraints on anti-tumor immunity for patients with melanoma. Cancer journal. 2012;18(2):153-9.
32. Ahmadzadeh M, Johnson LA, Heemskerk B, Wunderlich JR, Dudley ME, White DE, et al. Tumor antigen-specific CD8 T cells infiltrating the tumor express high levels of PD-1 and are functionally impaired. Blood. 2009;114(8):1537-44.
33. Topalian SL, Drake CG, Pardoll DM. Targeting the PD-1/B7-H1(PD-L1) pathway to activate anti-tumor immunity. Current opinion in immunology. 2012;24(2):207-12.
34. Thompson RH, Gillett MD, Cheville JC, Lohse CM, Dong H, Webster WS, et al. Costimulatory B7-H1 in renal cell carcinoma patients: Indicator of tumor aggressiveness and potential therapeutic target. Proceedings of the National Academy of Sciences of the United States of America. 2004;101(49):17174-9.
35. Gao Q, Wang XY, Qiu SJ, Yamato I, Sho M, Nakajima Y, et al. Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. Clinical cancer research : an official journal of the American Association for Cancer Research. 2009;15(3):971-9.
36. Hamanishi J, Mandai M, Iwasaki M, Okazaki T, Tanaka Y, Yamaguchi K, et al. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. Proceedings of the National Academy of Sciences of the United States of America. 2007;104(9):3360-5.
37. Konishi J, Yamazaki K, Azuma M, Kinoshita I, Dosaka-Akita H, Nishimura M. B7-H1 expression on non-small cell lung cancer cells and its relationship with tumor-infiltrating lymphocytes and their PD-1 expression. Clinical cancer research : an official journal of the American Association for Cancer Research. 2004;10(15):5094-100.
38. Mu CY, Huang JA, Chen Y, Chen C, Zhang XG. High expression of PD-L1 in lung cancer may contribute to poor prognosis and tumor cells immune escape through suppressing tumor infiltrating dendritic cells maturation. Med Oncol. 2011;28(3):682-8.
39. Gettinger S, Horn L, Antonia SJ, Spigel DR, Gandhi L, Sequist LV, et al. CLINICAL ACTIVITY AND SAFETY OF ANTI-PROGRAMMED DEATH-1 (PD-1) (BMS-936558/MDX-1106/ONO-4538) IN PATIENTS (PTS) WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC). ESMO. 2012:Abstract #1237PD.
40. Ciuleanu T, Stelmakh L, Cicenas S, Miliauskas S, Grigorescu AC, Hillenbach C, et al. Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study. The lancet oncology. 2012;13(3):300-8.

41. Garassino MC, Martelli O, Broggini M, Farina G, Veronese S, Rulli E, et al. Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial. The lancet oncology. 2013.
42. Linsley PS, Bradshaw J, Greene J, Peach R, Bennett KL, Mittler RS. Intracellular trafficking of CTLA-4 and focal localization towards sites of TCR engagement. Immunity. 1996;4(6):535-43.
43. Linsley PS, Brady W, Urnes M, Grosmaire LS, Damle NK, Ledbetter JA. CTLA-4 is a second receptor for the B cell activation antigen B7. The Journal of experimental medicine. 1991;174(3):561-9.
44. Walunas TL, Lenschow DJ, Bakker CY, Linsley PS, Freeman GJ, Green JM, et al. CTLA-4 can function as a negative regulator of T cell activation. Immunity. 1994;1(5):405-13.
45. Krummel MF, Allison JP. CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation. The Journal of experimental medicine. 1995;182(2):459-65.
46. Krummel MF, Allison JP. CTLA-4 engagement inhibits IL-2 accumulation and cell cycle progression upon activation of resting T cells. The Journal of experimental medicine. 1996;183(6):2533-40.
47. Freeman GJ, Borriello F, Hodes RJ, Reiser H, Hathcock KS, Laszlo G, et al. Uncovering of functional alternative CTLA-4 counter-receptor in B7-deficient mice. Science. 1993;262(5135):907-9.
48. Linsley PS, Greene JL, Brady W, Bajorath J, Ledbetter JA, Peach R. Human B7-1 (CD80) and B7-2 (CD86) bind with similar avidities but distinct kinetics to CD28 and CTLA-4 receptors. Immunity. 1994;1(9):793-801.
49. Walunas TL, Bakker CY, Bluestone JA. CTLA-4 ligation blocks CD28-dependent T cell activation. The Journal of experimental medicine. 1996;183(6):2541-50.
50. Greene JL, Leytze GM, Emswiler J, Peach R, Bajorath J, Cosand W, et al. Covalent dimerization of CD28/CTLA-4 and oligomerization of CD80/CD86 regulate T cell costimulatory interactions. The Journal of biological chemistry. 1996;271(43):26762-71.
51. Carreno BM, Bennett F, Chau TA, Ling V, Luxenberg D, Jussif J, et al. CTLA-4 (CD152) can inhibit T cell activation by two different mechanisms depending on its level of cell surface expression. Journal of immunology. 2000;165(3):1352-6.
52. Schneider H, Downey J, Smith A, Zinselmeyer BH, Rush C, Brewer JM, et al. Reversal of the TCR stop signal by CTLA-4. Science. 2006;313(5795):1972-5.
53. Brunner MC, Chambers CA, Chan FK, Hanke J, Winoto A, Allison JP. CTLA-4-Mediated inhibition of early events of T cell proliferation. Journal of immunology. 1999;162(10):5813-20.
54. Agata Y, Kawasaki A, Nishimura H, Ishida Y, Tsubata T, Yagita H, et al. Expression of the PD-1 antigen on the surface of stimulated mouse T and B lymphocytes. International immunology. 1996;8(5):765-72.
55. Dong H, Zhu G, Tamada K, Chen L. B7-H1, a third member of the B7 family, co-stimulates T-cell proliferation and interleukin-10 secretion. Nature medicine. 1999;5(12):1365-9.
56. Latchman Y, Wood CR, Chernova T, Chaudhary D, Borde M, Chernova I, et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. Nature immunology. 2001;2(3):261-8.
57. Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Molecular and cellular biology. 2005;25(21):9543-53.
58. Bennett F, Luxenberg D, Ling V, Wang lM, Marquette K, Lowe D, et al. Program death-1 engagement upon TCR activation has distinct effects on costimulation and cytokine-driven proliferation: attenuation of ICOS, IL-4, and IL-21, but not CD28, IL-7, and IL-15 responses. Journal of immunology. 2003;170(2):711-8.
59. Saunders PA, Hendrycks VR, Lidinsky WA, Woods ML. PD-L2:PD-1 involvement in T cell proliferation, cytokine production, and integrin-mediated adhesion. European journal of immunology. 2005;35(12):3561-9.
60. Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T

