A PILOT TRIAL OF IPILIMUMAB WITH NIVOLUMAB FOR PATIENTS WITH RESECTED STAGES IIIB/IIIC/ IV MELANOMA

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Study Product: Nivolumab (NSC 748726)
Ipilimumab (NSC 732442)

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NIVOLUMAB (NSC 748726 – Approved agent, supplied by BMS)
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SYNOPSIS

TITLE

A Pilot Trial of Ipilimumab with NIVOLUMAB for Patients with Resected Stages IIIB/IIIC/ IV Melanoma

PROTOCOL NUMBERS

S16-00098 (Perlmutter Cancer Center)

CA209-905(Bristol-Myers Squibb Co.)

OBJECTIVES

The primary objective of this study is to assess the safety and tolerability of treatment with NIVOLUMAB in combination with ipilimumab in HLA unrestricted subjects with resected Stages IIIB/IIIC/IV melanoma.

The secondary objectives of this study are to:

- evaluate the immune response to treatment with the study drugs at Week 12
- assess the preliminary efficacy of the study drugs as measured to time to relapse.

OVERVIEW OF STUDY DESIGN

This is a pilot, phase II, open-label, single center study of NIVOLUMAB in combination with ipilimumab. NIVOLUMAB is an FDA-approved fully human monoclonal antibody (HuMAb) against programmed death-1 (PD-1). (See STUDY DRUGS, DOSES, AND ADMINISTRATION). Ipilimumab is a FDA-approved fully human monoclonal antibody against cytotoxic T lymphocyte antigen-4 (CTLA-4)

The study will consist of 4 periods: Screening (up to 4 weeks), Induction Treatment (up to 1 12-week cycle of induction therapy with ipilimumab and NIVOLUMAB), Treatment/Follow-up (up to 48 weeks of NIVOLUMAB), and Survival Follow-up. Each induction treatment cycle is comprised of 4 doses of NIVOLUMAB and 4 doses of ipilimumab given every three weeks for a total of 12 weeks (cycle 1) with a tumor assessment at the end of cycle 1 at week 12.

At the end of the Induction Treatment Period (Week 12) subjects without evidence of relapse radiologically and clinically will be able to continue to receive NIVOLUMAB treatment 480mg every 4 weeks for 48 weeks. Subjects who relapse at the disease evaluations at Weeks 12, 24 or later will not receive further treatment with NIVOLUMAB.

Patients who experience a DLT to NIVOLUMAB and ipilimumab during or after cycle 1 will not receive further treatment with NIVOLUMAB and ipilimumab.

Subjects who prematurely discontinue 1 or both study drugs will complete the remaining study visits and associated evaluations (without dosing of 1 or both study drugs, as applicable) indefinitely until withdrawal of consent for follow-up or death.

Dosing during cycle 1 will consist of: 3 mg/kg of NIVOLUMAB + ipilimumab at 1 mg/kg

Dosing during cycles 2-5 will consist of flat dose NIVOLUMAB at 480 mg

Since the drugs will be given concurrently, it will not be possible to attribute dose-limiting toxicities to one or the other drug during the first 12 weeks of therapy.

Subjects who withdraw from the study during Cycle 1 for reasons other than a DLT will be replaced.

No dose escalations or de-escalations are permitted within each subject's treatment. NIVOLUMAB or ipilimumab dose adjustments are allowed only if there has been ± 10% weight change since the previous treatment (Induction/Treatment Period only). No dose escalations or de-escalations are allowed during cycles 2-5 due to the use of flat dosing of NIVOLUMAB at 480 mg every 4 weeks.

NUMBER OF SUBJECTS (PLANNED)

Up to 25 subjects (20 in this trial with five to account for drop-outs) will be enrolled in the study.

BLINDING AND RANDOMIZATION

This is an open-label study. Eligible subjects will be treated in the order they enter the study.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Subjects will have no HLA restriction, and have a histological diagnosis of Stages IIIB/IIIC/IV Melanoma that has been completely resected, rendering them free of disease.

STUDY DRUGS, DOSES AND MODE OF ADMINISTRATION

NIVOLUMAB will be supplied as a sterile, preservative-free solution in 10 mL vials at a concentration of 10 mg/mL; which, in cycle 1, based on the subject's weight, may be diluted with sterile normal saline (0.9% sodium chloride). NIVOLUMAB (3 mg/kg) will be administered as a 30-minute i.v. infusion.

Starting 4 weeks after the last co-administered dose in cycle 1, subjects will be administered a flat dose

480 mg nivolumab IV every 4 weeks (Q4W) in cycles 2-5.

Ipilimumab will be supplied as a sterile, preservative-free solution in 10mL (50 mg) or 40 mL (200 mg) vials at a concentration of 5 mg/mL; which, based on the subject's weight, may be diluted with sterile normal saline (0.9% sodium chloride). Ipilimumab (1 mg/kg) will be administered as a 30-minute i.v. infusion.

On days when both study drugs are administered, nivolumab (BMS-936558) will be given before the ipilimumab.

DURATION OF TREATMENT/STUDY PARTICIPATION

The expected maximum duration of nivolumab treatment for a subject is 60 weeks. The expected maximum duration of ipilimumab treatment for a subject is 12 weeks.

The expected maximum duration of a subject's participation in this study is 3 years.

CRITERIA FOR EVALUATION

Safety

Evaluation of safety and tolerability will include ongoing review of clinical laboratory tests (blood and urine sampling for clinical laboratory parameters), pregnancy testing, Eastern Cooperative Oncology Group (ECOG) performance status, physical examination including vital sign measurements, electrocardiogram (ECG), chest radiography, and adverse events. Safety will also include evaluations of immune safety and immunogenicity.

Dose-limiting Toxicity

A DLT is defined as a NIVOLUMAB and/or ipilimumab-related $\geq$ Grade 3 adverse event occurring within 29 days after the first dose of study drugs excluding: Grade 3 adverse event of tumor flare (defined

as local pain, irritation, or rash localized at sites of known or suspected tumor), Grade 3 rash, Grade 3 immune-related adverse event (irAE, defined below) that resolves to a Grade 1 or less within 28 days, or a transient (resolving within 6 hours of onset) Grade 3 infusion-related adverse event. A Grade 3 irAE that resolves to a Grade 1 or less within 28 days, while not constituting a DLT, may preclude further administration of NIVOLUMAB or NIVOLUMAB with ipilimumab to the subject. Grade 2 irAEs may require skipping a dose unless resolved to grade 1 or less at the time of drug administration. Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. Version 4.0 of the CTCAE is identified and located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of Version 4.0 of CTCAE).

Toxicities occurring more than 28 days after the first dose will be monitored and discussed with BMS.

Immune-Related Adverse Events

An irAE is defined as a clinically significant adverse event of any organ that is associated with either study drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

Given the intended mechanism of action of NIVOLUMAB and ipilimumab, particular attention will be given to adverse events that may follow enhanced T-cell activation such as dermatitis and colitis, or other irAEs.

Immunology

Blood and peripheral blood mononuclear cell samples will be collected and evaluated by leukapheresis or peripheral blood draw for flow cytometry (T cell, B cell, NK, monocytes, CD3, CD4, CD8, CD4/CD8, CD11b, CD11c, CD14, CD20, CD25, CD33, CD56, CD69, CD71, CD73, CD80, CD127, FOXp3, LAG3, TIGIT, BTLA, Tim3, CTLA-4, PD-1, PD-L1, CD244, OX-40, 41-BB, CD40, CD4/MHC Class II positive cells, and CD8/MHC Class II positive cells), serum cytokines (IL-6, IL-10, TNF-β, ING-gamma, TGF-β, neopterin and sIL-2R), cellular immune function (tetramer and/or ELIspot assays utilizing melanoma and other control antigens).

Serum samples will be collected and cryopreserved to study molecules that may be implicated in regulating anti-melanoma immune responses and/or NIVOLUMAB or ipilimumab activity such as soluble MICA, compounds detected by mass spectroscopy including those associated with wound healing, complement and the acute phase response, chemokines or cytokines, or antibodies to melanoma antigens.

Efficacy

Using imaging results (computed tomography/magnetic resonance imaging [chest, abdomen, pelvis, and brain] and photography of lesions) as well as clinical examination, presence of relapse will be evaluated and treatment decisions will be made by the Investigator (who is also the Sponsor). Scans and measurements may be reviewed by independent radiologists at a later date or any time during the study.

The primary efficacy endpoint is relapse free survival as determined by the results of Investigator evaluations.

STATISTICAL METHODS

A sample size of up to 20 subjects with 5 additional patients to accommodate drop-outs is based on the study design for safety evaluation requirements.

The incidence, relationship to therapy, and severity of adverse events will be summarized using descriptive statistics. Changes in clinical laboratory tests, ECOG, vital signs, ECGs, chest radiography, and immune safety results will be summarized using descriptive statistics. Immunogenicity results will be provided as a listing.

Immune response will be summarized using descriptive statistics..

Efficacy evaluations (RFS) will be summarized using descriptive statistics.

