Title: A phase II study of combination immunotherapy with ipilimumab and nivolumab in patients with advanced non-small cell lung cancer resistant to anti-PD-1-axis therapy

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TITLE: A phase II study of combination immunotherapy with ipilimumab and nivolumab in patients with advanced non-small cell lung cancer resistant to anti-PD-1-axis therapy

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Contents

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PROTOCOL SYNOPSIS:

Title of Study: A phase II study of combination immunotherapy with ipilimumab and nivolumab in patients with advanced non-small cell lung cancer resistant to anti-PD-1-axis monotherapy
Primary Investigator: Scott Gettinger, MD
Study Center(s): Yale Cancer Center/Smilow Cancer Hospital and Yale Care Centers, New Haven, CT
Concept and Rationale: Approximately 20 percent of unselected patients with advanced non-small cell lung cancer (NSCLC) and progression during or after standard first line chemotherapy will experience tumor response to nivolumab[1-4]. Treatment options for patients who are not responsive to programmed death 1 (PD-1) axis inhibitor therapy are limited, and the mechanisms of primary resistance are poorly understood. The combination of nivolumab and ipilimumab is currently FDA approved for the treatment of advanced melanoma based on superiority to either agent alone[5]. The results of a phase I study evaluating combination therapy with nivolumab and ipilimumab in patients with advanced NSCLC (NCT01454102) were presented at the annual American Society of Clinical Oncology (ASCO) meeting in 2016[6]. Dosing of nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks yielded an objective response rate (ORR) by RECIST v1.1 of 39%, with one-year survival rate of 69% and grade 3-4 treatment-related adverse event rate of 33%. These results prompted an ongoing phase III study comparing this regimen to standard first line chemotherapy, nivolumab monotherapy or combination therapy with chemotherapy and nivolumab for patients with advanced NSCLC (NCT02477826). We propose a trial to evaluate if the addition of ipilimumab to nivolumab after primary resistance to anti-PD-1 axis therapy can lead to objective radiographic tumor regression. It is hypothesized that ipilimumab will enable more effective immune priming in some patients, resulting in the trafficking of tumor-specific cytotoxic T cells to the tumor, as well as depletion of tumor-permissive T regulatory cells. With concurrent nivolumab, PD-1 inhibition in the tumor will enable effective anti-tumor attack by tumor-specific T cells. Serial tumor biopsies and blood collections will allow interrogation of changes in the tumor microenvironment (and periphery) that support this hypothesis. We will primarily enroll patients who have experienced progression of NSCLC after anti-PD-1-axis therapy without initial response to such therapy ('primary resistance'). A smaller cohort of patients with acquired resistance to anti-PD-1 axis therapy (i.e. progression after initial response) will additionally be accrued.
Primary Objective/ Endpoint: - To determine the objective response rate (ORR) using RECIST v1.1 to nivolumab and ipilimumab when administered in combination to patients with pre-treated advanced

NSCLC who have experienced primary resistance to anti-PD-1 axis therapy as their last line of systemic therapy.

Secondary Objective(s)/ Endpoint(s):

- To determine the objective response rate (ORR) using immune related Response Criteria (irRC) to nivolumab and ipilimumab when administered in combination to patients with pre-treated advanced NSCLC who have experienced primary resistance to anti-PD-1 axis therapy as their last line of systemic therapy.
- To determine progression-free (RECIST v1.1 and irRC) and overall survival with nivolumab and ipilimumab when administered in combination to patients with pre-treated advanced NSCLC who have experienced primary resistance to anti-PD-1 axis therapy as their last line of systemic therapy.
- To determine ORR and progression free survival (PFS) by RECIST v1.1 and irRC, and overall survival, with nivolumab and ipilimumab in patients with pre-treated advanced NSCLC who have experienced acquired resistance to anti-PD-1 axis therapy as their last line of systemic therapy.
- To characterize the safety profile of nivolumab and ipilimumab when administered in combination, and feasibility of sequential biopsies, in patients with pre-treated advanced NSCLC who have experienced primary or acquired resistance to anti-PD-1 axis therapy as their last line of systemic therapy.
- To evaluate changes in the tumor microenvironment and blood after adding ipilimumab to nivolumab in patients with primary and acquired resistance to anti-PD-1-axis as their last line of systemic therapy.

Study Design:

This a phase II study employing a Simon two-stage design to evaluate the primary endpoint of ORR by RECIST v1.1 to combination therapy with nivolumab 3 mg/kg administered intravenously (IV) every 2 weeks, with ipilimumab 1 mg/kg administered IV every 6 weeks, in patients with advanced NSCLC and primary resistance to anti-PD-1 axis therapy. If there is at least one response or prolonged stability (> 24 weeks) using irRC appreciated in the first 10 patients who initiate trial therapy, a total of 40 patients will be enrolled. An additional 10 patients with acquired resistance to anti-PD-1 axis therapy will be enrolled in an exploratory cohort receiving the same therapy.

Tumor biopsies (and blood collection for pharmacodynamic studies) will be performed just prior to initiating trial therapy, and 9 to 10 weeks after receiving first dose of trial therapy.

Main Criteria for Inclusion/Exclusion:

Inclusion

- Age ≥18 years
- Histologically or cytologically documented, locally advanced or metastatic (i.e., Stage IIIB not eligible for definitive chemoradiotherapy, Stage IV, or recurrent) NSCLC (per the American Joint Committee /AJCC staging system)
- ECOG performance status of 0 to 2

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- Anti- PD-1 Axis therapy (anti-PD-1 or anti-PD-L1, e.g. nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab) must be the most recent systemic anti-tumor treatment received in all patients, with documented progressive disease:
    a. Patients to be enrolled to the primary cohort (primary resistance) must have had progressive disease or stable disease less than 24 weeks as the best clinical response to anti-PD-1-axis therapy.
    b. Patients to be enrolled to the exploratory cohort (acquired resistance) must have had stable disease for at least 24 weeks, partial response, or complete response as the best clinical response to anti-PD-1-axis therapy, with subsequent progression of disease.
- Chemotherapy naive and treated patients will be eligible, with no limit on number of prior therapies. Patients with NSCLC known to harbor an ALK rearrangement, or EGFR mutation known to be sensitive to FDA approved tyrosine kinase inhibitors (TKI), are only eligible after experiencing disease progression (during or after treatment) or intolerance to an FDA approved EGFR TKI or ALK TKI, respectively:
    a. Patients with TKI treated EGFR mutant NSCLC harboring the secondary EGFR T790M tumor must have received prior osimertinib.
    b. Patients with crizotinib treated ALK rearranged NSCLC must have received a next generation ALK inhibitor (e.g. ceritinib, alectinib or brigatinib).
- At least one tumor amenable to incisional, excisional, core or forceps (transbronchial) biopsy. Patients must be willing to undergo tumor biopsies before starting trial therapy, and 9 to 10 weeks after initiation of therapy:
    a. If the initial biopsy will be excisional, the excised tumor cannot be counted as a target lesion and there must be another lesion amenable to incisional, excisional, core or forceps biopsy. In this scenario, the second biopsy can only be excisional if the lesion to be excised is not a target lesion.
    b. Cytology tumor specimens (e.g. from fine-needle biopsies, or drainage of pleural/ pericardial or ascites fluid) are not acceptable. Biopsies of bone lesions that do not have a soft tissue component are also not acceptable (i.e. decalcified tumor samples are not acceptable).
- Adequate hematologic and end-organ function

Exclusion

- Subjects must not have a history of life-threatening toxicity related to prior anti-PD-1 axis therapy:
    a. Subjects with history of anti-PD-1 axis therapy toxicities that are unlikely to recur with standard countermeasures (e.g., hormone replacement after adrenal crisis) are eligible.
- Prior treatment with anti-CTLA-4 therapeutic antibodies
- Symptomatic or untreated CNS metastases. Patients with a history of treated asymptomatic CNS metastases are eligible, provided they meet all of the following criteria:
    a. No evidence of interim progression between the completion of CNS-directed therapy and the start of trial therapy.

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b. No ongoing requirement for dexamethasone as therapy for CNS disease; anticonvulsants at a stable dose are allowed.
c. Completed stereotactic radiosurgery at least 1 week prior to Cycle 1, Day 1 or whole-brain radiation at least 2 weeks prior to Cycle 1, Day 1.

- History of leptomeningeal carcinomatosis
- Prior palliative radiotherapy outside the CNS within 2 weeks of the first dose of study drug
- Treatment with systemic immunosuppressive medications (including but not limited to, dexamethasone at doses > 2 mg daily (or equivalent dose of other corticosteroids), cyclophosphamide, tacrolimus, sirolimus, azathioprine, methotrexate, thalidomide, and antitumor necrosis factor [anti-TNF] agents) within 2 weeks prior to initiating trial therapy (Inhaled or topically applied steroids, and acute and chronic standard-dose NSAIDs are permitted. Replacement steroids are also permitted).

Intervention and Mode of Delivery:

Nivolumab 3 mg/kg IV every 2 weeks and Ipilimumab 1 mg/kg IV every 6 weeks

Duration of Intervention and Evaluation:

Combination therapy with ipilimumab and nivolumab will be continued until disease progression or unacceptable toxicity. Patients with progression of disease by RECIST v1.1 without decline in performance status will be allowed to continue trial therapy if their treating physician believes they are deriving clinical benefit from study therapy.

Both RECIST v1.1 and immune-related response criteria (irRC) will be used to assess response to therapy. All patients who receive at least one dose each of ipilimumab and nivolumab will be considered evaluable.