cell stimulation, but only receptor ligation prevents T cell activation. Journal of immunology. 2004;173(2):945-54.
61. Ishida Y, Agata Y, Shibahara K, Honjo T. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. The EMBO journal. 1992;11(11):3887-95.
62. Barber DL, Wherry EJ, Masopust D, Zhu B, Allison JP, Sharpe AH, et al. Restoring function in exhausted CD8 T cells during chronic viral infection. Nature. 2006;439(7077):682-7.
63. Day CL, Kaufmann DE, Kiepiela P, Brown JA, Moodley ES, Reddy S, et al. PD-1 expression on HIV-specific T cells is associated with T-cell exhaustion and disease progression. Nature. 2006;443(7109):350-4.
64. Grosso J, Horak CE, Inzunza D, Cardona DM, Simon JS, Gupta AK, et al. Association of tumor PD-L1 expression and immune biomarkers with clinical activity in patients (pts) with advanced solid tumors treated with nivolumab (anti-PD-1; BMS-936558; ONO-4538). J Clin Oncol. 2013;31(Suppl):Abstr 3016.
65. Topalian SL, Sznol M, Brahmer JR, McDermott DF, Smith DC, Gettinger SN, et al. Nivolumab (anti-PD-1; BMS-936558; ONO-4538) in patients with advanced solid tumors: Survival and long-term safety in a phase I trial. J Clin Oncol. 2013;31(Suppl):Abstr 3002.
66. Powderly JD, Koeppen H, Hodi FS, Sosman JA, Gettinger SN, Desai R, et al. Biomarkers and associations with the clinical activity of PD-L1 blockade in a MPDL3280A study. J Clin Oncol. 2013;31(Suppl):Abstr 3001.
67. Taube JM, Anders RA, Young GD, Xu H, Sharma R, McMiller TL, et al. Colocalization of inflammatory response with B7-h1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape. Science translational medicine. 2012;4(127):127ra37.
68. Callahan MK, Horak CE, Curran MA, Hollman T, Schaer DA, Yuan J, et al. Peripheral and tumor immune correlates in patients with advanced melanoma treated with combination nivolumab (anti-PD-1, BMS-936558, ONO-4538) and ipilimumab. J Clin Oncol. 2013;31:suppl; abstr 3003.
69. Antonia SJ, Goldberg SB, Balmanoukian AS, Sanborn RE, Steele K, Narwal R, et al. Phase Ib study of MEDI4736, a programmed cell death ligand-1 (PD-L1) antibody, in combination with tremelimumab, a cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) antibody, in patients (pts) with advanced NSCLC. ASCO Meeting Abstracts. 2015;33(15_suppl):3014.
70. Subramanian J, Govindan R. Lung cancer in never smokers: a review. J Clin Oncol. 2007;25(5):561-70.
71. Sun S, Schiller JH, Gazdar AF. Lung cancer in never smokers--a different disease. Nature reviews Cancer. 2007;7(10):778-90.
72. Samet JM, Avila-Tang E, Boffetta P, Hannan LM, Olivo-Marston S, Thun MJ, et al. Lung cancer in never smokers: clinical epidemiology and environmental risk factors. Clinical cancer research : an official journal of the American Association for Cancer Research. 2009;15(18):5626-45.
73. Rudin CM, Avila-Tang E, Harris CC, Herman JG, Hirsch FR, Pao W, et al. Lung cancer in never smokers: molecular profiles and therapeutic implications. Clinical cancer research : an official journal of the American Association for Cancer Research. 2009;15(18):5646-61.
74. Lee YJ, Kim JH, Kim SK, Ha SJ, Mok TS, Mitsudomi T, et al. Lung cancer in never smokers: change of a mindset in the molecular era. Lung cancer. 2011;72(1):9-15.
75. Couraud S, Zalcman G, Milleron B, Morin F, Souquet PJ. Lung cancer in never smokers - A review. European journal of cancer. 2012.
76. Govindan R, Ding L, Griffith M, Subramanian J, Dees ND, Kanchi KL, et al. Genomic Landscape of Non-Small Cell Lung Cancer in Smokers and Never-Smokers. Cell. 2012;150(6):1121-34.
77. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA, Jr., Kinzler KW. Cancer genome landscapes. Science. 2013;339(6127):1546-58.