ABBREVIATION

Abbreviation	Term
β-HCG	beta human chorionic gonadotropin
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
APC	antigen-presenting cells
AST	aspartate aminotransferase
BMS	Bristol-Myers Squibb
BOR	Best Overall Response
BORR	Best Overall Response Rate
CI	confidence interval
CR	Complete Response
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTLA-4	cytotoxic T lymphocyte-associated antigen 4
DC	dendritic cells
DLT	dose-limiting toxicity
DNA	deoxyribosenucelic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ESI	event of special interest
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HBV SAg	hepatitis B virus surface antigen
HCV RNA	hepatitis C virus ribonucleic acid
HIV	human immunodeficiency virus
HPF	high power field
HuMAb	human monoclonal antibody
i.v.	intravenous, intravenously
ICF	informed consent form
ICH	International Conference on Harmonisation
IL-2	interleukin-2
INF	Interferon
irAE	Immune-related adverse event
IRB	Institutional Review Board
irCR	Immune-related complete response
irPD	Immune-related progressive disease
irPR	Immune-related partial response

Abbreviation	Term
irRC	Immune-related Response Criteria
irSD	Immune-related stable disease
mAb	monoclonal antibody
NIVOLUMAB	PD-1-specific, fully human IgG4 mAb
MedDRA	Medical Dictionary for Regulatory Activities
mWHO	Modified World Health Organization
MPR	Mixed Lymphocyte Reaction
MTD	maximum tolerated dose
NCI	National Cancer Institute
PBMC	peripheral blood mononuclear cells
PCC	Perlmutter Cancer Center
PD-1	Programmed Death–1
PD-L1	Programmed Death–Ligand 1
PI	Propidium Iodide
PR	Partial Response
PVG	Pharmacovigilance
SAE	serious adverse event
RECIST	Response Evaluation Criteria in Solid Tumors
SOC	system/organ/class
SOP	standard operating procedure
SPD	Sum of Product Diameters
SSAE	Serious or Significant Adverse Event
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
ULN	upper limit of normal
URTI	upper respiratory tract infection
US	United States of America
UTI	urinary tract infection
WBC	white blood cell
WHO	World Health Organization

TABLE 1: TIME AND EVENTS SCHEDULE

Examination	**Screening**	**Cycle 1 Treatment Period** [11,13] (Visits must occur ± 7 days of the scheduled visit)					**Cycle 2-5 Treatment Period**[11, 13] (Visits must occur ± 7 days of scheduled visit; Every 4 weeks for 48 weeks)						**Study Completion/Early Withdrawal** (Visit to occur 12 week ± week after last dose)	**Survival Follow-up**
Visit	1	2	3	4	5	6	7	8	9	10	11	12		
Week	-1	1	4	7	10	12								
Timepoint (Day)	-28 to -1	1	22	43	64	78								
Safety Procedures														
Vital Signs[5]	●	●	●	●	●	●	●	●	●	●	●	●	●	
Height	●	●				●						●	●	
Weight	●	●	●	●	●	●	●	●	●	●	●	●	●	
Screening Procedures														
Informed Consent/ HIPAA[9]	●													
Inclusion/Exclusion criteria	●													
Demographics/ medical history	●													
Serum β-HCG pregnancy test [4]	●													
Hepatitis B and C testing	●													
HIV testing	●													

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Week	-1	1	4	7	10	12								
Timepoint (Day)	-28 to -1	1	22	43	64	78								
Safety Assessments														
Physical examination	●	●	●	●	●	●	●	●	●	●	●	●	●	
ECOG performance	●	●	●	●	●	●	●	●	●	●	●	●	●	
Electrocardiogram [6]	●													
Chest radiograph [6]	●													
Hematology [7]	●	●	●	●	●	●	●	●	●	●	●	●	●	
Serum chemistries [7]	●	●	●	●	●	●	●	●	●	●	●	●	●	
Urinalysis	●	●			●	●						●	●	
Immune safety assays [7]	●				●							●	●	
Urine pregnancy test [4]		●	●	●	●	●	●	●	●	●	●	●		
Concomitant medications	●	●	●	●	●	●	●	●	●	●	●	●	●	
Baseline medical history	●													
Adverse events	●	●	●	●	●	●	●	●	●	●	●	●	●	

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Visit	1	2	3	4	5	6	7	8	9	10	11	12		
Week	-1	1	4	7	10	12								
Timepoint (Day)	-28 to -1	1	22	43	64	78								
Research Procedures														
• Sample for immunogenicity[7]		•			•							• 13	•	
• Serum for cytokine panel[7]		•			•							• 13	•	
• Cellular immune assays[7]		•			•							• 13	•	
• Cryopreserved serum[7]		•			•							• 13	•	
• Tissue Submission[14]		•	•[15]	•[15]	•[15]	•[15]	•[15]	•[15]	•[15]	•[15]	•[15]	• 15		•[15]

Efficacy Procedures															
CT/MRI (neck, chest, abdomen, pelvis) [9, 12]	●					●	● 14						●	14 ●	●
CT/MRI (Brain)	●					●	● 14						●	14 ●	●
Follow-up contact[10]															●
Study Drug Administration															
Ipilimumab[11]		●	●	●	●										
Nivolumab [2,11]		●	●	●	●	●[13]	●	●	●	●	●	●			

Key: CT = computed tomography, HIV = human immunodeficiency virus; ECOG = Eastern Cooperative Oncology Group; MRI = magnetic resonance imaging

FOOTNOTES:

[1]Every effort should be made to infuse NIVOLUMAB in a 60-minute timeframe.

[2] The NIVOLUMAB dosage may be adjusted if there is a ± 10% weight change since the previous weight measurement only during cycle 1 Induction Treatment. No dose escalations or de-escalations are allowed during cycles 2-5 due to the use of flat dosing of NIVOLUMAB at 480 mg every 4 weeks. No dose escalations or de-escalations are allowed during cycles 2-5 due to the use of flat dosing of NIVOLUMAB at 480 mg every 4 weeks.

[3] Informed consent must be signed before initiation of any study drug treatment or procedure. It may be signed more than 28 days before the first dose.

[4] Pregnancy testing must be performed before any study drug is administered. The test result must be negative for a subject to receive study drug(s).

[5] Vital signs will be monitored immediately prior to the NIVOLUMAB infusion; every 15 minutes during the 30 or 60-minute NIVOLUMAB infusion; and 15 and 30 minutes after completion of the NIVOLUMAB infusion. When slowing or re-starting the NIVOLUMAB infusion due to an infusion reaction/adverse event, vital signs should be monitored every 15 minutes or as directed by the Investigator until the infusion is completed, and 15 and 30 minutes after completion of the infusion and/or the subject is stabilized.

[6] These evaluations are for baseline reference; subsequent evaluations may be performed if clinically indicated.

[7] Sample to be drawn/collected pre-treatment at visits where 1 or more study drug will be administered. Hematology and serum chemistries for Cycle 1 Day 1 will not be re-drawn if screening labs were completed within 72 hours prior to study drug administration. This treatment group will draw amylase and lipase also.

[8] CT neck will be done only in patients with prior disease in the head and neck

[9] In patients who have not had disease progression, re-imaging should be performed every 6-12 months (minimum of every 12 months) for the first 2 years, then every 12 months (at the discretion of the treating physician) indefinitely or until progression.

[10] Survival statuses for all patients who have discontinued from study treatment will be collected every 6 months (+/- 1 month) until death, lost to follow-up, or withdrawal of consent for survival follow-up. Follow-up contact may be done in person at the study center or by telephone; survival information may be obtained from family members or other medical professionals caring for the patient. Survival information including post-study treatment modalities and date and site of disease progression will be documented in the source documents and survival eCRF. Social security death index (SSDI) and other public records will be used if necessary to confirm survival status and/or date of death.

[11] There is only one 12 week induction treatment cycle (cycle 1). The ipilimumab will be at 1 mg/kg every 3 weeks for 4 doses during the 12 week induction cycle, and NIVOLUMAB will be at 3 mg/kg every 3 weeks for 4 doses during the 12 week induction treatment cycle then at 480mg every 4 weeks for 48 weeks during cycles 2-5.

[12] To be obtained every 12 weeks. Patients that discontinue therapy for any reason will only have the immunology procedures collected at the next mandated protocol timepoint, but not thereafter.

[13] Radiology exams will be completed prior to dosing at week 12 and every 12 weeks prior to each dosing visit.

[14] Tissue will be submitted, if available, as outlined in section 5.6.1

[15] Tissue from any post-relapse biopsy will be requested for analysis by immunohistochemistry as outlined in section 5.6.1.

1. INTRODUCTION AND RATIONALE

1.1. Disease Description

In the United States, it is estimated that in 2016, approximately 84,000 patients were diagnosed with malignant melanoma, and that there were an estimated 9,200 deaths from melanoma.[1] Melanoma is the most serious form of skin cancer and strikes adults of all ages. The male to female incidence ratio of melanoma is 1.3:1, respectively. Melanoma is primarily a disease of whites; rates are more than 10 times higher in whites than in African Americans. Melanoma incidence rates have been increasing for at least 30 years. In the most recent time period, rapid increases have occurred among young white females (3.8% annual increase since 1995 in those aged 15 to 34 years) and older white men (8.8% annual increase since 2003 in those 65 and older).

Treatment for melanoma includes removal of the primary growth and surrounding normal tissue and sentinel lymph node biopsy to determine stage. More extensive lymph node surgery may be done if lymph node metastases are present. Melanomas with deep invasion or that have spread to lymph nodes may be treated with immunotherapy, radiation therapy, and/or surgery and chemotherapy. Advanced cases of melanoma are treated with palliative surgery, immunotherapy, and/or chemotherapy, and sometimes radiation therapy.

Melanoma is more likely than other skin tumors to spread to other parts of the body. The 5- and 10-year relative survival rates for persons with melanoma are 91% and 90%, respectively. For localized melanoma, the 5-year survival rate is 99%; 5-year survival rates for regional and distant stage diseases are 65% and 16%, respectively. About 80% of melanomas are diagnosed at a localized stage.

1.2. Principles of the Proposed Therapies

The importance of the immune system for controlling the emergence and progression of cancer, historically a question of heated debate, is now widely accepted. Advances in immunology and oncology have revealed a chronic and dynamic interplay between host and tumor, suggesting that the ability of the tumor to evade the immune response often determines the clinical course of the disease.[2] Enhancement of the magnitude and potency of tumor antigen-specific adaptive cellular responses by CD8 and CD4 T cells is a major goal in cancer immunotherapy.

T-cell activity is controlled by antigen-specific stimuli sensed by the T-cell receptor and by the combined activity of both positive (costimulatory) and negative (coinhibitory) T-cell surface molecules. Inhibition of these negative regulatory receptors, referred to as checkpoint blockade, results in the enhanced activation of T-cell responses and potent antitumor activity in preclinical models. One of the most extensively studied negative regulatory receptors is programmed death-1 (PD-1 [CD279]). Advances in the understanding of mechanisms that regulate T-cell activation have allowed the rational design of new strategies for immunotherapy of tumors, including melanoma. A monoclonal antibody recognizing PD-1 (NIVOLUMAB) is an immunotherapy currently approved for melanoma, non-small cell lung cancer, renal cell cancer and non-Hidgkins lymphoma, and is in development as an anticancer agent for multiple

other indications. The proposed mechanism of action of NIVOLUMAB is interference of the interaction of PD-1 with its ligands PD-L1 (CD274) and PD-L2 (CD273). Preclinical and clinical data indicate that NIVOLUMAB has anticancer activity.