Tumor response will be based on tumor assessments at screening, every 9 weeks from the first dose (for the first 24 weeks) and thereafter every 12 weeks until investigator-assessed initial disease progression.

Statistical Methods:

For the primary endpoint of objective response rate (ORR) by RECIST v1.1 among patients with primary resistance to anti-PD-1-axis therapy, a Simon two-stage design will be employed. The design is based on our intuition for a very low anticipated response rate and not on any specific experimental evidence. The study will terminate early if there are no responses or prolonged stability ($\geq$ 24 weeks) using irRC among the first 10 patients enrolled. Otherwise we will enroll a maximum of 40 patients with primary resistance and reject the null hypothesis of no objective response if we observe 4 or more positive responses. For a null hypothesis with a 5% ORR and alternative with a 19% ORR, this criterion has significance level 0.1 and power greater than 85%. The null and alternative hypothesis rates are not motivated by experimental evidence but rather, are examples of one pair of hypotheses that can be tested using this design.

Progression-free survival will be estimated with derivation of the corresponding 95% CI, plotted using the Kaplan-Meier method. Overall survival will be plotted using the Kaplan-Meier method.

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Time-to-event endpoints (PFS, OS) will be analyzed using the Kaplan-Meier plots. We will correlate OSS and PFS with ORR using Cox proportional hazards regression methods.No formal statistical analyses will be conducted on the 10 additional patients with acquired resistance, though the finding of immune related response in 1 or more patients would be unexpected, and should prompt further study.

Funding, Regulatory, and Feasibility Issues:

- Ipilimumab and nivolumab will be supplied by Bristol Myers Squibb Company.
- Bristol Myers Squibb Company will provide additional trial funding, including funding of serial biopsies.
- IND for trial therapy to be held by Scott Gettinger.

Patient Acceptability/Ethics and Consent Issues:

None anticipated

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1. OBJECTIVES AND ENDPOINTS

1.1. Primary Objective/ Endpoint

To determine the objective response rate (ORR) using RECIST v1.1 to nivolumab and ipilimumab when administered in combination to patients with pre-treated advanced NSCLC who have experienced primary resistance to anti-PD-1 axis therapy as their last line of systemic therapy.

1.2. Secondary Objectives/ Endpoints

A. To determine the objective response rate (ORR) using immune related Response Criteria (irRC) to nivolumab and ipilimumab when administered in combination to patients with pre-treated advanced NSCLC who have experienced primary resistance to anti-PD-1 axis therapy as their last line of systemic therapy.
B. To determine progression-free (RECIST v1.1 and irRC) and overall survival with nivolumab and ipilimumab when administered in combination to patients with pre-treated advanced NSCLC who have experienced primary resistance to anti-PD-1 axis therapy as their last line of systemic therapy.
C. To determine ORR and progression free survival (PFS) by RECIST v1.1 and irRC, and overall survival, in patients with pre-treated advanced NSCLC who have experienced acquired resistance to anti-PD-1 axis therapy as their last line of systemic therapy
D. To characterize the safety profile of nivolumab and ipilimumab when administered in combination, and feasibility of sequential biopsies, in patients with pre-treated advanced NSCLC who have experienced primary or acquired resistance to anti-PD-1 axis therapy as their last line of systemic therapy
E. To evaluate changes in the tumor microenvironment and blood after adding ipilimumab to anti- PD-1 axis therapy in patients with primary and acquired resistance to anti-PD-1-axis as their last line of systemic therapy

2. BACKGROUND

2.1. Introduction

Lung cancer remains the most common cancer worldwide[7], and is the leading cause of cancer related deaths in the United States, with an estimated 159,000 deaths in 2014[8]. Non-small cell lung cancer (NSCLC), which is the largest subgroup of lung cancer (~80%), is most often diagnosed at an advanced stage when standard first line systemic therapies result in a median survival of only 10-12 months in the healthiest patients, with one year survival rates of 40-50%[9]. Second line therapies are less effective, with associated median survival of 8 months, and one-year survival rate of approximately 30%[10,11]. Currently, no more than 2 lines of chemotherapy are recommended/FDA approved for advanced NSCLC, with lack of clear survival benefit.

A small percentage of patients with advanced NSCLC (approximately 15%) are found to have tumors driven by an epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) rearrangement. Treatment of such patients with small molecule EGFR tyrosine kinase inhibitors (TKI) or ALK TKIs respectively, can lead to high response rates; however, the majority of patients will experience progression of disease within a year of starting therapy.

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Programmed death 1 (PD-1) is an inhibitory receptor up-regulated on activated T cells, which suppresses T cell effector function upon binding to one of its two ligands, PD ligand 1 (PD-L1) or PD ligand 2 (PD-L2). PD-L1 is broadly expressed on hematopoietic cells, while PD-L2 expression is mainly found on dendritic cells. PD-1 inhibition in certain situations can protect against an excessive inflammatory response and the development of clinically apparent autoimmunity; however, in the setting of cancer, can be co-opted by tumors to suppress anti-tumor immunity at the site of the tumor. Indeed, PD-L1 upregulation has been demonstrated on several tumors, and has generally been associated with a poorer prognosis. Over the last 5 years, durable anti-tumor responses have been appreciated with a number of PD-1 and PD-L1 antagonist antibodies in clinical trials across a number of solid malignancies, including NSCLC.

Nivolumab, an IgG4 antagonist antibody against PD-1, is currently FDA approved for use in patients with advanced NSCLC who have experienced disease progression after standard platinum-based doublet chemotherapy. In patients with advanced squamous NSCLC, nivolumab was found to be superior to standard salvage docetaxel, with median over survival of 9.2 vs. 6 months (HR 0.59, 95% CI 0.44 to 0.79; p<0.001); and response rate of 20% vs 9%. Median duration of response was not reached with nivolumab, and 8.4 months with docetaxel[2]. In similar trial enrolling only patients with non-squamous NSCLC, nivolumab also improved overall survival compared to docetaxel with median survival of 12.2 months vs. 9.4 months (HR 0.73, 95% CI 0.59 to 0.89; p=0.002) with response rates of 19% vs. 12%. Duration of response was 17.2 months with nivolumab, compared to 5.6 months with docetaxel[12]. Nivolumab is also FDA approved for use in unresectable or metastatic melanoma, advanced renal cell carcinoma after anti-angiogenic therapy and classical Hodgkins disease that has relapsed or progressed after autologous hematopoietic stem cell transplantation and post-transplantation brentuximab vedotin.

Pembrolizumab, another IgG4 antagonist antibody to PD-1, is also approved for use in patients with advanced NSCLC and progressive disease after standard platinum based doublet chemotherapy. However, unlike nivolumab which is FDA approved regardless of tumor PD-L1 expression, pembrolizumab can only be prescribed to patients with tumor PD-L1 protein expression (i.e. at least 1% of tumor cells showing PD-L1 expression). Initial approval was based on a large phase I trial which reported a response rate of 45% in 73 patients with high PD-L1 expression, with median duration of response of 12.5 months. Among the 57 patients with previously treated advanced NSCLC, response rate was 44%. A subsequent phase III trial randomized 1034 patients with advanced pre-treated NSCLC with at least 1% of tumor cells demonstrating PD-L1 expression to salvage pembrolizumab (2mg/ kg or 10 mg/kg dose) versus docetaxel. Overall survival and response rates were higher with the pembrolizumab arms; median survival/response rates were 10.4 months/ 18% (2mg/kg dose) and 12.7 months/ 18% (10 mg/kg dose) versus 8.5 months/ 9% for the docetaxel treated group [HR 0.71, 95% CI 0.58-0.88 and 0.61, 95% CI 0.49-0.75, respectively][13]. In October 2016, the FDA additionally approved the use of pembrolizumab in the first-line setting for patients with advanced NSCLC with high PD-L1 tumor expression (i.e. at least 50% of tumor cells expressing PD-L1). Approval was based on a Phase III trial demonstrating improvement in progression-free and overall survival with pembrolizumab compared to standard platinum-based doublet chemotherapy in patients with untreated advanced PD-L1 high tumors, with median of PFS 10.3 months versus 6 months (HR 0.50, 95% CI 0.37 to 0.68; p<0.001) and estimated rate of overall survival at 6 months of 80% in the

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pembrolizumab group versus 72.4% in the chemotherapy group (HR 0.60, 95% CI 0.41 to 0.89; p=0.005)[14].

Cytotoxic T lymphocyte antigen 4 (CTLA-4) is another immune checkpoint inhibitor receptor which is upregulated on naïve T cells when presented with antigen. It is also constitutively expressed on T regulatory cells. Upon engagement with CD80 or CD86 expressed on antigen presenting cells, it delivers an inhibitors signal resulting in downregulation of immune responses. Antagonist antibodies to CTLA-4 have shown activity across tumor types in early studies, including advanced NSCLC.

Ipilimumab, an IgG1 antagonist antibody against CTLA-4, was initially FDA-approved for use as monotherapy in patients with unresectable or metastatic melanoma on the basis of an OS advantage found in comparison with an investigational tumor vaccine and placebo as part of a randomized, double-blind, double-dummy trial[15]. It was later approved as adjuvant monotherapy for patients with completely resected cutaneous melanoma with lymph node involvement. Recently, ipilimumab was approved for use in combination with nivolumab for patients with unresectable or metastatic melanoma based on a phase III trial demonstrating an improvement in progression free survival compared to either ipilimumab or nivolumab alone. The combination was associated with more toxicity; grade 3 or 4 treatment related adverse events were reported in 16%, 27% and 55% of patients treated with nivolumab alone, ipilimumab alone, or combination therapy, respectively[5].