78. Simpson AJ, Caballero OL, Jungbluth A, Chen YT, Old LJ. Cancer/testis antigens, gametogenesis and cancer. Nature reviews Cancer. 2005;5(8):615-25.
79. van der Bruggen P, Traversari C, Chomez P, Lurquin C, De Plaen E, Van den Eynde B, et al. A gene encoding an antigen recognized by cytolytic T lymphocytes on a human melanoma. Science. 1991;254(5038):1643-7.
80. Chen YT, Scanlan MJ, Sahin U, Tureci O, Gure AO, Tsang S, et al. A testicular antigen aberrantly expressed in human cancers detected by autologous antibody screening. Proceedings of the National Academy of Sciences of the United States of America. 1997;94(5):1914-8.
81. Heemskerk B, Kvistborg P, Schumacher TN. The cancer antigenome. EMBO J. 2013;32(2):194-203.
82. Lennerz V, Fatho M, Gentilini C, Frye RA, Lifke A, Ferel D, et al. The response of autologous T cells to a human melanoma is dominated by mutated neoantigens. Proc Natl Acad Sci U S A. 2005;102(44):16013-8.
83. Segal NH, Parsons DW, Peggs KS, Velculescu V, Kinzler KW, Vogelstein B, et al. Epitope landscape in breast and colorectal cancer. Cancer Res. 2008;68(3):889-92.
84. Matsushita H, Vesely MD, Koboldt DC, Rickert CG, Uppaluri R, Magrini VJ, et al. Cancer exome analysis reveals a T-cell-dependent mechanism of cancer immunoediting. Nature. 2012;482(7385):400-4.
85. DuPage M, Cheung AF, Mazumdar C, Winslow MM, Bronson R, Schmidt LM, et al. Endogenous T cell responses to antigens expressed in lung adenocarcinomas delay malignant tumor progression. Cancer cell. 2011;19(1):72-85.
86. DuPage M, Mazumdar C, Schmidt LM, Cheung AF, Jacks T. Expression of tumour-specific antigens underlies cancer immunoediting. Nature. 2012;482(7385):405-9.
87. Castle JC, Kreiter S, Diekmann J, Lower M, van de Roemer N, de Graaf J, et al. Exploiting the mutanome for tumor vaccination. Cancer Res. 2012;72(5):1081-91.
88. van Rooij N, van Buuren MM, Philips D, Velds A, Toebes M, Heemskerk B, et al. Tumor exome analysis reveals neoantigen-specific T-cell reactivity in an ipilimumab-responsive melanoma. J Clin Oncol. 2013;31(32):e439-42.
89. Rodenko B, Toebes M, Hadrup SR, van Esch WJ, Molenaar AM, Schumacher TN, et al. Generation of peptide-MHC class I complexes through UV-mediated ligand exchange. Nature protocols. 2006;1(3):1120-32.
90. Toebes M, Coccoris M, Bins A, Rodenko B, Gomez R, Nieuwkoop NJ, et al. Design and use of conditional MHC class I ligands. Nature medicine. 2006;12(2):246-51.
91. Bakker AH, Hoppes R, Linnemann C, Toebes M, Rodenko B, Berkers CR, et al. Conditional MHC class I ligands and peptide exchange technology for the human MHC gene products HLA-A1, -A3, -A11, and -B7. Proceedings of the National Academy of Sciences of the United States of America. 2008;105(10):3825-30.
92. Hadrup SR, Bakker AH, Shu CJ, Andersen RS, van Veluw J, Hombrink P, et al. Parallel detection of antigen-specific T-cell responses by multidimensional encoding of MHC multimers. Nature methods. 2009;6(7):520-6.
93. Andersen RS, Kvistborg P, Frosig TM, Pedersen NW, Lyngaa R, Bakker AH, et al. Parallel detection of antigen-specific T cell responses by combinatorial encoding of MHC multimers. Nature protocols. 2012;7(5):891-902.
94. Thompson RH, Dong H, Lohse CM, Leibovich BC, Blute ML, Cheville JC, et al. PD-1 is expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. Clinical cancer research : an official journal of the American Association for Cancer Research. 2007;13(6):1757-61.
95. Mumprecht S, Schurch C, Schwaller J, Solenthaler M, Ochsenbein AF. Programmed death 1 signaling on chronic myeloid leukemia-specific T cells results in T-cell exhaustion and disease progression. Blood. 2009;114(8):1528-36.