Major limitations of recent cancer vaccine strategies have been that low levels of poorly reactive T cells are generated due to counter-regulatory signals, tolerance to self tumor antigens limits the avidity of resulting T cells, and high levels of T regulatory cells are observed in cancer patients. The ability to vaccinate cancer patients may be improved not only by increasing the total quantity of induced T cells, but by also increasing their recognition efficiency (RE) or avidity for cognate peptide presented by tumor cells. It has been suggested that modulation of costimulatory signals in vaccinated mice can selectively induce high avidity T cells that are specific for self and non-self antigens.[3,4]. We hypothesize that PD-1 blockade combined with CTLA-4 blockade using ipilimumab would have a favorable effect on the expansion and activity of human CD8+ T cytotoxic lymphocytes (CTLs) specific for tumor-associated antigens (ie, self antigens), which would translate into improved anti-cancer therapy.

1.2.1. NIVOLUMAB

The PD-1 receptor is predominantly expressed on activated T and B lymphocytes, as well as memory T lymphocytes.[5,6,7,8] The interaction of PD-1 with its ligands, PD-L1 and PD-L2, which are expressed on APC and dendritic cells (DC), transmits negative regulatory stimuli to down modulate the activated T-cell immune response. Loss of effective immune response to antigens expressed by tumors may be a significant factor in tumor progression. PD-L1 expression has also been found on a number of tumors and may be a mechanism by which tumors can directly engage PD-1 to evade an effective antitumor immune response. PD-1 engagement on T cells by PD-L1$^+$ APC or PD-L1$^+$ tumor cells in the tumor microenvironment and the tumor-draining lymph nodes may prematurely limit effective immune responses. High PD-1 expression on antigen-specific T cells, as a consequence of chronic antigenic stimulation, is thought to be a marker of T-cell exhaustion or anergy. Antibody-mediated blockade of the interaction of PD-1 with its main ligand, PD-L1, can lead to the reversal of antigen specific anergy.

1.2.2. Ipilimumab

The CTLA-4 receptor is predominantly expressed on activated T effector cells and regulatory T cells. It binds its ligands CD80 and D86 on dendritic cells and antigen presenting cells and mediates a signal that like PD-1 down modiulated T cell proliferation and activation. Its action is mostly at the immune priming phase in the lymph nodes, and differs from PD-1 in that it acts not at the tumor microenvironment but in lymphoid tissue earlier in the immune response. Its abrogation with a human IgG1 antibody has been associated with clinical benefit in phase III studies but also a high degree of immune related adverse events[9-12]. Its use as an adjuvant has been shown in stage III melanoma to prolong relapse-free survival, and recently published data suggest that it prolongs overall survival in stage III resected melanoma with a hazard ratio of 0.72, establishing a rationakle for its use in an adjuvant strategy in combination with NIVOLUAMB[13-14].

1.3. Preclinical Summary of NIVOLUMAB

NIVOLUMAB has been shown to bind specifically to the PD-1 receptor of the CD28 family. In vitro assays have demonstrated that NIVOLUMAB does not react with the other members of this family. NIVOLUMAB has also demonstrated the ability to block binding of its ligands, PD-L1 and PD-L2, and to enhance T-cell proliferation and IFN-γ release in vitro. A surrogate anti-murine PD-1 antibody was effective in inhibiting tumor growth in several syngeneic tumor models.

In binding studies using fresh, frozen human tissues, NIVOLUMAB demonstrated reactivity with lymphocytes in a variety of tissues. There was also moderate to strong cytoplasmic staining of rare to occasional endocrine cells in the adenohypophysis. This was considered to be low affinity binding as the intensity was moderate to strong at 10 µg/mL and was not present at 1 µg/mL. This unexpected reactivity to endocrine cells is not expected to have physiological consequences due to the limited availability of cytoplasmic compartments in vivo. Similar staining patterns were observed in cynomolgus monkey tissues indicating that this is an appropriate animal species to evaluate the potential toxicities of NIVOLUMAB. In a cardiovascular, safety pharmacology study in cynomolgus monkeys, there were no significant effects of administration of 10 or 50 mg/kg of NIVOLUMAB on electrocardiographic parameters. NIVOLUMAB was also well tolerated when administered weekly at doses of 1, 10 or 50 mg/kg/dose for 5 weeks and when administered bi-weekly at doses of 10 and 50 mg/kg for 3 months. There were no adverse clinical findings or changes in clinical or anatomic pathology parameters in these studies.

In a study of cynomolgus monkeys which were administered multiple doses of ipilimumab, a fully human mAb to CTLA-4, in combination with NIVOLUMAB, 1 monkey at the highest dose level (10 mg/kg ipilimumab/50 mg/kg NIVOLUMAB) died 1 day following the fourth and last doses of ipilimumab and NIVOLUMAB, respectively. This early death was attributed to acute gastric dilation, assessed as possibly related to administration of ipilimumab plus NIVOLUMAB. Clinical observations in the days before death included persistent diarrhea, reduced food consumption, weight loss, decreased activity, dehydration, and hypothermia. Pathology findings included marked gas distention of the stomach and

moderate gas dilatation of the duodenum, jejunum, ileum, cecum, and colon (correlated with decreased thickness of the gastric and intestinal wall, submucosal and muscularis), mottled, dark red, purple, tan discoloration of the lung (correlated with vascular congestion and a pulmonary granuloma), abnormal appearance of the lung due to atelectasis and hyperinflation (no microscopic correlate), decreased thymus size (correlated with marked, diffuse thymic atrophy), and purple discoloration of the neck and thorax (no microscopic correlate). One microscopic finding of uncertain relationship to ipilimumab plus NIVOLUMAB administration was identified in the kidney: mild multifocal tubular dilation and epithelial degeneration in the renal cortical tubules. Myeloid and eosinophil hypercellularity and erythroid hypocellurity were identified in the bone marrow. Myeloid and eosinophil hypercellularity were believed to be a secondary response to inflammation in the lung and not related to ipilimumab/NIVOLUMAB treatment. The cause of the erythroid hypocellularity was considered uncertain. Additional microscopic findings considered to be related to inappetence or physiological stress and not test article treatment included thymic involution/atrophy, pancreatic acinar cell degranulation, secretory depletion of the adrenal cortex, zona fasciculate and vascular congestion in several organs examined. All other gross observations or microscopic findings were considered incidental. There was no evidence of colitis upon gross or microscopic pathology evaluation of the gastrointestinal tract. The animal did develop diarrhea and this occurred in the cohort receiving the highest doses of the test articles. Therefore, the death may possibly be related to administration of ipilimumab and NIVOLUMAB and may be an immune-mediated gastrointestinal toxicity.

In addition to the case described above, there was an increased incidence of persistent diarrhea in the high-dose animals in this study (5 of 10 animals affected vs 0 of 10 control animals) and an incidence of diarrhea in 1 of 10 low-dose animals.

1.4. Clinical Summary

Prior clinical studies have been conducted with NIVOLUMAB in combination with a peptide vaccine. In this clinical study we will administer NIVOLUMAB in combination with IPILIMUMAB for resected melanoma.

There are currently no open adjuvant trials for children 16-21 years of age with resected high risk melanoma. In prior adjuvant trials conducted by the investigator at Moffitt Cancer Center, such patients ages 16-21 have been routinely included. That population is also treated in the community with adjuvant high dose interferon alpha, which has minimal efficacy in overall survival. In a recently published study, 33 pediatric patients under 21 were treated with ipilimumab immunotherapy (Merchant MS, Wright M, Baird K, Wexler LH, Rodriguez-Galindo C, Bernstein D, Delbrook C, Lodish M, Bishop R, Wolchok JD, Streicher H, Mackall CL. Phase I Clinical Trial of Ipilimumab in Pediatric Patients with Advanced Solid Tumors. Clin Cancer Res. 2016 Mar 15;22(6):1364-70. doi: 10.1158/1078-0432.CCR-15-0491. Epub 2015 Nov 3. PMID: 26534966) demonstrating that the toxicity was quite similar to that seen in adult patients over 21. There is no reason to postulate that the side effects of nivolumab would be any different in the 16-21 population than in an older cohort of resected melanoma patients. The only other alternative for these patients would be off-protocol ipilimumab adjuvant therapy at the FDA approved 10 mg/kg dose, which has a 41% rate of grades 3-4 toxicity, regarded by many as a very toxic regimen[13]. Therefore, given the prior safe experience of the investigator with the age 16-21 population being treated

on immunotherapy adjuvant melanoma trials, the safety of ipilumumab alone documented in the literature in this cohort, the lack of effective or non-toxic alternative therapy available, it is felt that it is appropriate to include the age 16-21 population in the current trial.

1.4.1. NIVOLUMAB

Three Phase 1, dose-escalating clinical studies (at dose levels ranging from 0.01 mg/kg to 10 mg/kg) have been initiated with NIVOLUMAB: 2 in oncology (MDX1106-01 and MDX1106-03 [Phase 1b]) and 1 in hepatitis (MDX1106-02)[15]. Data entered into the NIVOLUMAB database as of 28 May 2009 show that 76 subjects have received 1 or more doses of NIVOLUMAB (25 at the highest 10 mg/kg dose level). In these studies, there was no pattern in the incidence, severity, or relationship of adverse events to NIVOLUMAB dose level. The main toxicities noted include fatigue, anemia, increase in blood alkaline phosphatase, decrease in weight, and lymphopenia. No dose-limiting toxicities have been observed, and only 1 subject (1 mg/kg) experienced a serious adverse event considered to be related to NIVOLUMAB (colitis). There were no study drug-related deaths.