The combination of nivolumab and ipilimumab is currently being evaluated in patients with advanced NSCLC, with results from a phase I reported at the annual American Society of Clinical Oncology (ASCO) meeting in 2016 (see Section 2.2.2). Based on promising results, a phase III trial was initiated randomizing patients with PD-L1 positive tumors to standard platinum based doublet chemotherapy, nivolumab alone or combination of nivolumab and ipilimumab. Patients with PD-L1 negative tumors are randomized to combination therapy with nivolumab and ipilimumab to standard platinum doublet chemotherapy with or without concurrent nivolumab.

2.2. Study Rationale

It is hypothesized that pharmacologic antagonism of CTLA-4 can overcome resistance to anti-PD-1-axis monotherapy in subjects with advanced NSCLC by enabling more effective tumor immune priming and/or releasing immune suppression mediated by T regulatory cells. This approach is supported by preclinical studies, and clinical studies in advanced melanoma demonstrating superiority of combination therapy with nivolumab and ipilimumab compared to either agent alone. Preliminary results from large phase I/dose expansion clinical trials evaluating combination therapy with anti-CTLA-4 and anti-PD-1 axis therapy in advanced NSCLC further support evaluation of combination therapy NSCLC[6,16]. We propose a trial to evaluate whether the addition of ipilimumab to nivolumab after primary resistance to anti-PD-1-axis therapy can lead to objective radiographic tumor regression. Serial tumor biopsies (and blood collections) will allow interrogation of changes in the tumor microenvironment (and periphery) that support this hypothesis.

2.2.1. Pre-Clinical Studies

In vitro combinations of nivolumab plus ipilimumab increase IFN-γ 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

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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[17].

2.2.2 Clinical Studies

The combination of nivolumab and ipilimumab is currently FDA approved for use in patients with unresectable or metastatic melanoma. Approval was based on a phase III study randomizing 945 previously untreated stage III or IBV melanoma to nivolumab alone, nivolumab combined with ipilimumab, or ipilimumab alone. Progression free survival (co-primary endpoint with overall survival) was 11.5 months with nivolumab plus ipilimumab (95% CI, 8.9 to 16.7), as compared to 2.9 months (95% CI 2.8 to 3.4) with ipilimumab (hazard ratio for death or disease progression, 0.42; 99.5% CI, 0.31 to 0.57; P<0.001) and 6.9 months (95% CI, 4.3 to 9.5) with nivolumab (hazard ratio for the comparison with ipilimumab, 0.57; 99.5% CI, 0.43 to 0.76; P<0.001). Overall response rates were 44% (nivolumab alone), 58% (nivolumab plus ipilimumab) and 19% (ipilimumab alone). Although the trial was not powered to compare treatments by PD-L1 expression, both nivolumab alone and in combination with ipilimumab resulted in a similar prolongation of progression free survival compared to ipilimumab alone in patients with PD-L1 positive tumors (with overall response rate slightly higher numerically with combination therapy at 72% % compared to nivolumab alone at 58%)[5].

The combination of nivolumab and ipilimumab has been evaluated as first line therapy for patients with advanced NSCLC with promising activity. Safety and efficacy results from two combination arms varying the schedule of ipilimumab (nivolumab 3mg/kg every 2 weeks with ipilimumab 1 mg/kg administered either once every 6 or 12 weeks), are shown below (Table 2.2.1 & 2.2.2, Figure 2.2.1). Also shown below is another arm of the trial evaluating first line nivolumab monotherapy (3mg/kg every 2 weeks) in patients with advanced NSCLC. Therapy in all arms was continued until disease progression or unacceptable toxicity. Patients were allowed to continue therapy despite progression of disease if they were felt to be deriving clinical benefit without worsening of their performance status. The primary endpoint of all arms was safety and tolerability, with secondary endpoints of ORR (RECIST v1.1) and PFS at 24 weeks.

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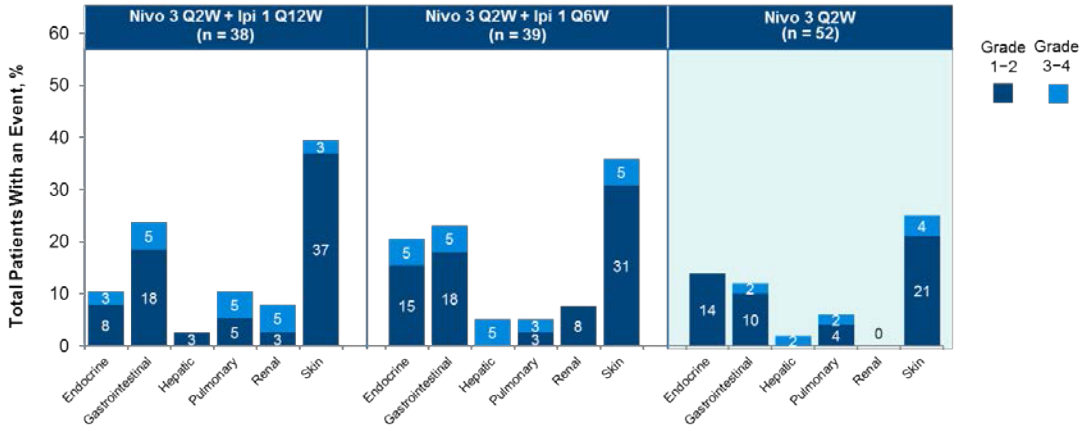
TABLE 2.2.1: Nivolumab Plus Ipilimumab in First-line NSCLC: Safety Summary

	Nivo 3 Q2W + Ipi 1 Q12W (n = 38)		Nivo 3 Q2W + Ipi 1 Q6W (n = 39)		Nivo 3 Q2W (n = 52)	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Treatment-related AEs, %	82	37	72	33	71	19
Treatment-related AEs leading to discontinuation, %	11	5	13	8	10	10

- There were no treatment-related deaths
- Treatment-related grade 3–4 AEs led to discontinuation at a third of the rate seen with older combination arms using higher or more frequent doses of ipilimumab[6]

FIGURE 2.2.1: Nivolumab Plus Ipilimumab in First-line NSCLC: Treatment-related Select AEs



- All treatment-related pulmonary events were pneumonitis
- Grade 1–2 hypersensitivity/infusion reaction occurred in 5% and 6% of patients in the nivo 3 Q2W + ipi 1 Q12W and monotherapy groups, respectively

TABLE 2.2.2: Nivolumab Plus Ipilimumab in First-line NSCLC: Summary of Efficacy

	Nivo 3 Q2W + Ipi 1 Q12W (n = 38)	Nivo 3 Q2W + Ipi 1 Q6W (n = 39)	Nivo 3 Q2W (n = 52)
Confirmed ORR, % (95% CI)	**47** (31, 64)	**39** (23, 55)	**23** (13, 37)
Median duration of response, mo (95% CI)	NR (11.3, NR)	NR (8.4, NR)	NR (5.7, NR)
Median length of follow-up, mo (range)	12.9 (0.9–18.0)	11.8 (1.1–18.2)	14.3 (0.2–30.1)
Best overall response, %			
Complete response	0	0	8
Partial response	47	39	15
Stable disease	32	18	27
Progressive disease	13	28	38
Unable to determine	8	15	12
Median PFS, mo (95% CI)	8.1 (5.6, 13.6)	3.9 (2.6, 13.2)	3.6 (2.3, 6.6)
1-year OS rate, % (95% CI)	NC	69 (52, 81)	73 (59, 83)

NC = not calculated (when >25% of patients are censored); NR = not reached

Combination data based on a February 2016 database lock; monotherapy data based on a March 2015 database lock except for OS data, which are based on an August 2015 database lock

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2.2.3. Rationale for Shorter Infusion Times

Previous clinical studies of nivolumab monotherapy and ipilimumab monotherapy and the combination of nivolumab and ipilimumab have used a 60-minute infusion duration for nivolumab and 90-minute infusion duration for ipilimumab (1-3 mg/kg dosing for both). However, both nivolumab and ipilimumab have been administered at up to 10 mg/kg with the same infusion duration.

In Study CA209010 (a Phase 2, randomized, double-blinded, dose-ranging study of nivolumab in subjects with advanced/metastatic clear cell RCC), a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg and 18.5% at 10 mg/kg). All the events were Grade 1-2 and were manageable. An infusion duration of 30 minutes for 3 mg/kg nivolumab (30% of the dose provided at 10 mg/kg) would not be expected to present any safety concerns compared to the prior experience at 10 mg/kg nivolumab dose infused over a 60-minute duration.

Similarly, ipilimumab at 10 mg/kg has been safely administered over 90 minutes. In the CA184022 study, where ipilimumab was administered up to a dose of 10 mg/kg, on-study drug related hypersensitivity events (Grade 1-2) were reported in 1 (1.4%) subject in the 0.3 mg/kg and in 2 (2.8%) subjects in the 10 mg/kg group. There were no drug-related hypersensitivity events reported in the 3 mg/kg group. Across the 3 treatment groups, no Grade 3-4 drug-related hypersensitivity events were reported, and there were no reports of infusion reactions. Ipilimumab 10 mg/kg monotherapy has also been safely administered as 90-minute infusion in large Phase 3 studies in prostate cancer (CA184043) and as adjuvant therapy for stage 3 melanoma (CA184029), with infusion reactions occurring in subjects. Administering 1 mg/kg of ipilimumab represents one-tenth of the 10 mg/kg dose.

Infusion reactions including high-grade hypersensitivity reactions have been uncommon across nivolumab or ipilimumab clinical studies or the combination of nivolumab and ipilimumab. A 30-minute break after the first infusion for combination cohort will ensure the appropriate safety monitoring before the start of the second infusion. Overall, a change in safety profile is not anticipated with 30-minute infusion of nivolumab, ipilimumab or combination.