96. Zhang Y, Huang S, Gong D, Qin Y, Shen Q. Programmed death-1 upregulation is correlated with dysfunction of tumor-infiltrating CD8+ T lymphocytes in human non-small cell lung cancer. Cellular & molecular immunology. 2010;7(5):389-95.
97. Fourcade J, Sun Z, Benallaoua M, Guillaume P, Luescher IF, Sander C, et al. Upregulation of Tim-3 and PD-1 expression is associated with tumor antigen-specific CD8+ T cell dysfunction in melanoma patients. J Exp Med. 2010;207(10):2175-86.
98. Baitsch L, Baumgaertner P, Devevre E, Raghav SK, Legat A, Barba L, et al. Exhaustion of tumor-specific CD8(+) T cells in metastases from melanoma patients. The Journal of clinical investigation. 2011;121(6):2350-60.
99. Vesely MD, Kershaw MH, Schreiber RD, Smyth MJ. Natural innate and adaptive immunity to cancer. Annual review of immunology. 2011;29:235-71.
100. Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annual review of immunology. 2005;23:515-48.
101. Al-Shibli KI, Donnem T, Al-Saad S, Persson M, Bremnes RM, Busund LT. Prognostic effect of epithelial and stromal lymphocyte infiltration in non-small cell lung cancer. Clinical cancer research : an official journal of the American Association for Cancer Research. 2008;14(16):5220-7.
102. Sharpe AH, Wherry EJ, Ahmed R, Freeman GJ. The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. Nature immunology. 2007;8(3):239-45.
103. Cerami EG, Gross BE, Demir E, Rodchenkov I, Babur O, Anwar N, et al. Pathway Commons, a web resource for biological pathway data. Nucleic acids research. 2011;39(Database issue):D685-90.
104. Robinson JT, Thorvaldsdottir H, Winckler W, Guttman M, Lander ES, Getz G, et al. Integrative genomics viewer. Nature biotechnology. 2011;29(1):24-6.
105. De Baets G, Van Durme J, Reumers J, Maurer-Stroh S, Vanhee P, Dopazo J, et al. SNPeffect 4.0: on-line prediction of molecular and structural effects of protein-coding variants. Nucleic Acids Res. 2012;40(Database issue):D935-9.
106. Larson DE, Harris CC, Chen K, Koboldt DC, Abbott TE, Dooling DJ, et al. SomaticSniper: identification of somatic point mutations in whole genome sequencing data. Bioinformatics. 2012;28(3):311-7.
107. Koboldt DC, Zhang Q, Larson DE, Shen D, McLellan MD, Lin L, et al. VarScan 2: somatic mutation and copy number alteration discovery in cancer by exome sequencing. Genome Res. 2012;22(3):568-76.
108. Saunders CT, Wong WS, Swamy S, Becq J, Murray LJ, Cheetham RK. Strelka: accurate somatic small-variant calling from sequenced tumor-normal sample pairs. Bioinformatics. 2012;28(14):1811-7.
109. Cibulskis K, Lawrence MS, Carter SL, Sivachenko A, Jaffe D, Sougnez C, et al. Sensitive detection of somatic point mutations in impure and heterogeneous cancer samples. Nat Biotechnol. 2013;31(3):213-9.
110. Engels B, Engelhard VH, Sidney J, Sette A, Binder DC, Liu RB, et al. Relapse or eradication of cancer is predicted by peptide-major histocompatibility complex affinity. Cancer cell. 2013;23(4):516-26.
111. Lundegaard C, Lamberth K, Harndahl M, Buus S, Lund O, Nielsen M. NetMHC-3.0: accurate web accessible predictions of human, mouse and monkey MHC class I affinities for peptides of length 8-11. Nucleic acids research. 2008;36(Web Server issue):W509-12.
112. Lundegaard C, Lund O, Nielsen M. Accurate approximation method for prediction of class I MHC affinities for peptides of length 8, 10 and 11 using prediction tools trained on 9mers. Bioinformatics. 2008;24(11):1397-8.
113. Khalili JS, Hanson RW, Szallasi Z. In silico prediction of tumor antigens derived from functional missense mutations of the cancer gene census. Oncoimmunology. 2012;1(8):1281-9.