Preliminary efficacy results for the 2 cancer studies showed sustained responses to NIVOLUMAB in 3 subjects, 1 each in the 1 mg/kg (renal carcinoma), 3 mg/kg (colorectal cancer), and 10 mg/kg (renal carcinoma) dose cohorts. The times to response (and durations of response) were 56 days (57 + days), 57 days (530 + days), and 85 (295 + days) for the 1 mg/kg, 3 mg/kg, and 10 mg/kg dose subjects, respectively. A fourth subject with melanoma has been stable for 14+ months, and is still receiving NIVOLUMAB 10 mg/kg. Preliminary efficacy results from the single-dose hepatitis C study showed a transient response in 1 subject in the 0.1 mg/kg dose cohort (≥ 0.5-log or greater decrease from the baseline viral load, repeated on ≥ 2 consecutive measures) that was not clinically meaningful. CA209037 was a multicenter, open-label study that randomized (2:1) patients with unresectable or metastatic melanoma to receive either nivolumab administered intravenously at 3 mg/kg every 2weeks or investigator's choice of chemotherapy (ICC), either single-agent dacarbazine 1000 mg/m^2 every 3 weeks or the combination of carboplatin AUC 6 every 3 weeks plus paclitaxel 175 mg/m^2 every 3 weeks. The efficacy results indictaed that responses were significantly higher in the NIVOLUMAB arm than the investigator choice arms, 32% versus 11%, leading to the FDA and EMA approvals of NIVOLUMAB in 2014[14-19]. Further randomized trials indicated the superiority of NIVOLUMAB as treatment for metastatic disease.

Due to the moderate level of clinical experience with NIVOLUMAB, all expected toxicities have not been fully defined.

1.4.2. Rationale for the Original NIVOLUMAB + Peptide Vaccine Clinical Study

Clinical data indicated a potential for treatment with NIVOLUMAB in combination with a peptide vaccine to augment the T-cell immune response against specific melanoma antigens and result in antitumor effects that might prolong time to relapse in patients at very high risk of recurrence. The

previous experience did not justfy the inclusion of a peptide vaccine in the current cohort of patients with resected melanoma, so the current cohort includes patients treated with NIVOLUMAB + ipilimumab.

1.4.3 Rationale for the NIVOLUMAB + ipilimumab clinical study

As of the 15-Feb-2013 clinical cut-off in trial CA209004, in which patients received the combination of ipilimumab with NIVOLUMAB concurrently or sequentially, of the 52 subjects evaluable for response, 21 subjects (40%) had an objective response by modified World Health Organization (mWHO) criteria[20-21]. In an additional 2 subjects (4%) there was an unconfirmed objective response. In Cohort 1 (0.1 mg/kg nivolumab + 3 mg/kg ipilimumab), 3 out of 14 evaluable subjects had an objective response by mWHO (21%); 1 CR and 2 PRs with an additional PR by immune-related mWHO criteria (irPR). 55 In Cohort 2 (1 mg/kg nivolumab + 3 mg/kg ipilimumab), 9 out of 17 evaluable subjects had an objective response by mWHO (53%; 3 CRs (18%), 6 PRs (35%) with two additional subjects experiencing immune-related SD (irSD). In Cohort 2a (3 mg/kg nivolumab +1 mg/kg ipilimumab), 6 out of 15 response evaluable subjects had an objective response rate by mWHO (40%; 1 CR (7%), 5 PRs (33%) with 2 additional uPRs (13%) and 2 irSDs and 1 irPR). In Cohort 3 (3 mg/kg nivolumab + 3 mg/kg ipilimumab), 3 out of 6 evaluable subjects had an objective response by mWHO (50%; 3 PRs (50%) with 1 additional irPR and 1 irSD. Preliminary analysis revealed 16 of the 52 evaluable subjects (31%) had > 80% reduction in the size of target tumor lesions by the week 12 evaluation. This is compared to < 2% for 3 mg/kg ipilimumab monotherapy based on CA184020 (N=540) and < 3% for nivolumab monotherapy based on CA209003 (N=94, 0.1-10 mg/kg. Follow-up phase II data in the randomized CA209-069 study of nivolumab + ipilimumab versus ipilimumab alone showed a 61% response rate and a 55% rate of grades 3-4 irAEs for the combination at the nivolumab dose of 1 mg/kg and ipilimumab at 3 mg/kg in the induction portion of the trial over the first 12 weeks. These data led to the FDA approval of the combination regimen for unresectable melanoma in 2015[20-21]. The most common (reported at > 10% incidence) treatment related AEs with the combonation are fatigue, rash, pruritus, diarrhea, lipase increased, pyrexia, ALT increase, AST increased, amylase increased and vitiligo. Although the preliminary data suggests an increase in adverse event frequency of nivolumab combined with ipilimumab compared to ipilimumab monotherapy or nivolumab monotherapy, there were no unexpected adverse events noted in the combination of nivolumab and ipilimumab. In addition, many of the Grade 3-4 adverse events associated with the nivolumab combined with ipilimumab were laboratory in nature, without clinical sequelae and adverse events have been manageable and reversible following intervention dose delays or with systemic steroid treatment. While the grade 3 irAE rate in that trial was 53%, the regimen was felt to be well tolerated, with a high level of clinical activity. The choice of the combination of NIVOLUMAB and ipilimumab at the chosen doses for cohort 4 of the predecessor trial MCC 15651 at Moffitt Cancer Center was based on

the results of that study.[22] In the experience of 20 patients treated in cohort 4, 10 have had toxicity that precluded finishing 12 weeks of therapy, suggesting that for patients with resected stages 3C and 4 melanoma, the regimen of ipilimumab at 3 mg/kg and NIVOLUMAB at 1 mg/kg every 3 weeks for 4 doses may be difficult to tolerate, and suggesting that an alternative regimen of ipilimumab at 1 mg/kg and NIVOLUMAB at 3 mg/kg every 3 weeks for 4 doses was worthy of testing in cohort 5 at Moffitt. In that experience, 17 of the 20 patients treated were able to continue past the 12-week combination period. In that cohort, treatment was for 2 years with nivolumab alone after the 12-week induction with nivolumab and ipilimumab[23]. In the current protocol, an additional 20 patients will be treated with the same doses as cohort 5 at Moffitt (ipilimumab 1/nivolumab 3) and the total duration of nivolumab treatment alone will be 1 year, in order to gather further feasibility and toxicity experience with this adjuvant regimen.

1.4.4 Rationale for evaluation of PD-L1 Expression as a Predictive Biomarker

PD-L1 is expressed by many tumor types and its expression has been noted to correlate with decreased immune system function and worse clinical prognosis. It is hypothesized that PD-L1 expression within the tumor microenvironment, either on tumor cells, macrophages or lymphocytes is a means of evading immune system detection and destruction. Still others postulate that PD-L1 expression on tumor cells is a surrogate for interferon-gamma release from neighboring activated T cells and thus portends a good prognosis for immunotherapy agents, and in particular, agents targeting the PD-1/PD-L1 axis. Preliminary data from two small retrospective analyses supports the latter hypothesis in metastatic melanoma. PD-L1 positive status was associated with improved OS, irrespective of treatment, relative to PD-L1 negative status in subjects with metastatic melanoma (n=56). Similarly, objective responses to nivolumab were limited to subjects defined as PD-L1 positive in a subset of subjects from study CA209003 (n = 42), which included 18 melanoma subjects. In both of these studies, a prototype immunohistochemistry (IHC) assay was used and PD-L1 positive status was defined as > 5% tumor cell membrane staining within a tumor tissue sample. Based on these initial data, BMS is in the process of developing a reproducible diagnostic IHC assay that can be used to measure PD-L1 expression in tumor tissue. Using the verified version of the diagnostic assay, BMS has assessed additional tumor biopsy specimens from 38 CA209003 melanoma subjects for PD-L1 expression. Using a cutoff of 5% tumor cell membrane staining, 45% of subjects were defined as PD-L1 positive, consistent with the rate previously reported by Taube et al (STM 2012) at 45% (24/56 subjects) in metastatic melanoma. With this verified version of the assay, an ORR of 44% (7/16) was observed in subjects with > 5% tumor-cell positivity and 17% (3/18) in subjects with < 5 % tumor cell positivity. The limited preliminary evidence suggests that PD-L1 expression may be a prognostic marker that may also predict for nivolumab clinical activity. Therefore, we will obtain pre-

treatment FFPE tissue from all patients in the current trial, and perform IHC staining for PD-L1 at BMS to derive preliminary data whether tumor PD-L1 expression is associated with outcome in patients receiving NIVOLUMAB or combined ipilimumab + NIVOLUMAB as adjuvant therapy.

1.4.5 **Rationale for Flat Dosing of NIVOLUMAB**

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

Using the PPK model, nivolumab steady-state trough, peak and time-averaged concentration (Cminss, Cmaxss, and Cavgss, respectively) were predicted for a flat nivolumab dose of 240 mg Q2W and compared to those following administration of 3 mg/kg Q2W in NSCLC, melanoma, and RCC subjects. A dose of 240 mg nivolumab is identical to a dose of 3 mg/kg for subjects weighing ~ 80 kg, which is the approximate median body weight of subjects in the Phase 2 and 3 BMS clinical studies of nivolumab monotherapy. From the simulations, the geometric mean values of Cminss, Cmaxss, and Cavgss with flat dosing are slightly (< 15%) higher than that produced by a 3 mg/kg dose, and the coefficient of variation (cv%) in these measures of exposure are only slightly (< 10%) greater than that of 3 mg/kg dosing. Given the similarity of nivolumab PK across tumor types and the similar exposures predicted following administration of a 240 mg flat dose compared to 3 mg/kg, it is expected that the safety and efficacy profile of nivolumab following a flat dose will be similar to that of 3 mg/kg nivolumab dose.