3. PATIENT SELECTION

3.1. Inclusion Criteria

A. Signed Informed Consent

B. Ability to comply with the protocol

C. Age ≥18 years

D. Histologically or cytologically documented, locally advanced or metastatic (i.e., Stage IIIB not eligible for definitive chemoradiotherapy, Stage IV, or recurrent) NSCLC (per the American Joint Committee /AJCC staging system)

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E. ECOG performance status of 0 to 2

F. Measurable disease, as defined by RECIST v1.1. Previously irradiated lesions can be counted as target lesions if clearly progressing after radiation.

G. Chemotherapy-naive and treated patients will be eligible, with no limit on number of prior therapies. Patients with NSCLC known to harbor an ALK rearrangement, or EGFR mutation known to be sensitive to FDA-approved tyrosine kinase inhibitors (TKI), are only eligible after experiencing disease progression (during or after treatment) or intolerance to an FDA approved EGFR TKI or ALK TKI, respectively.

    a. Patients with TKI-treated EGFR mutant NSCLC harboring the secondary EGFR T790M tumor must have received prior osimertinib
    b. Patients with crizotinib-treated ALK rearranged NSCLC must have received a next generation ALK inhibitor (e.g. ceritinib, alectinib or brigatinib)

H. Prior palliative radiotherapy must have been completed at least 2 weeks before the first dose of study drug.

I. Anti- PD-1 Axis therapy (anti-PD-1 or anti-PD-L1, e.g. nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab) must be the most recent systemic anti-tumor treatment received in all patients, with documented progressive disease. Last administration of anti-PD-1 axis therapy must have been at least 3 weeks before the first dose of study drug.

    a. Patients to be enrolled to the primary cohort (primary resistance) must have had progressive disease or stable disease less than 24 weeks as the best clinical response to anti-PD-1-axis monotherapy
    b. Patients to be enrolled to the exploratory cohort (acquired resistance) must have had stable disease for at least 24 weeks, partial response, or complete response as the best clinical response to anti-PD-1-axis monotherapy, with subsequent progression of disease

J. At least one tumor amenable to incisional, excisional, core or forceps (transbronchial) biopsy. Patients must be willing to undergo tumor biopsies before starting trial therapy, and 9 to 10 weeks after initiation of therapy.
    a. If the initial biopsy will be excisional, the excised tumor cannot be counted as a target lesion and there must be another lesion amenable to incisional, excisional, core or forceps biopsy. In this scenario, the second biopsy can only be excisional if the lesion to be excised is not a target lesion.
    b. Cytology tumor specimens (e.g. from fine-needle biopsies, or drainage of pleural/ pericardial or ascites fluid) are not acceptable. Biopsies of bone lesions that do not have a soft tissue component are also not acceptable (i.e. decalcified tumor samples are not acceptable).

K. For female patients of childbearing potential and male patients with partners of childbearing potential, agreement (by patient and/or partner) to use a highly effective form(s) of contraception (i.e., one that results in a low failure rate [‹1% per year] when used consistently and correctly) and to continue its use for 6 months after the last dose of trial therapy. Highly effective contraception is one with a failure rate of ‹0.1%. Birth

control pills on their own do not achieve that rate.

a. Women of childbearing potential must have a negative pregnancy test (serum or urine) within 72 hours of the start of study drug administration
b. Women who have recently given birth must no longer be breastfeeding

L. Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 14 days prior to the first study treatment:

- Neutrophils ≥1500 cells/µL (without granulocyte colony-stimulating factor support within 2 weeks prior to Cycle 1, Day 1)
- Platelets ≥75,000/µL (transfusion to achieve this level is not permitted within 2 weeks of the first study drug administration)
- Hemoglobin ≥9.0 g/dL
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 x institutional upper limit of normal (ULN) with the following exceptions: Patients with documented liver metastases: AST and/or ALT≤5 x ULN
- Serum bilirubin ≤1.5 x ULN (Patients with known Gilbert disease who have serum bilirubin level ≤3 x ULN may be enrolled)
- Serum creatinine ≤1.5 x ULN or creatinine clearance ≥50 mL/min

3.2. Exclusion Criteria

A. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects who require intermittent use of inhaled steroids or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement, or psoriasis not requiring systemic therapy (within the past 3 years) will not be excluded from the study.

B. Interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity

C. Subjects must not have a history of life-threatening toxicity related to prior anti-PD-1 axis therapy

a. Subjects with history of anti-PD-1 axis therapy toxicities that are unlikely to recur with standard countermeasures (e.g., hormone replacement after adrenal crisis) are eligible.

D. Prior treatment with anti-CTLA-4 therapeutic antibodies

E. Symptomatic or untreated CNS metastases. Patients with a history of treated asymptomatic CNS metastases are eligible, provided they meet all of the following criteria:

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a. No evidence of interim progression between the completion of CNS-directed therapy and the start of trial therapy.
b. No ongoing requirement for dexamethasone as therapy for CNS disease; anticonvulsants at a stable dose are allowed.
c. Completed stereotactic radiosurgery at least 1 week prior to Cycle 1, Day 1 or whole-brain radiation at least 2 weeks prior to Cycle 1, Day 1

F. History of leptomeningeal carcinomatosis

G. Prior palliative radiotherapy outside the CNS within 2 weeks of the first dose of study drug.

H. Treatment with systemic immunosuppressive medications (including but not limited to, dexamethasone at doses > 2 mg daily (or equivalent dose of other corticosteroids), cyclophosphamide, tacrolimus, sirolimus, azathioprine, methotrexate, thalidomide, and antitumor necrosis factor [anti-TNF] agents) within 2 weeks prior to initiating trial therapy (Inhaled or topically applied steroids, and acute and chronic standard-dose NSAIDs are permitted. Replacement steroids are also permitted).

I. Subjects must not have received vaccines containing live virus for prevention of infectious diseases within 12 weeks prior to the first dose of study drug.

a. The use of inactivated seasonal influenza vaccines (eg, Fluzone®) will be permitted on study without restriction.

J. Any approved systemic anti-cancer therapy, within 3 weeks prior to initiation of study treatment; the following exception is allowed:
- TKIs approved for treatment of NSCLC discontinued > 7 days prior to Cycle 1, Day 1. The baseline scan must be obtained after discontinuation of prior TKIs.

K. Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 21 days prior to enrollment; the following exceptions are allowed:
- Unapproved/experimental TKIs discontinued 14 days prior to Cycle 1, Day 1

L. Known infection with HIV, HBV or HCV. Patients with prior exposure to hepatitis, but no evidence of active or chronic infection, may be eligible.
- Subjects with positive hepatitis C antibody and negative quantitative hepatitis C by polymerase chain reaction are eligible.

M. Active systemic infection requiring systemic antibiotic treatment within 72 hours prior to first dose of study treatment

N. Uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure, unstable angina pectoris, or psychiatric illness/social situations that would limit compliance with study requirements

O. Major surgery or traumatic injury within 4 weeks of starting study drug

P. Women who are pregnant or lactating.

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Q. Any underlying medical condition that in the Principal Investigator's opinion will make the administration of study drug hazardous to the patient or would obscure the interpretation of adverse events.

4. TREATMENT PLAN

4.1. Study Design

This is a phase II study employing a 2-stage design to evaluate the primary endpoint of ORR to combination therapy with nivolumab 3 mg/kg administered intravenously (IV) every 2 weeks with ipilimumab 1 mg/kg administered IV every 6 weeks in patients with advanced NSCLC and primary resistance to anti-PD-1 axis therapy. If there is at least 1 response or prolonged stability ($\geq$ 24 weeks) using irRC appreciated in the first 10 patients who initiate trial therapy, an additional 30 patients will be enrolled to a total of 40 patients. An additional 10 patients with acquired resistance to anti-PD-1 axis therapy will be enrolled in an exploratory cohort receiving the same therapy.

4.1.1. Tumor Biopsies and Pharmacodynamic Blood Draws

A trial tumor biopsy will be required of all enrolled patients before starting treatment. A second mandatory tumor biopsy will be performed between day 56 and 70 of trial therapy (9-10 weeks after initiation of therapy). These on-trial tumor biopsies must be collected via core, forceps, or incision/ excision. Although the second biopsy will generally be obtained from the same site as the first one, there may be circumstances when another tumor site would alternatively be biopsied (e.g. lesion initially biopsied becomes too small to safely and/or effectively biopsy).

Optional biopsies may be performed at sites of response (including partial response, or stable disease at least 24 weeks) or progression while on treatment. We anticipate that such biopsies will help to characterize changes in the tumor immune microenvironment that play a role in mitigating response or resistance to treatment, respectively.

If archived tumor tissue from a biopsy performed prior to enrollment is available, unstained slides or block will be requested for additional analysis of biomarkers (as consented to in the informed consent document).

Blood draws to characterize the peripheral anti-tumor immunologic milieu will be collected prior to the initiation of combination therapy. Serial draws will be performed 2 weeks, 4 weeks, 6 weeks, and 9 weeks after the initiation of therapy (should correspond with timing of on-treatment biopsy) as well as at the time of disease progression.

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4.2. Description, packaging, labeling and storage of study drugs

Table 4.2: Study Drugs

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Nivolumab Solution for Injection	100 mg (10 mg/mL)	10 mL per vial/ Open-label	5 per carton/ Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8° C. Protect from light and freezing
Ipilimumab Solution for Injection	200 mg (5mg/mL)	40 mL vial/Open-label	4 vials per carton/Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8° C. Protect from light and freezing

4.3. Treatment Schedule and Dosing Plan

Enrolled subjects will receive treatment with nivolumab 3 mg/kg as a 30-minute infusion every 2 weeks and ipilimumab 1 mg/kg as a 30-minute infusion 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. 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 to the nearest milligram. There will be no dose modifications allowed.