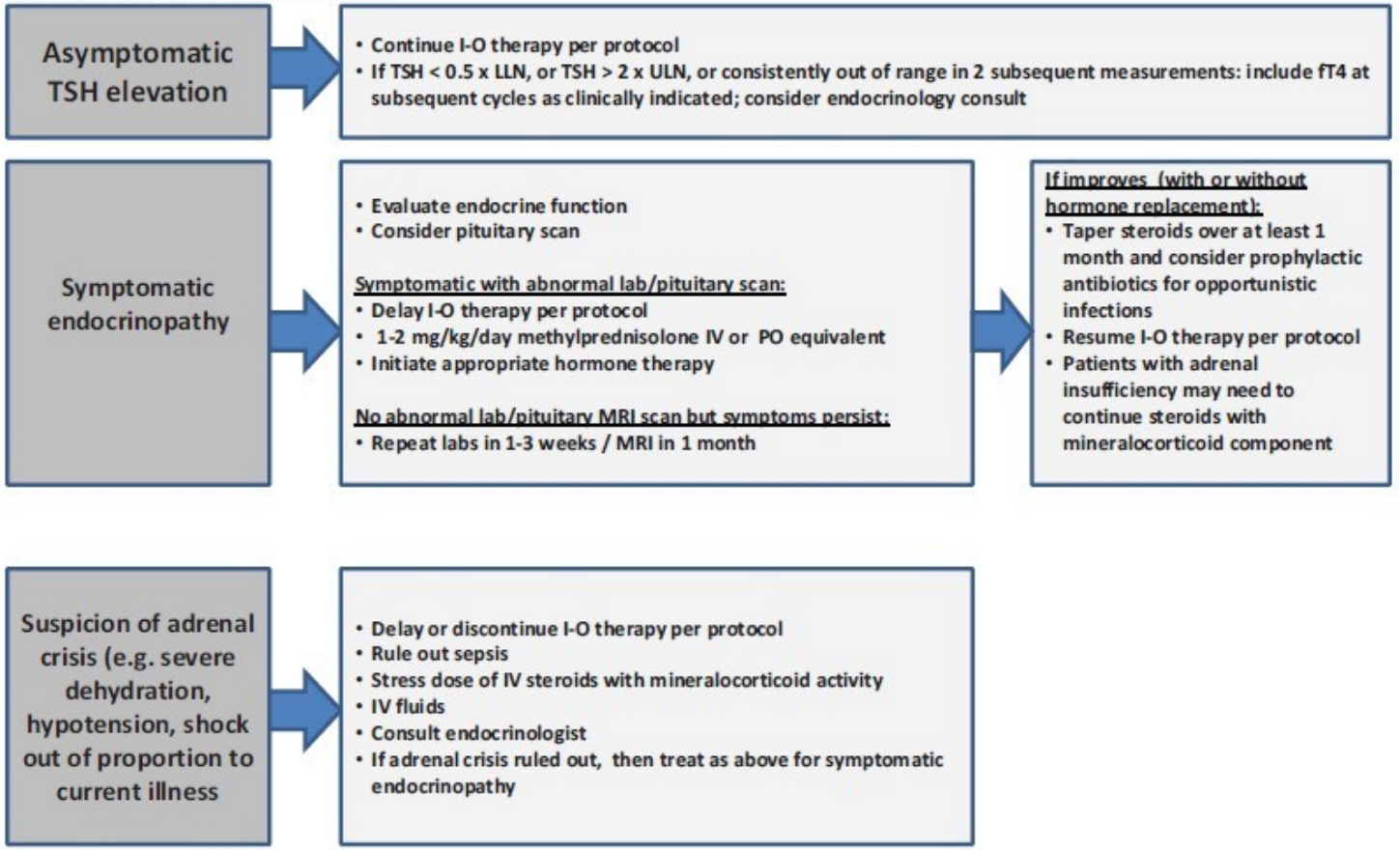
114. Lin Y, Gallardo HF, Ku GY, Li H, Manukian G, Rasalan TS, et al. Optimization and validation of a robust human T-cell culture method for monitoring phenotypic and polyfunctional antigen-specific CD4 and CD8 T-cell responses. Cytotherapy. 2009;11(7):912-22.
115. Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbe C, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clinical cancer research : an official journal of the American Association for Cancer Research. 2009;15(23):7412-20.

20.0 APPENDICES

Appendix 1: Endocrinopathy management algorithm

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.

\

Appendix 2: GI adverse event management algorithm

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.