Across the various tumor types in the BMS clinical program, nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy has been found to be relatively flat. Taken together, the PK, safety, and efficacy data indicate that the safety and efficacy profile of flat nivolumab dose every 2 weeks will be similar to that of a 3 mg/kg nivolumab every 2 weeks. In this study after completion of the combination portion of the study, all subjects will receive flat dose 480 mg nivolumab every 4 weeks (Q4W), which provides a more convenient dosing regimen for subjects. Based on PK modeling and simulations, administration of

nivolumab 480 mg Q4W will be started after steady state is achieved with the combination regimen. While 480 mg Q4W is predicted to provide greater (approximately 20%) maximum steady state concentrations and lower (approximately 10%) steady state trough concentrations, these exposures are predicted to be within the exposure ranges observed at doses up to 10 mg/kg Q2W used in the Phase 1 nivolumab clinical program, and are not considered to put subjects at increased risk. Similar to the nivolumab Q2W dosing monotherapy regimen, the exposures predicted following administration of nivolumab 480 mg Q4W, are on the flat part of the exposure-response curves for previously investigated tumors, melanoma and NSCLC, and are not predicted to affect efficacy. Based on these data, nivolumab 480 mg Q4W is expected to have similar efficacy and safety profiles to nivolumab 3 mg/kg Q2W.

Hence, doubling the dose of nivolumab from 240 mg to 480 mg would extend the dosing interval from 2 weeks to 4 weeks. Thus a flat dose of 480 mg every 4 weeks is recommended for investigation in the maintenance phase of this study during cycles 2-5.

STUDY OBJECTIVES

1.5. Primary Objective

The primary objective of this study is to assess the safety and tolerability of treatment with NIVOLUMAB in combination with ipilimumab in subjects with resected Stages IIIB/IIIC/ IV melanoma.

1.6. Secondary Objectives

The secondary objectives of this study are to:

- evaluate the immune response to treatment with the study drugs at Week 12.
- assess the preliminary efficacy of the study drugs as defined by an assessment of time to relapse

2. OVERVIEW OF STUDY DESIGN

2.1. General Design and Study Schema

This is a pilot, phase II, open-label, single center, multi-dose, study of NIVOLUMAB in combination with ipilimumab. NIVOLUMAB is an FDA-approved fully human monoclonal antibody (HuMAb) against programmed death-1 (PD-1). (See STUDY DRUGS, DOSES, AND ADMINISTRATION). Ipilimumab is a FDA-approved fully human monoclonal antibody against cytotoxic T lymphocyte antigen-4 (CTLA-4)

The study will consist of 4 periods: Screening (up to 4 weeks), Treatment (up to 1 12-week cycle), Treatment/Follow-up (up to 1 year), and Survival Follow-up. Each treatment cycle is comprised of 4 doses of NIVOLUMAB and 4 doses of ipilimumab given every three weeks for a total of 12 weeks (cycle 1) with a tumor assessment at the end of cycle 1 at week 12.

At the end of the Treatment Period (Week 12) subjects without evidence of relapse radiologically and clinically will be able to continue to receive NIVOLUMAB with flat dosing at 480mg every 4 weeks for 48 additional weeks. Subjects who relapse at the disease evaluations at Weeks 12, 24 or later will not receive further treatment with NIVOLUMAB.

Patients who experience a DLT to NIVOLUMAB and ipilimumab during or after cycle 1 will not receive further treatment with NIVOLUMAB and ipilimumab.

Subjects who prematurely discontinue 1 or both study drugs will complete the remaining study visits and associated evaluations (without dosing of 1 or both study drugs, as applicable) indefinitely until withdrawal of consent for follow-up or death.

Dosing in cycle 1 will consist of**:** 3 mg/kg of NIVOLUMAB + ipilimumab at 1 mg/kg

Since the drugs will be given concurrently, it will not be possible to attribute dose-limiting toxicities to one or the other drug during the first 12 weeks of therapy.

Subjects who withdraw from the study during Cycle 1 for reasons other than a DLT will be replaced.

No dose escalations or de-escalations are permitted within each subject's treatment. NIVOLUMAB or ipilimumab dose adjustments are allowed only if there has been ± 10% weight change since the previous treatment (Induction Treatment Period only). No dose escalations or de-escalations are allowed during cycles 2-5 due to the use of flat dosing of NIVOLUMAB at 480 mg every 4 weeks.

2.2. Primary Endpoint

The primary efficacy analysis is time to relapse. Time to relapse will be summarized using descriptive statistics. Scanning and exams to detect recurrence will be conducted every 3 months until 2 years from finishing treatment, then every 6-12 months (minimum of every 12 months) for 2 years, then yearly thereafter.

2.3. Secondary Endpoint

Overall survival will be the secondary efficacy endpoint; patients will be followed for survival indefinitely as indicated in the study schema.

2.4. Benefit/risk ethical assessment

2.4.1 Benefit

The potential benefits to subjects with study participation are improved overall survival. The information obtained from this research may help others with this disease in the future.

2.4.2 Potential Risks of Study drugs

NIVOLUMAB and Ipilimumab

In the Phase 1 MDX1106-01 (single dose [with possible retreatment] cancer) study a single instance of an inflammatory colitis serious irAE has been reported. This event occurred after the subject received 5 doses of 1 mg/kg NIVOLUMAB administered over 8 months and approximately 8 weeks after the last dose was administered. Twenty-one subjects have safely received at least 1 dose of 10 mg/kg, 6 received 2 or more 10 mg/kg doses, including 1 subject who has received 9 (10 mg/kg) doses over 18 months. Low grade irAEs have included arthropathies and declines in thyroid-stimulating hormone. Administration of NIVOLUMAB in the ongoing MDX1106-02 (single dose hepatitis) and MDX1106-03 (multiple dose cancer) studies has been well tolerated to date. In the current BMS CA209007 adjuvant study, no DLTs

have been observed during the 29 day DLT period, but two episodes of grade 3 colitis have been observed after week 12, causing treatment with vaccine plus NIVOLUMAB to be discontinued. Both patients recovered fully with prolonged steroid tapers and are currently free of disease more than a year after the episode(s) of colitis.

Other possible toxicities with NIVOLUMAB, and ipilimumab may be anticipated based on general experience with other mAbs, preclinical data, and clinical studies with similar investigational agents. Possible toxicities could affect the immune system, hematologic, cardiovascular, hepatic, musculoskeletal, and other systems, and may include:

- **Infusion reactions:** Fever, chills, shakes, itching, rash, hyper- or hypotension, difficulty breathing. It is likely that most infusion-related adverse events will occur within the first 24 hours after beginning the infusion, and may be treated by slowing or interruption of the infusion, or with supportive treatment as indicated in Section 5.2.2.
- **Widespread immune activation/cytokine storm:** Cytokine storm adverse events may initially look like allergic reaction/hypersensitivity, but are distinguished by more sustained and profound hemodynamic disturbances related to the widespread release of cytokines such as IL-1 and tumor necrosis factor (TNF). Symptoms may include fever, myalgia, change in mental status, hypotension, pulmonary infiltrates, metabolic acidosis and acute renal failure. Cytokine storm has been observed with an agonistic anti-CD28 antibody (TGN1412), but is not expected with NIVOLUMAB and/or ipilimumab, and has not been observed in human subjects with cancer or hepatitis C treated to date.
- **Immune-related adverse events:** It is possible that syndromes may develop that are most consistent with an underlying enhanced immune response as the driving factor. Such events may consist of persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, or cardiomyopathy. Experience with ipilimumab indicates that irAEs are typically low grade and self limited, more often occur after multiple doses, and most frequently involve the GI tract (diarrhea/colitis), skin (rashes), liver (hepatitis), and endocrine systems (a variety of endocrinopathies). See. section 8.5.
- **Gastrointestinal system:** Colitis is characterized by new onset of diarrhea, which may be accompanied by abdominal pain and/or GI bleeding. Events of Grade 3 or Grade 4 diarrhea as well as Grade 2 diarrhea with blood in stool should be evaluated for colitis. Subjects should be instructed to report all events of diarrhea immediately to the Investigator. **Any ≥ Grade 2 diarrhea/colitis must be reported to the BMS, within 24 hours using the rapid notification procedures described in Section 8.6.**
- **Inflammatory hepatotoxicities:** Hepatotoxicity has been observed in the ipilimumab program, and in the concurrent NIVOLUMAB/ipilimumab study [58]. Hepatocytes have been shown to express PD-L1 in the setting of IFN-γ and may occur in the presence of inflammation due to chronic viral hepatitis or immune-related heightened reactivity. PD-1 blockade may result in enhanced hepatic inflammation.

- **Immune suppression:** Subjects should be monitored for signs of new infection or return of a previous infection, with rash, fever, chills, other localizing symptoms, or sepsis that could require antibiotics either as prevention or treatment.
- **Musculoskeletal system:** Muscle or joint aches, swelling, or weakness.
- **Blood:** A decrease in blood components (platelets, white or red cells) that could lead to infection, bleeding, or anemia.
- **Heart:** Irregular heart rhythm or heart attack.
- **Skin:** The most likely adverse events are rash and pruritus, which generally resolve when study drug is discontinued.

  Human anti-human antibodies: In preliminary analyses, emergence of anti-NIVOLUMAB antibodies following treatment has not been observed to date. Neutralizing antibodies have not been observed with the use of ipilimumab. Such antibodies were detected at baseline (pre-treatment) in 4 of 36 subjects treated with NIVOLUMAB (Protocol MDX1106-01). The reactivity in 1 of these subjects was likely due to endogenous interference in the assay, as this subject had subsequent positive post-dose results. The other 3 subjects had negative post-dose results. In the 1 subject with positive baseline and post-baseline results, there appears to have been no impact of immunoreactivity on the safety of NIVOLUMAB.

2.5. Study Duration

The expected maximum duration of NIVOLUMAB treatment for a subject is 1.25 years (60 weeks). Expected maximum duration of nivolumab with ipilimumab treatment is 12 weeks.

The expected maximum duration of a subject's participation in this study is 3 years with survival follow-up to continue indefinitely until withdrawal of consent for follow-up or death.

3. STUDY POPULATION

Up to 25 subjects may be enrolled. Subjects must meet all the inclusion criteria and none of the exclusion criteria to receive a treatment assignment.

3.1. Inclusion Criteria

Subjects must meet the following criteria at Screening to be eligible to participate in the study.