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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. If an acute infusion reaction is noted, subjects should be managed according to Section 4.8.5.

Doses of nivolumab and/or ipilimumab may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment.

4.3.1. Dose Delay Criteria

Dose delay criteria apply to all drug-related AEs. Treatment delays are allowable up to 6 weeks for nivolumab and 12 weeks for ipilimumab from the last dose (any dose delays greater than this will require approval from the medical monitor).

Tumor assessments for all subjects should continue as per protocol **even if dosing is delayed.**

Nivolumab and ipilimumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related adverse event, except for fatigue and laboratory abnormalities
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related AE
- Grade 3 drug-related laboratory abnormality with the following exceptions:
    - Grade 3 lymphopenia or asymptomatic amylase or lipase elevation does not require dose delay
    - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation
    - Any AE, laboratory abnormality or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Participants who have drug-related toxicities that meet the criteria for dose delay should have both drugs (ipilimumab and nivolumab) delayed until retreatment criteria are met. (Exceptions apply to the retreatment criteria after dose delay of ipilimumab and nivolumab for Grade ≥ 3 amylase and lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and that are attributed to ipilimumab alone.)

Rescheduling:

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 (every 2 weeks $\pm$ 3 days) and ipilimumab (every 6 weeks $\pm$ 5 days) may be adjusted within the permitted $\pm$ 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.

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

A dose delay of ipilimumab which results in no ipilimumab dosing for > 12 weeks requires ipilimumab discontinuation, with exceptions as noted in Section 4.3.3.2.

4.3.2. Dose Reductions

There will be no dose reductions for nivolumab or ipilimumab

4.3.3. Criteria to Resume Dosing

4.3.3.1 Criteria to Resume Nivolumab Dosing

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

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- For subjects with Grade 2 AST, ALT, or Total bilirubin elevations, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (see package insert) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the PI.
- Subjects with Grade 1-3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the PI
- 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.
- Participants who delay study treatment due to any Grade ≥ 3 amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis, and that is assessed by the investigator to be related to ipilimumab and not to nivolumab, may resume nivolumab when the amylase or lipase abnormality has resolved to Grade < 3. The PI should be consulted prior to resuming nivolumab in such participants.
- Dose delay of nivolumab that results in treatment interruption of > 6 weeks requires treatment discontinuation, with exceptions as noted in Section 4.3.4.
- One exception to note is when ipilimumab and nivolumab doses are delayed due to drug-related Grade ≥ 3 amylase or lipase abnormalities not associated with symptoms or clinical manifestations of pancreatitis. If the investigator assesses the Grade ≥ 3 amylase or lipase abnormality to be related to ipilimumab and not related to nivolumab, nivolumab may be

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resumed when the amylase or lipase abnormality resolves to Grade < 3 but ipilimumab may only be resumed when the amylase or lipase abnormality resolves to Grade 1 or baseline. Investigator attribution of this toxicity to the ipilimumab dosing must be clearly noted in the participant's medical chart. The PI should be consulted prior to resuming nivolumab in such participants.

- If any of the above mentioned syndromes occur only after administration of nivolumab with ipilimumab and not after nivolumab-only doses, and the investigator feels that ipilimumab is the cause, nivolumab may be resumed if the above criteria are met

4.3.3.2 Criteria to Resume Ipilimumab Dosing

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

- Participants may resume treatment in the presence of Grade 2 fatigue.
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Participants with baseline Grade 1 AST/ALT or total bilirubin elevations who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT or total bilirubin.
- Participants with combined Grade 2 AST/ALT and total bilirubin values meeting discontinuation parameters (Section 4.3.4) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the PI.
- Participants who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≤ 10 mg/day.
- Subjects with Grade 1-3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the PI.
- Dose delay of ipilimumab which results in no ipilimumab dosing for > 12 weeks requires ipilimumab discontinuation, with exceptions as noted in Section 4.3.4. 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.

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

In general, participants who meet criteria to resume ipilimumab will also have met criteria to resume nivolumab, so it should be feasible to synchronize dosing of both drugs when resuming ipilimumab. In order to facilitate this, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted ± 5 day window, as long as consecutive nivolumab doses are given at least 12 days apart.

One exception to note is when ipilimumab and nivolumab doses are delayed due to drug-related

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Grade ≥ 3 amylase or lipase abnormalities not associated with symptoms or clinical manifestations of pancreatitis. If the investigator assesses the Grade ≥ 3 amylase or lipase abnormality to be related to ipilimumab and not related to nivolumab, nivolumab may be resumed when the amylase or lipase abnormality resolves to Grade < 3 but ipilimumab may only be resumed when the amylase or lipase abnormality resolves to Grade 1 or baseline. Investigator attribution of this toxicity to the ipilimumab dosing must be clearly noted in the participant's medical chart. The PI should be consulted prior to resuming nivolumab in such participants.

4.3.4. Treatment Discontinuation Criteria

For all subjects, global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration' in the source data. Every effort should be made to document objective progression (i.e., radiographic confirmation) even after discontinuation of treatment.

4.3.4.1. Nivolumab or Ipilimumab Dose Discontinuation

Treatment with nivolumab or ipilimumab must be permanently discontinued for any of the following:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, or recurs with the following exceptions for laboratory abnormalities, diarrhea, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
    - Grade 3 drug-related diarrhea, colitis, neurologic toxicity, 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. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
    - 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 require discontinuation:
            - Grade ≥ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation. In most cases of Grade 3 AST or ALT elevation, study drug(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug(s), a discussion between the investigator and the PI must occur.
            - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin), except for the following events which do not require discontinuation:

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  - Grade 4 neutropenia ≥ 7 days
  - Grade 4 lymphopenia or leukopenia
  - 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 endocrinopathy adverse events, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the PI.
- Any Grade ≥ 2 drug-related pneumonitis or interstitial lung disease that does not resolve with dose delay and systemic steroids (also see package insert for Pulmonary Adverse Event Management)
- 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/ ipilimumab dosing.
- Any event that leads to delay in dosing lasting > 6 weeks (or 12 weeks for ipilimumab) from the previous dose requires discontinuation, with the following exceptions:
  1. Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
  2. Dosing delays lasting > 6 weeks (or 12 weeks for ipilimumab) from the previous dose that occur for non-drug-related reasons may be allowed if approved by the PI.
- In the case of pregnancy, the investigator must immediately notify the Sponsor or designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please contact the Sponsor or designee within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the PI must occur.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks (or 12 weeks for ipilimumab), the PI must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

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 participant meets criteria for discontinuation and investigator is unable to determine whether the event is related to both or one study drug, the participant should discontinue both nivolumab and ipilimumab and be taken off the treatment phase of the study. Continuation of ipilimumab after discontinuation of nivolumab is not allowed on study.

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4.4. Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

1 Disease progression (PD by RECIST 1.1 with exception discussed in section 4.6

2 Symptomatic deterioration of health status without objective evidence of disease progression. Every effort should be made to document objective progression of disease in such cases.

3 Unmanageable toxicity attributed to trial therapy (see section 4.9)

4 Development of intercurrent illness limiting the ability to comply with study or the development of uncontrolled concurrent illness that prevents further administration of treatment or confound the ability to interpret data

6 General or specific changes in the patient's condition rendering the patient unacceptable for further treatment in the judgment of the investigator

7 Patient request for discontinuation, patient withdrawal from study, or patient lost to follow up

8 Death

9 Study termination

4.5. Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 4.4 applies. The reason for study removal and the date the patient was removed must be documented.

4.6. Treatment Beyond Disease Progression

Subjects will be permitted to continue trial treatment beyond RECIST v1.1 defined PD as long as they meet the following criteria:

- Investigator-assessed clinical benefit and no rapid disease progression
- Subject is tolerating study treatment
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases, impending vital organ compromise)
- Subject provides written informed consent prior to receiving additional nivolumab and or ipilimumab treatment, using an informed consent form describing any reasonably foreseeable risks or discomforts, or other alternative treatment options. The decision to continue treatment beyond initial progression should be discussed with the PI.

Additionally, in cases where the majority of the disease is stable or responding, and progressing lesions can be controlled with local therapy (i.e. resection or radiotherapy), the patient may be continued on trial following local therapy.

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4.7. Duration of Follow Up

Patients who discontinue trial therapy will be followed for survival after removal from study until death.

4.8. General concomitant therapy and management of safety concerns

4.8.1. Concomitant therapy

Additional anti-tumor therapies are prohibited during study treatment. The use of corticosteroids or other immunosuppressive medications will not be allowed during study therapy (unless used to treat a drug related adverse event). Low-dose steroid use (≤2mg of dexamethasone or equivalent) as corticosteroid replacement therapy is allowed.

4.8.2. Management of Safety concerns

Measures will be taken to ensure the safety of patients participating in this trial, including the use of stringent inclusion and exclusion criteria (section 3.1 and 3.2) and close monitoring (as indicated below and in Sections 5 and 6). See Section 6 for complete details regarding safety reporting for this study.

4.8.3. Monitoring

Safety 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. (see appendix 1). Patients will be assessed for safety (including laboratory values) according to Section 5 Patients will be followed for safety for 100 days following the last dose of study treatment.

General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistries and blood counts (see Section 5 for the list and timing of study assessments). All SAEs and protocol-defined events of special interest (see Section 6) will be reported in an expedited fashion (see Section 6.5). In addition, investigators will review and evaluate observed AEs on a regular basis.