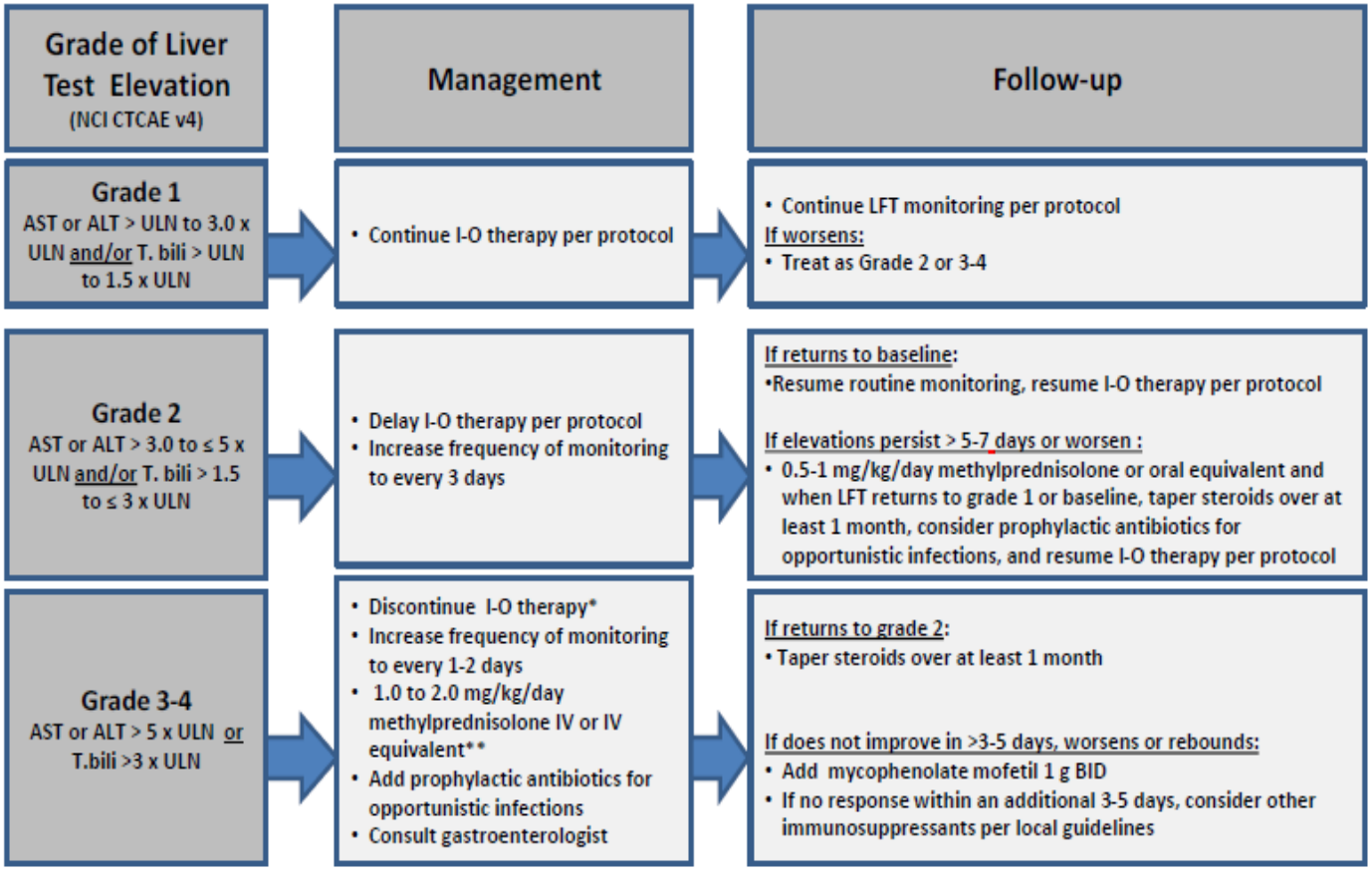
Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea: < 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat 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.

Appendix 3: Hepatic adverse event management algorithm

Hepatic Adverse Event Management Algorithm

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



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

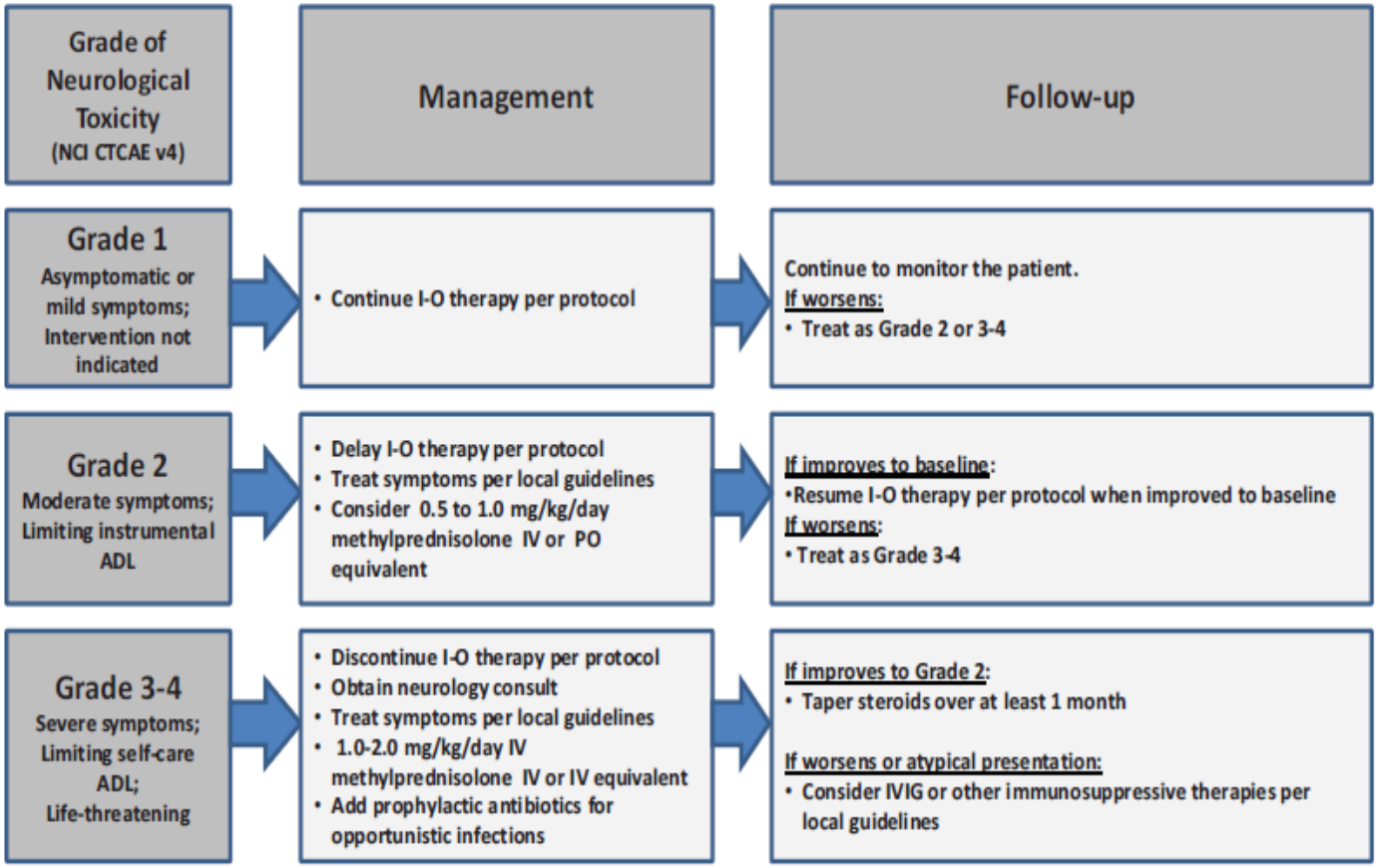
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