1. Be at least 16 years of age;
2. Histologic diagnosis of resected Stages IIIB/IIIC/ IV melanoma, with no evidence of disease clinically and radiologically, and negative surgical margins. All melanomas regardless of primary site of disease will be allowed;
3. Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 (Appendix 2);
4. Prior chemotherapy or immunotherapy (tumor vaccine, cytokine, or growth factor given to control the cancer) must have been completed at least 4 weeks before study drug administration, and all adverse events have either returned to baseline or stabilized;

5. Prior treated brain or meningeal metastases must be without magnetic resonance imaging (MRI) evidence of progression for at least 8 weeks and off immunosuppressive doses of systemic steroids (> 10 mg/day prednisone or equivalent) for at least 2 weeks before study drug administration;

6. Prior systemic radiation therapy must have been completed at least 4 weeks before study drug administration. Prior focal radiotherapy completed at least 2 weeks before study drug administration. No radiopharmaceuticals (strontium, samarium) within 8 weeks before study drug administration;

7. Immunosuppressive doses of systemic medications, such as steroids or absorbed topical steroids (doses > 10 mg/day prednisone or equivalent) must be discontinued at least 2 weeks before study drug administration;

8. Completed nitrosourea treatment at least 6 weeks before administration of any study drug;

9. Prior surgery that required general anesthesia must be completed at least 4 weeks before study drug administration. Surgery requiring local/epidural anesthesia must be completed at least 72 hours before study drug administration and subjects should be recovered;

10. Screening laboratory values must meet the following criteria:

–	white blood cells (WBCs)	≥ 2000 cells/μL
–	neutrophils	≥ 1500 cells/μL
–	platelets	≥ 100 x 10^3/μL
–	hemoglobin	≥ 9.0 g/dL
–	serum creatinine	≤ 2 mg/dL
–	AST	≤ 2.5 x upper limit of normal (ULN) without, and ≤ 5 x ULN with hepatic metastasis
–	ALT	≤ 2.5 x ULN without, and ≤ 5 x ULN with hepatic metastasis
–	bilirubin	≤ 2 x ULN (except subjects with Gilbert's syndrome, who must have total bilirubin < 3.0 mg/dL)

11. Females of childbearing potential must:

    use appropriate method(s) of contraception. *WOCBP should use an adequate method to avoid pregnancy for 23 weeks (30 days plus the time required for nivolumab to undergo five half-lives) after the last dose of investigational drug*

    Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of nivolumab

12. For female subjects to be considered as not having childbearing potential, they must meet 1 or more of the following criteria:
    - postmenopausal for at least 24 consecutive months;
    - surgically sterile (ie, have had a hysterectomy or bilateral oophorectomy);
    - females with irregular menstrual periods and/or on hormone replacement therapy must have a documented serum follicle stimulating hormone level > 35 mIU/mL;
13. Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year *Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product Women who are not of childbearing potential (ie, who are postmenopausal or surgically sterile as well as azoospermic men do not require contraception*
14. Subject must have read, understood, and provided written informed consent and HIPAA authorization after the nature of the study has been fully explained; and
15. Willing to adhere to the study visit schedule and the prohibitions and restrictions specified in this protocol.

3.2. Exclusion Criteria

Subjects who fulfill any of the following conditions at Screening will not be eligible for admission into the study:

1. History of severe hypersensitivity reactions to other mAbs;
2. Prior non-melanoma malignancy active within the previous 2 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix or breast;
3. Subjects with any active autoimmune disease (Appendix 3) or a documented history of autoimmune disease, or history of syndrome that required systemic steroids or immunosuppressive medications, except for subjects with vitiligo or resolved childhood asthma/atopy;
4. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS);
5. Positive tests for hepatitis B virus surface antigen (HBV SAg) or hepatitis C virus ribonucleic acid (HCV RNA) indicating active or chronic infection;
6. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PDL-2, or anti-CTLA-4 antibody (or any other antibody targeting T cell co-stimulation pathways);
7. Concurrent medical condition requiring the use of immunosuppressive medications, or immunosuppressive doses of systemic or absorbable topical corticosteroids;

8. Underlying medical condition (eg, a condition associated with diarrhea) that, in the Investigator's opinion, would make the administration of either study drug or both study drugs hazardous to the subject or obscure the interpretation of toxicity determination or adverse events;
9. Pregnant or nursing; or
10. Current participation in another clinical study involving treatment with medications, radiation or surgery, or prior participation in this study.
11. Patients are excluded if they have active brain metastases or leptomeningeal metastases. Subjects with brain metastases are eligible if metastases have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for [lowest minimum is 4 weeks or more] after treatment is complete and within 28 days prior to the first dose of nivolumab administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.
12. As there is potential for hepatic toxicity with nivolumab or nivolumab/ipilimumab combinations, drugs with a predisposition to hepatoxicity should be used with caution in patients treated with nivolumab-containing regimen.
13. Allergies and Adverse Drug Reaction
    a. History of allergy to study drug components
    b. History of severe hypersensitivity reaction to any monoclonal antibody

3.3. Inclusion of Women and Minorities

Both males and females of all races and ethnic groups are eligible for this trial.

3.4. Subject Recruitment and Screening

The patients who are eligible for this research study come directly from the study investigators' clinical patient population. Thus, the investigators are very familiar with their patients' disease status and potential eligibility given the protocol's inclusion and exclusion criteria. All efforts will be made to actively recruit and retain women and members of minority groups in this study. The investigator will approach eligible potential subjects and explain the study in a private room, including the reasons why subjects will be eligible, risks, benefits, and the regimes to be evaluated. The subjects will be given a chance to ask questions to the person consenting him/her and will be able to take the consent home to discuss it with family/friends prior to signing. If the subject agrees s/he will sign the consent form either at the first contact (if the investigator/delegate is convinced that the subject understands) or at the time of a return visit after having had time to study the consent in more depth. Study procedures will not begin until after the consent form has been properly obtained. The subject is entitled to decide not to participate in the trial, without affecting their right to other medical care, and may discontinue participation in the trial at any time without penalty or loss of benefits to which they are entitled.

3.4.1 Informed Consent

Consent will be obtained only by an investigator who has completed requisite training for human subject research and has been instructed by the Principal investigator about the research study and consent process.

The Investigator, or designee, will explain to each subject (or legally authorized representative) the nature of the research study, its purpose, the procedures involved, the expected duration of subject participation, alternative treatment, the potential risks and benefits involved and any discomfort which may occur during the subject's participation in the study. The Investigator will review the informed consent form with patients and address any questions or concerns prior to obtaining written informed consent for participation. Each subject will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.For patients ages 16-17, parents will sign the informed consent, and children will sign an Assent, which will accompany the Consent Form. Children who turn 18 during the course of their participation will be approached to go through the full consenting process and be asked to provide written informed consent in order to continue participation.

For non-English speaking patients, institutional translation services will be utilized. For these patients the consent letter and all other information will be administered orally and a witness, not related to the research project, will be present while the oral presentation is given. A short form will be utilized for the subject to sign in his/her name and the translator and/or witness must sign the short form. The translator will also sign the main consent form.

For patients who cannot read. A witness, not related to the research study will be present. The consent will be read to the patient. The patient will also be allowed to ask any questions s/he may have. The investigator will ask the patient questions to ensure s/he understands the study. If the investigator determines the subject understands the study, the patient will mark an X where his/her name would go and the witness will sign the consent form.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it. The subject will be given a copy of the signed document. The original signed consent document will be retained by the Investigator. If written consent is not possible, oral consent can be obtained if witnessed by a signed statement from 1 or more persons not involved in the study, attesting to the accuracy of the presentation, the apparent understanding of the subject and documenting why the subject was unable to read and sign the form. No subject can enter the study and no study-related procedures can be performed before his/her informed consent has been obtained.

The ICF (that complies with regulatory requirements and is considered appropriate for the study) must be submitted by the Investigator with the protocol for IRB approval.

3.4.2 Documentation of Consent

The Principal Investigator or IRB approved sub-investigator will be responsible for documentation in the medical record that consent has been obtained from all participants. A signed copy of the consent form will be given to each participant. Original consent forms will be stored in the subject's medical chart.

3.4.3 Demographic/Medical History/Current Medical Conditions, and Laboratory Abnormalities

Demographics and medical history will be obtained by the Investigator or designee during the Screening Period. Demographics will include date of birth, sex, ethnicity, and race. Relevant medical history should be recorded and should include prior/current medical conditions, and clinically significant laboratory abnormalities (excluding study disease-related abnormalities). All prior treatment for melanoma will be recorded. All non-melanoma medications used during the 28 days before the first dose of the study drugs will be recorded.

3.4.4 Review Inclusion/Exclusion Criteria Including Concomitant Medication

Inclusion and exclusion criteria will be reviewed by the Investigator to ensure that the subject qualifies for the study at Screening. All appropriate medication washout times will be discussed with the subject and documented; the ICF must be signed before discontinuing any medication.

3.4.5 Registration Procedures

3.4.5.1 General Guidelines

Each patient must sign and date an informed consent form before undergoing any study specific procedure unless a procedure is being performed as part of the patient's standard of care.

Enrollment in the study requires that all inclusion and exclusion criteria have been met. Enrollment occurs upon confirmation of registration from the NYULMC PCC Clinical Trials Office. The following materials must be submitted to the Research Coordinator for registration:

1. Complete signed and dated informed consent form
2. Complete signed and dated informed consent checklist
3. Complete signed and dated eligibility checklist
4. All supporting documentation verifying each criterion has been met

Registration will occur within 24 hours of research coordinator receipt of all of the above documents. A written confirmation of enrollment including a unique study identification number assigned by the research coordinator will be distinguished to the study team upon registration.

Pretreatment evaluation will therefore be as directed by standard clinical practice. Eligible subjects will be entered on study by the study coordinator.

All patients will be required to sign a written informed consent prior to being registered on this study. Every effort will be made to answer questions raised by patients and their families or advocates regarding the protocol and alternative therapies prior to asking a patient to sign the consent form.

Once eligibility is verified, a unique patient study number will be issued within 24 hours of receiving all required registration material. The patient will not be identified by name. This is the point, at which, the patient is considered on study. Subjects must not start any protocol procedures prior to registration.