Patients who have an ongoing study treatment–related adverse event upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anti-cancer treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or until it has been determined that study treatment or participation is not the cause of the AE.

4.8.4. Management for Immuno-Oncology Agent AEs

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab and ipilimumab are considered immuno- oncology agents in this protocol. Early recognition and management of AEs associated with immuno- oncology agents may mitigate severe toxicity. Please review the label/package insert for Management Algorithms developed to assist investigators in assessing and managing AEs.

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4.8.5. Treatment of Nivolumab or Ipilimumab Infusion Reactions

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the PI and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (Version 4) guidelines.

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

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

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

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

Stop the nivolumab or ipilimumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab or ipilimumab 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.

For future infusions, 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 or ipilimumab infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef 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)

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

5. STUDY ASSESSMENTS AND PROCEDURES

A window of -2 / +3 days can be applied to scheduled visits for nivolumab and ipilimumab administration if necessary for holidays, vacations, inclement weather, etc.

5.1. Screening Period

The following procedures and tests will be completed during this period to determine eligibility. All procedures to be completed within 28 days of first dose, except labs. All labs should be collected within 14 days of first dose.

1) History and physical examination

2) Measurement of height, weight and vital signs (including blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature).

3) Performance status evaluation

4) CBC with differential, serum chemistry (Na, K, Cl, CO2, BUN, creatinine, glucose, calcium), magnesium, phosphate, amylase, lipase, liver function tests (albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST), LDH, TSH (with reflex to free T3 and free T4)

5) Pregnancy test (serum or urine) for women of childbearing potential. Sexually active women of childbearing potential must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized.

6) Systemic tumor assessment with CT scan of the chest/abdomen/pelvis and CT or MRI Brain (MRI preferable). MRI brain required only if known or suspected brain metastases.

If eligible, a tumor biopsy and blood draw for research studies (approximately 2 tablespoons of blood) will be performed prior to initiation of therapy (see section 4.1.1).

5.2. On-Study Visits

The day of the nivolumab infusion (every 2 weeks) and the day of the ipilimumab infusion (every

6 weeks):

1) History and physical examination
2) Measurement of height, weight and vital signs (including blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature).
3) Performance status evaluation
4) Review concomitant medications
5) Adverse events assessment
6) CBC with differential, serum chemistry (Na, K, Cl, CO2, BUN, creatinine, glucose, calcium), magnesium, phosphate, liver function tests (albumin, total protein, alkaline phosphatase, total and, ALT, AST), LDH
7) Pregnancy test (serum or urine) for women of childbearing potential (every 6 weeks)
8) Administration of nivolumab and/or ipilimumab accordingly.
9) TSH with reflex free T4 and free T3 (every 6 weeks)

Tumor response assessment will occur every 9 weeks after initiating trial therapy for the first 24 weeks, and thereafter every 12 weeks.

Tumor biopsies (excision, core or forceps) will be performed 9 to 10 weeks after initiating trial therapy after the 4th or 5th nivolumab infusion to allow for analysis of pharmacodynamics changes related to trial therapy (see Sections 4.1.1 and 7). Blood will be drawn for correlative studies the day of the first four nivolumab infusions, and the week after the 5th nivolumab infusion.

5.3. Follow-up Visits

All patients who discontinue the study treatment will have a follow up visit at Day 28 ±7 days from the last study treatment.

1) History and physical examination
2) Measurement of height, weight and vital signs (including blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature).
3) Performance status evaluation
4) Review concomitant medications
5) Adverse events assessment
6) CBC with differential, serum chemistry (Na, K, Cl, CO2, BUN, creatinine, glucose, calcium), magnesium, phosphate, liver function tests (albumin, total protein, alkaline phosphatase, total, ALT, AST), LDH, and TSH with reflex free T4 and free T3
7) Tumor assessment with CT scan of the chest/abdomen/pelvis and brain every 9 weeks (+/- 5 days) until progression, withdrawal of consent, death, lost to follow-up, or start of a subsequent anti-cancer therapy

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All patients who discontinue early or who complete the study treatment period will be followed for survival. Survival follow-up information will be collected via telephone calls, patient medical records, and/ or clinic visits every 3 months +/- 14 days until death, loss to follow-up or study termination. All patients will be followed for survival unless the patient requests to be withdrawn from follow-up. If the patient withdraws from study treatment but not from follow-up, the study staff may use a public information source to obtain information about survival status.

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5.4. STUDY CALENDAR

W (week)	Pre-Tx	W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W 10	W 11	W 12	W 13	W 14	W 15	W 16	W 17 & Q2W	End of Tx
Nivolumab		X		X		X		X		X		X		X		X		X	
Ipilimumab		X						X						X				*W 19 & Q6W*	
Informed Consent	X																		
Demographics	X																		
Medical History	X																		
Concurrent Meds	X	X		X		X		X		X		X		X		X		X	X
Physical Exam	X	X		X		X		X		X		X		X		X		X	X
Vital Signs[1]	X	X		X		X		X		X		X		X		X		X	X
Height	X																		
Weight	X	X		X		X		X		X		X		X		X		X	X
ECOG PS	X	X		X		X		X		X		X		X		X		X	X
CBC w/diff, plts	X	X		X		X		X		X		X		X		X		X	X
Serum chemistry[2]	X	X		X		X		X		X		X		X		X		X	X
TSH[3]	X							X						X				*W 19 & Q6W*	X
Amylase/ Lipase	X																		X
B-HCG[4]	X							X						X				*W 19 & Q6W*	X
EKG	X																		
Adverse Event Evaluation	X	X		X		X		X		X		X		X		X		X	X
Trial Imaging	X									X								*W 18 & Q12W*	
Tumor Biopsy	X										X								
PD Blood Draw	X	X		X		X		X			X								X

1. Includes blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature
2. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
3. Reflex to Free T3 and T4 is TSH abnormal
4. Serum or urine pregnancy test (women of childbearing potential)
5. All screening procedures except labs to occur within 28 days of first dose. All labs to be collected within 14 days of first dose.

6. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

6.1 Safety Analysis

Safety will be analyzed for patients treated in this study. All patients who receive any amount of study drug will be evaluable for toxicity.

At each visit, a brief focused history will be obtained and any indication of treatment- related toxicity will be evaluated by appropriate examination and/or laboratory/radiographic studies.

Safety analyses will include summaries of adverse event rates and changes in laboratory results, as well as number of CTCAE (v4.0) toxicity grades for both laboratory and non-laboratory data.

The evaluation period should extend from date of first treatment until 100 days from discontinuation of treatment, and until resolution from all acute toxicities associated with the drug administration.

6.2 Definition of Adverse Event Terms

Adverse Event: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [NIH Guidelines, January 2001]

Serious Adverse Event (SAE): Any adverse drug experience occurring at any dose that results in any of the following outcomes:

1) Death
2) A life-threatening adverse drug experience
3) In-patient hospitalization or prolongation of existing hospitalization
4) Any persistent or significant disability/incapacity
5) A congenital anomaly/birth defect
6) Is a new cancer (that is not a condition of the study)
7) Is associated with an overdose
8) Is another important medical event
9) Pregnancy

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. [Code of Federal Regulations Title 21].

Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

“Serious” Versus “Severe” Adverse Events: There is a distinction between serious and severe AEs. Assessment of seriousness will be made solely by the serious criteria listed above.

Severity of AEs will be graded according to the NCI Common Terminology Criteria for Adverse Events v4.0. Therefore, serious events will not be automatically considered severe. For example, a stroke that results in only a limited degree of disability may be considered a mild (not severe) stroke, but it would still meet serious criteria and thus, be captured as an SAE. Similarly, severe events may not always be serious. An example would be an episode of severe, transient nausea which persists for

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several hours. This would be classified as a "severe" episode of nausea, but if it did not require treatment, intervention, or somehow meet other serious criteria, it would not be considered an SAE.

Life-threatening Adverse Drug Experience: Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e. it does not include a reaction that, had it occurred in a more severe form, might have caused death. [21CFR312.32(a)]

Unexpected Adverse Drug Experience: Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan. "Unexpected" as used in this definition, refers to an adverse drug experience that has not been previously observed rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

Laboratory test abnormalities: Laboratory abnormalities that constitute an adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for adverse events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. Please note that a dose hold or medication for a lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

6.3. Toxicity Grading

Toxicities will be graded according to the current version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. The full text of the NCI CTCAE is available online at: http://ctep.cancer.gov/forms/CTCAEv4.pdf

If a certain event or symptom is not described in the CTCAE grades, use the following grading scale:

Mild	Awareness of event, but easily tolerated
Moderate	Discomfort enough to cause some interference with usual activity
Severe	Inability to carry out usual activity
Very Severe	Debilitating, significantly incapacitates patient despite symptomatic therapy

6.4. Toxicity Attribution

Assessment of attribution is made by consideration of all clinically relevant data prior to, during, and after occurrence of the event, including diagnostic tests to assess the cause of the event.

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Clinically relevant data include, but are not limited to; underlying disease, past and present medical history (all concurrent non-malignant disease), concurrent medications, and timing between event and drug administration. The mechanism of action and prior toxicology of the study drug should be considered.

An adverse event is associated with the use of the drug when there is a reasonable possibility that the experience may have been caused by the drug. Potential attribution of an adverse event associated with trial therapy will be provided for all study drugs, nivolumab and/or ipilimumab.