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

Appendix 4: Neurological adverse event management algorithm

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.

Appendix 5: Pulmonary adverse event management algorithm

Pulmonary Adverse Event Management Algorithm

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

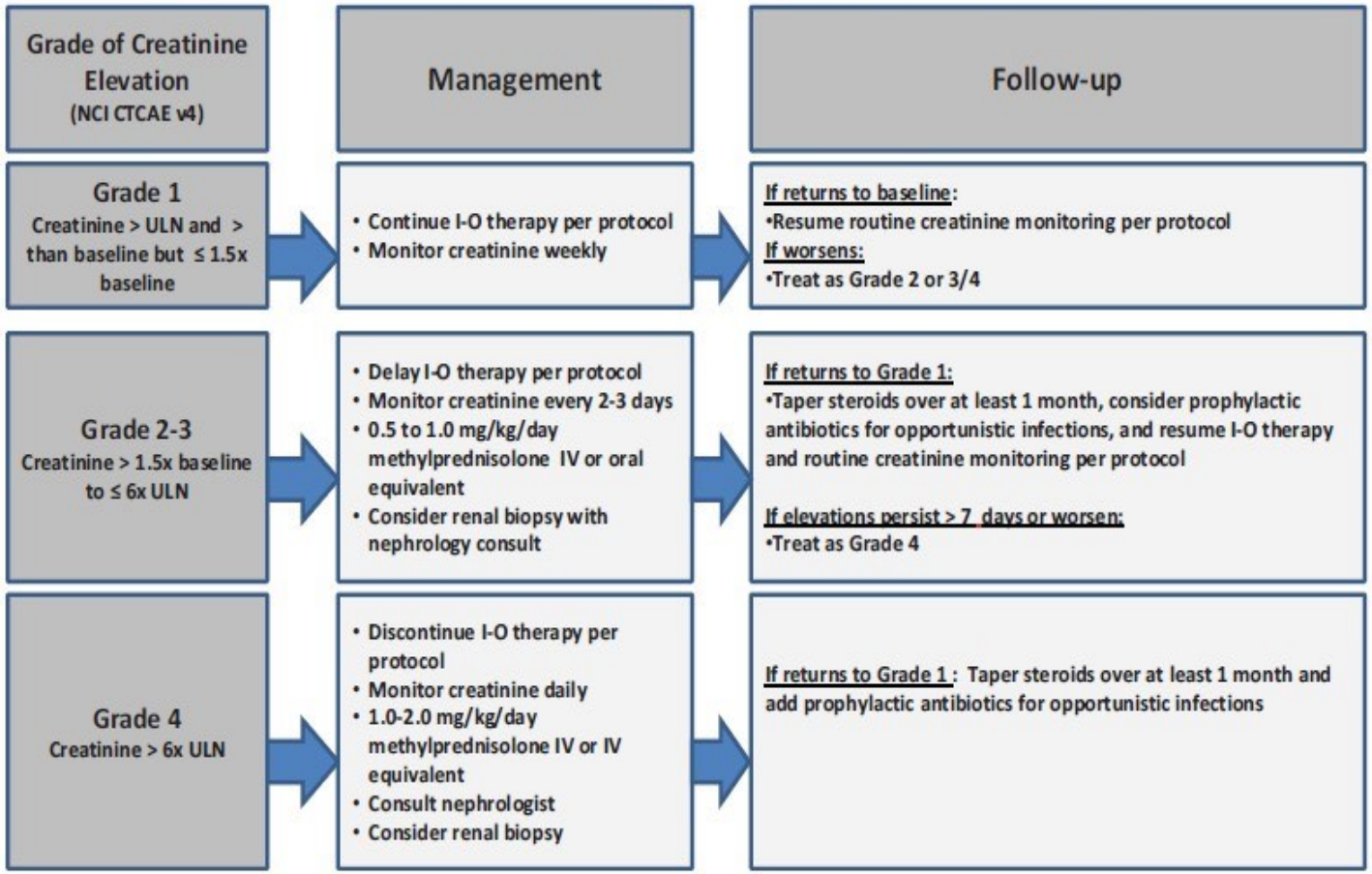
Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks **If worsens:** • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy , lung biopsy	• Re-image every 1-3 days **If improves:** • When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics **If not improving after 2 weeks or worsening:** • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	**If improves to baseline:** • Taper steroids over at least 6 weeks **If not improving after 48 hours or worsening:** • Add additional immunosuppression