3.4.6 Early Discontinuation Criteria and Procedures

3.4.6.1 Discontinuation of Study Drug

It is the right and duty of the Investigator to discontinue the study drugs of any subject if he feels that discontinuation of the study drugs is necessary to protect the subject, or that there are unmanageable factors that may interfere significantly with the study procedures and/or the interpretation of results.

Administration of the study drugs will be discontinued if the subject develops a DLT, documented relapse, or other intolerability to the study drugs.

Administration of the study drugs may be discontinued during the study for any of the following reasons:

- Adverse event(s)
- Protocol violation
- Subject withdrew consent
- Lost to follow-up
- Other
- Death

For subjects who discontinue the study drugs for any reason, the remaining study visits and associated evaluations (without dosing) should be completed. Patients who discontinue the study drug(s) due to a toxicity will be followed until the toxicity resolves to baseline. Patients will continue to be followed on the protocol schedule for radiology assessments and for relapse free survival. Pharmacokinetic samples will only be collected at the visit following study drug discontinuation.

All subjects will be followed for adverse events for at least 70 days after the last dose of study drugs and for survival follow-up indefinitely until withdrawal of consent or death.

3.4.6.2 Discontinuation from the Study

Subject participation in the study may be discontinued for any of the following reasons:

- Adverse event(s)
- Protocol violation
- Subject withdrew consent
- Lost to follow-up
- Disease relapse

- Death
- Other

For subjects who discontinue the study for any reason, all evaluations associated with the Study Completion/Early Withdrawal visit should be performed. All subjects will be followed for adverse events for at least 70 days after the last dose of study drugs.

If a subject withdraws consent for study participation, every attempt will be made to determine the reason. These subjects will be asked to allow survival follow-up contacts. Subject completion status (completed versus not completed) will be documented.

For subjects who discontinue from the study without completing the Study Completion/Early Withdrawal visit, only study drug-related adverse events will be collected.

4. TREATMENTS

On days when both study drugs will be administered, NIVOLUMAB will be administered before starting the ipilimumab infusion.

4.1. Description of NIVOLUMAB with ipilimumab Treatment

NIVOLUMAB will be supplied as a sterile, preservative-free solution in 10 mL vials at a concentration of 10 mg/mL; which, based on the subject's weight, may be diluted with sterile normal saline (0.9% sodium chloride). NIVOLUMAB (1, 3, or 10 mg/kg) will be administered as a 30-minute i.v. infusion. Although NIVOLUMAB has been infused generally over 60 minutes, a series of 20 patients have received the drug at 3 mg/kg or 10 mg/kg over 30 minutes without any increase in infusion reactions. Therefore, it is felt safe to administer NIVOLUMAB in this study over 30 minutes.

Ipilimumab will be supplied as a sterile, preservative-free solution in 40 mL (200 mg) vials at a concentration of 5 mg/mL; which, based on the subject's weight and dose level assignment, may be diluted with sterile normal saline (0.9% sodium chloride). Ipilumumab (3 mg/kg) has been administered as a 90-minute i.v. infusion. Since ipilimumab will be given at 1 mg/kg in this study, one third the dose previously used, it is felt appropriate to shorten the 90 minute infusion to 30 minutes, since the infusion rate will not change.

BMS, Inc. will manufacture and supply NIVOLUMAB and ipilimumab to the Sponsor-investigator.

4.2. Treatment Regimen

4.2.1 Toxicity management

4.2.1.1. Management:

For Grade 1 and 2 adverse events felt due to NIVOLUMAB or NIVOLUMAB with ipilimumab, symptomatic treatment is called for generally without a dose delay. For selected irAEs of grade II, especially colitis and ophthalmologic toxicity, one dose of NIVOLUMAB or NIVOLUMAB with

ipilimumab may be skipped until resolution of the toxicity to Grade 1 or less. Grade 3 irAEs that constitute dose limiting toxicity will cause treatment with NIVOLUMAB or NIVOLUMAB with ipilimumab to be discontinued permanently. For grade III irAEs that do not constitute DLT, do not require more than 2 weeks of systemic steroid treatment**,** and resolve within 28 days to grade I or less, with either one or no skipped doses, therapy with NIVOLUMAB or NIVOLUMAB with ipilimumab may continue at the same dose(s). There will be no dose reductions of NIVOLUMAB for an individual patient. Management of infusion reactions is defined in section 5.2.2 below.

4.2.1.2. Dose Delay:

NIVOLUMAB with ipilimumab administration should be delayed for the following:

- Any Grade ≥2 non-skin, drug-related adverse event, with the following exceptions:
    - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin, drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for AST, ALT, total bilirubin, amylase and lipase:
    - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 or greater toxicity
    - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 or greater toxicity
    - Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require a dose delay. It is recommended to consult with the BMS Medical Monitor for Grade 3 amylase or lipase abnormalities.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Because of the potential for clinically meaningful nivolumab or ipilimumab related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected pulmonary toxicity, GI, hepatotoxicity, endocrinopathy, skin toxicity, neurological toxicity and nephrotoxicity. For the overlapping adverse event management algorithms present in both the NIVOLUMAB and ipilimumab IB (**GI, hepatic, and endocrine** algorithms), the recommendations are to follow the NIVOLUMAB IB adverse event algorithms as opposed to the ipilimumab IB algorithms.

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

- Subjects may resume treatment in the presence of Grade 2 fatigue

- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 or less skin toxicity
- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment

If the criteria to resume treatment is met, the subject should restart treatment at the next scheduled timepoint per protocol. However, if the treatment is delayed past the next scheduled timepoint per protocol, the next scheduled timepoint will be delayed until dosing resumes. If treatment is delayed greater than 6 weeks, the subject must be permanently discontinued from study treatment, except as specified in the discontinuation section below.

4.2.1.3. Discontinuation

Treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reactions, and infusion reactions:
- Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation

Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:

- Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires Discontinuation
- Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
    - AST or ALT > 8 x ULN
    - Total bilirubin > 5 x ULN

- Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN

- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinued.
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. It is recommended to consult with the BMS Medical Monitor for grade 4 amylase or lipase abnormalities.
  - 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
- Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.

- Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.

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

4.2.1.4. Dose Adjustments, Dose Delays, and Missed Doses

There will be no dose adjustments allowed except if there has been ± 10% weight change since the previous treatment (cycle 1) visit. There will be no dose adjustments for ipilimumab. Starting 4 weeks after the last co-administered dose in cycle 1, subjects will be administered a flat dose 480 mg NIVOLUMAB IV every 4 weeks (Q4W) in cycles 2-5 and there will be no dose adjutsments for weight.

During the Induction Treatment Period (cycle 1) and Treatment/Follow-up periods (cycles 2-5), if there is a dose delay between 1 and 7 days, the procedures at the original scheduled visit should be performed as soon as possible. If the delay is more than 7 days, the visit and dose will be considered missed; the procedures at the next scheduled visit should be performed, and subsequent visits will follow every 2 weeks. Subjects with infusion delays > 35 days (ie, 2 missed doses + 7 days) should discontinue the study drugs and complete the remaining study visits (without dosing).

4.2.2. Infusion Reactions

NIVOLUMAB and/or ipilimumab may induce infusion or hypersensitivity reactions. If such a reaction were to occur, it may manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms.

Infusion reactions should be graded according to Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0) guidelines. Treatment recommendations are provided below and may be modified based on clinical judgment, local treatment standards and guidelines, and/or specific symptoms, as appropriate:

For Grade 1 symptoms: (Mild reaction [eg, localized cutaneous reactions including mild pruritus, flushing, rash.] requires infusion rate to be decreased; intervention may be indicated)

- Decrease the rate of the NIVOLUMAB and/or ipilimumab infusion until recovery from symptoms.
- Remain at bedside and monitor subject until resolution of symptoms. Diphenhydramine 50 mg, may be administered at the discretion of the treating physician.
- When symptoms resolve, restart the infusion at the original infusion rate.
- If a subject has an infusion reaction with NIVOLUMAB and/or ipilimumab, prophylactic preinfusion medications should be given prior to all subsequent NIVOLUMAB and/or ipilimumab infusions.
- The following prophylactic preinfusion medications are recommended prior to future infusions of NIVOLUMAB and/or ipilimumab: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional NIVOLUMAB and/or ipilimumab infusions.

For Grade 2 symptoms: (Moderate reaction [ie, any symptom not listed above (mild symptoms) or below (severe symptoms) such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic blood pressure > 80 mm Hg], requires infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, i.v. fluids]; prophylactic preinfusion medications indicated for ≤ 24 hours)

- Discontinue the NIVOLUMAB and/or ipilimumab infusion.
- Begin an i.v. infusion of normal saline, and treat the subject with diphenhydramine 50 mg i.v. (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen).
- Remain at bedside and monitor subject until resolution of symptoms. Corticosteroid therapy may be administered at the discretion of the treating physician.
- When symptoms resolve, restart the infusion at 50% of the original infusion rate; 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, immediately discontinue the infusion; no further NIVOLUMAB and/or ipilimumab will be administered at that visit. Administer diphenhydramine 50 mg i.v., and remain at bedside and monitor the subject until resolution of symptoms.
- If a subject has an infusion reaction with NIVOLUMAB and/or ipilimumab, prophylactic preinfusion medications should be given prior to all subsequent NIVOLUMAB an/or ipilimumab infusions.
- The following prophylactic preinfusion medications are recommended prior to future infusions of NIVOLUMAB and/or ipilimumab: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional NIVOLUMAB and/or ipilimumab administrations. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.
- The amount of NIVOLUMAB and/or ipilimumab infused must be recorded.

For Grade 3 or Grade 4 symptoms: (Severe reaction [eg, bronchospasm, generalized urticaria, systolic blood pressure < 80 mm Hg, or angioedema], Grade 3: prolonged [ie, requiring 6 or more hours to respond to symptomatic medication and/or discontinuation of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]. Grade 4: life-threatening; pressor or ventilatory support indicated).