Attribution Standards per NCI – CTEP:

Unrelated The Adverse Event is clearly not related to the investigational agent (s)

Unlikely The Adverse Event is doubtfully related to the investigational agent(s)

Possible The Adverse Event may be related to the investigational agent(s)

Probable The Adverse Event is likely related to the investigational agent(s)

Definite The Adverse Event is clearly related to the investigational agent(s)

6.5. Yale Principal Investigator Safety Reporting Requirements

6.5.1 Expedited Reporting of Unexpected SAEs

AEs classified as “serious” and “unexpected” that are possibly, probably, or definitely attributed to drug administration, or SAEs whose frequency exceeds expectations, require expeditious handling and reporting.

The PIs will promptly investigate all safety information related to an adverse experience. If the results of the PIs’ investigation show an adverse drug experience not initially determined to be reportable (based on whether the event is serious, unexpected, and associated with drug administration) is so reportable, the PIs will report such experience. Follow-up information to a safety report shall be submitted as soon as the relevant information is available.

6.5.2 Reporting to the Yale Human Investigation Committee

All SAEs, whether originating at Yale or a collaborating center, meeting the criteria for expedited reporting will be reported to the Yale University Human Investigation Committee (HIC) using HIC Form 710 FR 4: Unanticipated Problem Involving Risks to Subjects or Others (UPIRSOs), including Adverse Events (AEs) Reporting Form as per IRB Policy 710.

The HIC does not require reporting of any other Adverse Event type. A copy of the IRB Policy 710 Reporting Unanticipated Problems Involving Risks to Subjects or Others, including Adverse Events is available at:
http://www.yale.edu/hrpp/policies/documents/NewIRBPolicy710_UPIRSOSAE_4.3.2014_withflowchart_vF.PDF

6.5.3 Reporting to the Food and Drug Administration

This study will be conducted under an IND (Investigational New Drug application) that will be held by the Principal Investigator, Dr. Scott Gettinger. The Principal Investigator will report in an expedited manner all SAEs meeting the criteria of “serious”, “unexpected” and “related to study treatment”. Written safety reports will use a MedWatch Form 3500A. A “fillable pdf” version with

instructions is available at: http://www.fda.gov/medwatch/safety/FDA-3500A_Fillable_08-16-2006.pdf

There are two types of expedited safety reports to the FDA:

1. 7-Calendar-Day FDA Telephone or Fax Report: The sponsor-investigator will directly notify the FDA, within 7 calendar days after his initial receipt of the information, of any adverse event that is ALL of the following:

- Death or immediately life-threatening
- Unexpected
- Associated with the use of nivolumab or ipilimumab

Notification to the FDA will be made directly to the new drug review division in the Center for Drug Evaluation and Research or in the product review division for the Center for Biologics Evaluation and Research, whichever was responsible for the review of the IND. [21CFR312.32(c)] A written report of the event is to follow within 15 calendar days.

2. 15-Calendar-Day FDA Written Report: The sponsor-investigator will directly notify the FDA within 15 calendar days of any adverse event that is ALL of the following:

- Serious (due to non-fatal and non-life threatening criteria)
- Unexpected
- Associated with the use of nivolumab or ipilimumab

Note: Serious Adverse Events which do not meet the criteria for expedited reporting will be reported to the FDA in the IND Annual Report.

6.5.4 Reporting to Bristol Myers Squibb

Investigators must report all SAEs to Bristol Myers Squibb within the timelines described below. The completed MedWatch/case report should be faxed and/or emailed immediately upon completion to BMS Drug Safety at:

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

Relevant follow-up information should be submitted to BMS Drug Safety as soon as it becomes available.

SAE reports whether related or unrelated to nivolumab or ipilimumab will be transmitted to BMS within 24 hours of the Awareness Date.

Additional reporting requirements to BMS include the following:

- Any reports of pregnancy following the start of administration of nivolumab and within the follow-up period (for female patients within 5 months after the last dose of nivolumab or ipilimumab or the partner of a male patient within seven months of completing therapy) will be transmitted to BMS within 24 hours of the Awareness Date.
- All non-serious nivolumab or ipilimumab AEs originating from the study will be forwarded to BMS quarterly

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Follow-Up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e., D.O.B. initial, patient number), protocol description and number, if assigned, brief AE description, and notation that additional or follow-up information is being submitted. (The patient identifiers are important so that the new information is added to the correct initial report.)

Occasionally BMS may contact the reporter for additional information, clarification, or current status of the patient for whom and AE was reported. Relevant follow-up information should be submitted to BMS Drug Safety as soon as it becomes available and/or upon request.

6.5.5. Duration of Reporting of SAEs

From the administration of first treatment until 90 days (unless otherwise specified) subsequent to last treatment or withdrawal of subject, new onset adverse events will be captured. Follow-up and reporting of these events will follow the same procedure as for AEs observed during the study period. In addition, any unexpected Serious Adverse Event that occurs more than 90 days after drug administration but is possibly, probably or definitely attributed to drug administration will be recorded and reported.

6.6. Yale Safety Reporting and Monitoring (DSMP)

The Yale Cancer Center (YCC) Data and Safety Monitoring Committee (DSMC) will provide the primary oversight of data and safety monitoring. The Yale DSMC will review and monitor compliance, toxicity and deviations from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator.

The DSMC will review this protocol bi-annually, at a minimum. Information to be provided to the committee includes: a study narrative by the PI, a summary DSMC report produced by OnCore (which includes participant accrual, response, trial status history, SAEs, adverse events, deviations and survival); audit results, and monitoring reports, as applicable. Other information (e.g., scans, laboratory values, etc.) will be provided upon request. Upon completing the review, the DSMC will approve whether the study should continue as planned, require modification/ amendment, or be placed on administrative hold with accrual temporarily suspended.

Trials being monitored by the YCC DSMC will remain under the YCC DSMC purview until a DSMC review has occurred that includes the research activity of the last subject who completed the intervention, or until the DSMC feels there are no patient safety concerns that require further monitoring. The DSMC will determine the length of continued DSMC review.

The DSMC has authority to intervene in the conduct of these studies as necessary to ensure the safety of the participants and to maintain the highest quality in the clinical research performed at YCC. The DSMC has the authority to require additional monitoring and/ or more frequent reporting on study progress and serious adverse events.

6.7. Pregnancies

It is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial.

All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to Yale IRB.

6.8. Warnings and Precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochures. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

7. CORRELATIVE/SPECIAL STUDIES

Correlative studies will be conducted on serial tumor biopsy and blood specimens. All patients will undergo a tumor biopsy prior to initiation of trial therapy, and after their 5th treatment with nivolumab (study week 10). Blood will be drawn prior to each tumor biopsy to allow additional correlative studies.

<u>Tissue from Serial Tumor Biopsies:</u>

a. Multiplexed quantitative immunofluorescence will be used to evaluate multiple markers on tumor/ immune cells, including, but not limited to, PD-L1, PD-1, CK, CD4, CD8, CD20, Ki67, granzyme B, and IDO1.
b. RNA, TCR and DNA sequencing (with neoantigen analysis)
c. Additional studies, depending on tissue availability, may include: functional T cell studies (neoantigen stimulation assay, T cell culture) and generation of patient derived xenografts.

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Serial Blood Draws:

a. Mass cytometer (CyTOF 2, DVS Sciences) will be used to comprehensively characterize phenotypic (CD45, CD3, CD8, CD4, CD33, CD11b, CD123, CD56, CD16, CD20, CD66b, CD68, TBET, GATA-3, FOXP-3, CD14, CCR7, CD45RA, γδTCR) and functional (KI-67, HLA-DR, CD25, PD-1, CD80, CD16, IFNg, TNFa, Granzyme B, Caspase 3, PARP) changes of blood cells in relation to changes in tumor tissue.
b. Tetramer staining using neoantigenic peptides or ELISPOT (neoantigen stimulation assay).

8. CRITERIA FOR RESPONSE

Anti-tumor activity: data on objective response, progression free survival, and duration of response will be listed for all patients in the study and summarized overall.

Objective response is defined as a complete or partial response, as determined by investigator assessment using RECIST v1.1 and irRC (see appendix 3 and 4) and confirmed by repeat assessments ≥4 weeks after initial documentation. Patients not meeting these criteria, including patients without any post baseline tumor assessment, will be considered non-responders in the analysis of objective response.

Duration of objective response will be analyzed for the subset of patients who achieved an objective response. Duration of response is defined as the time from the initial complete or partial response to the time of disease progression or death, whichever occurs first. If a patient does not experience death or disease progression before the end of the study, duration of response will be censored at the day of the last tumor assessment. If no tumor assessments were performed after the date of the first occurrence of a complete or partial response, duration of objective response will be censored at the date of the first occurrence of a complete or partial response plus 1 day.

Progression-free survival is defined as the time from the first day of nivolumab treatment until progression of disease using RECIST v1.1 and irRC (see appendix 3 and 4). If a patient has not experienced progressive disease or death, PFS will be censored at the day of the last tumor assessment. Patients with no post baseline tumor assessments will be censored at the date of first study treatment plus 1 day.

Overall survival is defined as the time from the first day of treatment until death from any cause. If a patient has not experienced death, OS will be censored at the day of last follow-up.