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

Appendix 6: Renal adverse event management algorithm

Renal Adverse Event Management Algorithm

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

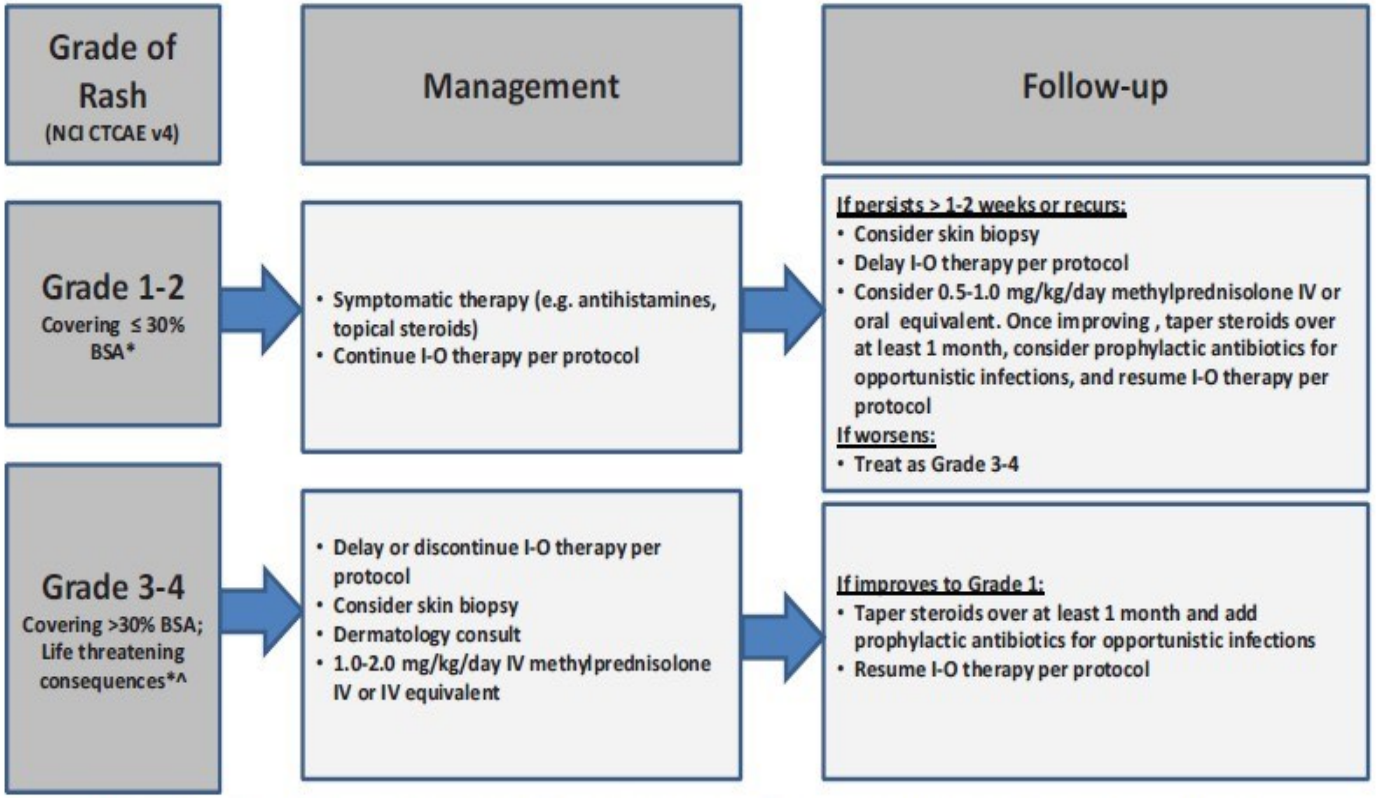


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Appendix 7: Skin adverse event management algorithm

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.