9. STATISTICAL CONSIDERATIONS

This trial is designed to determine the objective response rate (ORR) using RECIST v1.1 and irRC to nivolumab and ipilimumab when administered in combination to patients with advanced NSCLC and primary resistance to PD-1 axis inhibitor therapy. Details on the response criteria and its duration are described in Section 8 of this protocol. For our primary endpoint we will employ a Simon two-stage design. This design is based on our intuition for a very low response rate and not on any specific experimental evidence. The study design will terminate early if there are no responses or prolonged stability (≥ 24 weeks) using irRC among the first 10 patients enrolled. Otherwise we will enroll a maximum of 40 and reject the null hypothesis if we observe 4 or more

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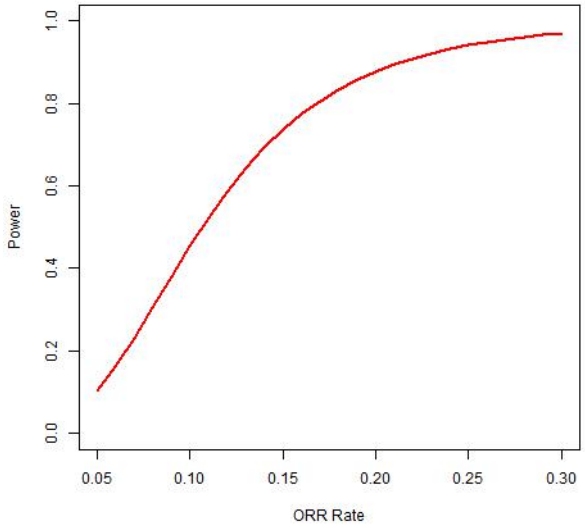
positive responses. For a null hypothesis with a 5% ORR and alternative with a 19% ORR, this criterion has significance level 0.1 and power greater than 85%. The null and alternative hypothesis rates are not motivated by experimental evidence but rather, are examples of one pair of hypotheses that can be tested using this design.
An operating characteristic of this design with other ORRs is plotted here:



We anticipate enrollment at a rate of at least 2 patients per month. Patients who drop out or leave the study before receiving any experimental treatment will be replaced. Patients who leave the study after receiving any study treatment will be considered as treatment failures and not be replaced.

Our secondary analyses correlate ORR, time-to-event measures and correlative metrics listed in Section 7. Specifically, duration of response, progression-free survival (PFS) and overall survival (OS) will be estimated along with the corresponding 95% CI, plotted using the Kaplan-Meier method. These plots will also be prepared separately by RECIST v 1.1 criteria and irRC and tested using the log-rank test. Duration of response, OS, and PFS are defined in Section 8.

Marker data and other metrics listed in Section 7 will be correlated to ORR and PFS using Cox proportional hazard regression methods. These values will be analyzed marginally using heatmaps and single linkage to identify any subpopulations.

The following analysis sets will be defined in this trial:

- Full Analysis Set: All subjects who receive at least 1 dose of any trial treatment.
- Completer Analysis Set: All subjects who complete the trial, all scheduled treatments, all biomarker assessments, and all tumor assessments.
- Safety Analysis Set: All subjects who receive at least 1 dose of any trial treatment but subsequently drop out of the study for any reason.
- Correlative Biomarker Set: All subjects who receive at least one dose of any trial treatment and have at least one set of correlative marker data listed in Section 7.

No formal statistical ORR analyses will be conducted on the 10 additional patients with acquired

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resistance, though the finding of immune related response in 1 or more patients would be unexpected, and should prompt further study.

Demographics and baseline laboratory results will be summarized by cohort (primary and acquired resistance to anti-PD-1 axis therapy) and by all patients using descriptive statistics.

Safety analysis will be performed in all treated subjects. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by cohort (primary and acquired resistance to anti-PD-1 axis therapy) and by all patients. All on-study AEs, drug-related AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, coagulation, chemistry, liver function and renal function will be summarized using worst grade per NCI CTCAE v 4.0 criteria.

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Appendix 1: NCI Common Terminology Criteria for Adverse Events (CTCAE)

Please use the following link to the NCI CTCAE website:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Appendix 2: Eastern Cooperative Oncology Group (ECOG) Performance Status

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

Appendix 3: Response Evaluation Criteria in Solid Tumors (RECIST)

Modified Excerpt from Original Publication

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1[18] are presented below, with slight modifications and the addition of explanatory text as needed for clarity.

Measurability of Tumor at Baseline

Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

a. Measurable Tumor Lesions

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

- 10 mm by CT or MRI scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

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Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Non-Target Lesions" for information on lymph node measurement.

b. Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

c. Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone lesions:

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

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. 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 loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. For this study, such lesions will be considered measurable if they are clearly progressing and meet other RECIST 1.1 criteria.

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Target Lesions: Specifications by Methods of Measurements

a. Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

b. Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during study. Imaging-based evaluation should always be the preferred option.

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and $\geq$ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

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

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

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward.</u> Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions since the same lesion may appear to have a different size using a new modality.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

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Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

Tumor Response Evaluation

Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and to use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

Baseline Documentation of Target and Non-Target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means in instances where patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is $>$ 10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but additionally, should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

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

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

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All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

Response Criteria

a. Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- Complete response (CR): disappearance of all target lesions

Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

- Partial response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline

In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

The appearance of one or more new lesions is also considered progression.

- Stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

b. Special Notes on the Assessment of Target Lesions

Lymph Nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to < 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met since a normal lymph node is defined as having a short axis < 10 mm.

Target Lesions That Become Too Small to Measure. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and BML (below measurable limit) should be

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ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked.)

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and, in that case, BML should not be ticked.

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

c. Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and, instead, should be assessed only qualitatively at the timepoints specified in the protocol.

- CR: disappearance of all non-target lesions and (if applicable) normalization of tumor marker level)

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) and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: unequivocal progression of existing non-target lesions

The appearance of one or more new lesions is also considered progression.

d. Special Notes on Assessment of Progression of Non-Target Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the 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. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has Only Non-Measurable Disease. This circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance, there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily

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quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large" or an increase in lymphangitic disease from localized to widespread or may be described in protocols as "sufficient to require a change in therapy." If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

e. New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

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

Evaluation of Response

a. Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table A3.1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table A3.2 is to be used.

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Table A3.1. Timepoint Response: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table A3.2. Timepoint Response: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

b. Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and, during the study, only two lesions were assessed, but those gave a sum of 80 mm; the patient will have achieved PD status, regardless of the contribution of the missing lesion.

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If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be "unable to assess" since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be "unable to assess" except where there is clear progression. Overall response would be "unable to assess" if either the target response or the non-target response is "unable to assess," except where this is clear evidence of progression as this equates with the case being not evaluable at that timepoint.

Table A3.3. Best Overall Response When Confirmation Is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

c. Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to

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overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the CRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables A3.1-A3.3.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment progression is confirmed, the date of progression should be the earlier date when progression was suspected.

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of complete response if the primary tumor is still present but not evaluated as a target or non-target lesion

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Appendix 4: Immune-Related Response Criteria

INTRODUCTION

Increasing clinical experience indicates that traditional response criteria (e.g., Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST v1.1] and World Health Organization [WHO]) may not be sufficient to characterize fully activity in the new era of target therapies and/or biologics. In studies with cytokines, cancer vaccines, and monoclonal antibodies, complete response, partial response, or stable disease has been shown to occur after an increase in tumor burden as characterized by progressive disease by traditional response criteria. Therefore, conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) does not necessarily reflect therapeutic failure. Long-term effect on the target disease must also be captured. The immune-related response criteria[19] (irRC) are criteria that attempt to do that by enhancing characterization of new response patterns that have been observed with immunotherapeutic agents (i.e., ipilimumab). (Note: The irRC only index and measurable new lesions are taken into account.)

GLOSSARY

Term	Definition
SPD	sum of the products of the two largest perpendicular diameters
Tumor burden	$SPD_{\text{index lesions}} + SPD_{\text{new, measurable lesions}}$
Nadir	minimally recorded tumor burden
irCR	immune-related complete response
irPD	immune-related progressive disease
irPR	immune-related partial response
irSD	immune-related stable disease
irBOR	immune-related best overall response

BASELINE ASSESSMENT USING irRC

Step 1. Identify the index lesions (five lesions per organ, up to ten visceral lesions and five cutaneous lesions).

Step 2. Calculate the SPD of all of these index lesions:

$$SPD = \sum_i \text{ (Largest diameter of lesion i)} \times \text{(Second largest diameter of lesion i).}$$

POST-BASELINE ASSESSMENTS USING irRC

Step 1. Calculate the SPD of the index lesions.

Step 2. Identify new, measurable lesions ($\geq 5 \times 5$ mm; up to five new lesions per organ: five new cutaneous lesions and ten visceral lesions).

Step 3. Calculate the SPD of the new, measurable lesions.

Step 4. Calculate the tumor burden:

$$\text{Tumor burden} = \text{SPD}_{\text{index lesions}} + \text{SPD}_{\text{new, measurable lesions}}$$

Step 5. Calculate the change in tumor burden relative to baseline and the change in tumor burden relative to nadir.

Step 6. Derive the overall response using the table below.

Overall Response	Criterion
irCR	Complete disappearance of all lesions (whether measurable or not, and no new lesions) confirmed by a repeat, consecutive assessment ≥ 4 weeks from the date first documented
irPR	Decrease in tumor burden $\geq 50\%$ relative to baseline confirmed by a consecutive assessment ≥ 4 weeks from the date first documented
irSD	Criteria for irCR, irPR, and irPD are not met; does not require confirmation
irPD	Increase in tumor burden $\geq 25\%$ relative to nadir confirmed by a consecutive assessment ≥ 4 weeks from the date first documented

irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irSD = immune-related stable disease.

DETERMINATION OF irBOR

Once a patient has completed all tumor assessments, his/her irBOR may be determined:

Condition	irBOR
At least one irCR	irCR
At least one irPR and no irCR	irPR
At least one irSD and no irCR and no irPR	irSD
At least one irPD and no irCR, no irPR, and no irSD	irPD

irBOR = immune-related best overall response; irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irSD = immune-related stable disease.

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