- Immediately discontinue the NIVOLUMAB and/or ipilimumab infusion. No further NIVOLUMAB or ipilimumab will be administered. The amount of NIVOLUMAB and/or ipilimumab infused must be recorded.
- Begin an i.v. infusion of normal saline, and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1.0 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for i.v. administration, and/or diphenhydramine 50 mg i.v. with methylprednisolone 100 mg i.v. (or equivalent), as needed.
- Remain at bedside and monitor subject until recovery from symptoms.
- Subject should be monitored until the Investigator is comfortable that the symptoms will not recur.
- The Investigator should follow the institutional guidelines for the treatment of anaphylaxis.

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

4.2.3. Treatment Reactions: Definitions, Monitoring, and Management

Potential toxicities including infusion and post-infusion reactions were defined above for NIVOLUMAB and/or ipilimumab (Section 5.2.2). These events will be closely monitored.

Therapy to prevent or treat local and/or systemic reactions following either study drug administration may include analgesics, antipyretics and antihistamines. Additionally, if necessary, corticosteroids may be temporarily added or increased for up to 7 days after study drug(s) administration.

4.2.4. Dose Limiting Toxicity: Definition, Monitoring, Management

(Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. Version 4.0 of the CTCAE is identified and located on the CTEP website at **HTTP://CTEP.CANCER.GOV/PROTOCOLDEVELOPMENT/ELECTRONIC_APPLICATIONS/CTC.HTM**. All appropriate treatment areas should have access to a copy of Version 4.0 of CTCAE.)

4.2.4.1. Definition

A DLT is defined as a NIVOLUMAB or NIVOLUMAB with ipilimumab related Grade 3 or greater adverse event other than the exceptions noted occurring within 29 days after the first dose excluding: Grade 3 adverse event of tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor), Grade 3 rash, Grade 3 immune-related adverse event (irAE, defined below) that resolves to a Grade 1 or less within 28 days, or a transient (resolving within 6 hours of onset) Grade 3 infusion-related adverse event. A Grade 3 irAE that resolves to a Grade 1 or less within 28 days, while not constituting a DLT for dose escalation purposes, may preclude further administration of NIVOLUMAB and/or ipilimumab to the subject.

The following are excluded from the definition of a DLT:

- Grade 3 rash,
- Grade 3 irAE that resolves to a Grade 1 or less within 28 days, or
- A transient (resolving within 6 hours of onset) Grade 3 infusion-related adverse event.

A Grade 3 irAE that resolves to a Grade 1 or less within 28 days, while not constituting a DLT, may preclude further administration of the study drugs to the subject. A DLT will be considered related to 1 or both study drugs unless there is a clear, well-documented, alternative explanation for the toxicity. Toxicities occurring more than 28 days after the first dose will be monitored and discussed with BMS.

All adverse events that meet DLT criteria, as well as any Grade 3 or 4 infusion reactions whether or not the event is a DLT, must be reported using the rapid notification procedures described in Section 9.6.

Patients who discontinue treatment for toxicities will continue on the protocol radiology evaluation schedule every 12 weeks once the toxicity resolves to obtain relapse-free survival data.

4.2.5. Stopping Rules for Dose-limiting Toxicity

If 3 or more of the first 6 subjects or 4 or more of the first 10 or 40% of subjects or more in this cohort of 20 patients experiences a DLT during Cycle 1, accrual will stop pending consultations between the sponsor, BMS and the FDA.

4.2.5.1. Other Stopping Rules During Enrollment

Enrollment will be held at any time during the study if either of the following study drug-related, Grade 4 or 5 toxicities occurs:

- colitis with perforation and/or requiring colectomy, or
- hepatic failure.

The Sponsor-investigator will discuss such cases with BMS to decide whether to resume enrollment and/or to jointly discuss such cases with the FDA. IRBs will be notified by the Sponsor-investigator of all cases and decisions regarding continued enrollment.

4.2.6. Stopping Rules for Clinical Deterioration

Accumulating clinical evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses may follow delayed kinetics of weeks or months, and can be preceded by initial apparent progression with appearance of new lesions or some enlarging lesions while certain index lesions are regressing ("mixed response"). It is thus reasonable to allow subjects experiencing apparent relapse in this trial to continue to receive treatment until relapse is confirmed at the next imaging assessment. These considerations should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment.

Such deterioration will be assessed to have occurred after a clinical event that, in the Investigator's opinion, is attributable to disease relapse, is unlikely to reverse with continued study treatment and therefore indicates that the subject is not benefiting from study treatment Examples of events that may, in the Investigator's opinion, indicate a lack of clinical benefit include, but are not limited to, the following:

- Performance status decrease of at least 2 points from baseline.
- Skeletal related events defined by the following:
  - pathologic bone fracture in the region of cancer involvement,
  - cancer related surgery to bone, and
  - spinal cord or nerve root compression.
- Development of new central nervous system metastases.

Or any setting where the initiation of new anti-neoplastic therapy has been deemed beneficial to the subject even in the absence of any such documented clinical events.

4.3. Method for Assigning Subjects to Treatment group

Up to 25 subjects (20 in this trial with five to account for drop-outs) will be enrolled in the study. All subjects will receive the same treatment regimen.

4.4. Preparation and Administration of Study Drug

NIVOLUMAB will be given at the following dosages: 3 mg/kg in cycle 1; starting 4 weeks after the last co-administered dose in cycle 1, subjects will be administered a flat dose 480 mg NIVOLUMAB IV every 4 weeks (Q4W) in cycles 2-5.

Ipilimumab will be given at the following dosage: 1 mg/kg

NIVOLUMAB will be administered before ipilimumab in cycle 1.

NIVOLUMAB and/or ipilimumab will be administered as an i.v. infusion, using a volumetric pump with a 0.2 micron in-line filter at the protocol-specified dose(s) and rate. NIVOLUMAB and/or ipilimumab are **not** to be administered as an i.v. push or bolus injection. No incompatibilities between NIVOLUMAB and/or ipilimumab and polyolefin bags have been observed.

4.4.1 Preparation

As NIVOLUMAB and ipilimumab are stored at refrigerated temperatures (2° to 8°C), allow the appropriate number of vials to stand at room temperature for approximately 5 minutes.

1. Ensure that the solution is clear, colorless and free from particulate matter on visual inspection. If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall, etc. Do not enter into each vial more than once. Any partial vials should be safely discarded per the site standard operating procedures (SOPs) and should not be re-used.
2. Aseptically withdraw the required volume of NIVOLUMAB and/or ipilimumab into a syringe and place into an empty i.v. bag. For patients during ther Induction Treatment cycle 1 only, based on the subject's weight, the concentrated NIVOLUMAB and/or ipilimumab solution may be diluted with sterile normal saline (0.9% sodium chloride) for a total volume of 60 mL. In cases where the total volume is more than 60 mL, no additional dilution is necessary. For patients receiving flat dosing of 480 mg NIVOLUMAB in cycles 2-5, there will be no dilution.
3. Mix by GENTLY inverting several times. DO NOT shake.
4. Visually inspect the final solution. If the infusion is not clear or the contents appear to contain precipitate, BMS should be notified, the solution discarded and the information documented.
5. Record the time that the study drug was prepared on the i.v. bag label(s).

4.4.2 Administration

NIVOLUMAB and/or ipilimumab should be administered under the supervision of a physician experienced in the use of i.v. agents. NIVOLUMAB and/or ipilimumab are **not** to be administered as an i.v. push or bolus injection. Prophylactic medications administered preinfusion, as described in Section

5.2.2, may be given if a subject had a reaction during a previous NIVOLUMAB and/or ipilimumab infusion.

NIVOLUMAB and/or ipilimumab should be administered as follows:

- Attach the i.v. bag containing the NIVOLUMAB and/or ipilimumab solution to the infusion set, 0.2 μM in-line filter, and infusion pump.
- The infusion rate of the infusion pump should be adjusted to allow for a total infusion time of 30 minutes for NIVOLUMAB , and 30 minutes for ipilimumab
- At the end of each infusion, flush the line with an adequate amount of normal saline.

4.5. Subject Compliance Monitoring

NIVOLUMAB and/or ipilimumab will be administered at the study site and recorded on the case report form (CRF) and captured in Velos. Subjects will be administered NIVOLUMAB and/or ipilimumab in a hospital setting under the supervision of appropriate study personnel. Radiation therapy will be administered at the study site. Subjects who are significantly non-compliant may be withdrawn from the study by the investigator and/or sponsor-investigator. The investigator and/or sponsor-investigator have the right to discontinue a subject from study treatment or withdraw a subject from the study at any time.

4.6. Concomitant Therapy

All medications taken within 28 days before the administration of the first dose of any study drugs and all concomitant therapy administered during the study until 70 days after last dose of any study drug will be recorded, along with the reason for and details of therapy use.

Information on all prior and concomitant therapy for melanoma, including chemotherapies, biochemotherapies, immunotherapies, radiation, surgery, biologics, and experimental therapy will be collected.

No concomitant medication information will be collected following subject discontinuation from the study except for concomitant medication use associated with study drug-related adverse events or adverse events that lead to discontinuation from the study.

4.6.1. Permitted Therapy

Subjects will be permitted topical or systemic concomitant treatment with prednisone ≤ 10 mg/day (or equivalent). Inhaled or intranasal corticosteroids (with minimal systemic absorption) may be continued if the subject is on a stable dose. Non-absorbed intra-articular steroid injections will be permitted. Systemic corticosteroids required for the control of infusion reactions or irAEs must be tapered and be at non-immunosuppresive doses (≤ 10 mg/day of prednisone or equivalent) for at least 2 weeks before the next study drug administration.

Efforts should be made to keep all other concurrent medications at stable doses during the study and to refrain from starting any new medications, unless clinically indicated.

Therapy to prevent or treat local and/or systemic reactions following the infusion of either study drug may include analgesics, antipyretics and antihistamines. Additionally, if necessary, corticosteroids may be temporarily added or increased for up to 7 days post-infusion. Other therapies considered necessary for the subject's well-being may be administered at the discretion of the Investigator.

4.6.2. Prohibited Therapy

The following medications are prohibited during the course of the study:

- other anticancer agents
- immunosuppressive agents
- immunosuppressive doses of systemic steroids or topical steroids whose absorption is expected to result in systemically immunosuppressive steroid levels
- other investigational drugs
- non-oncologic vaccines (during the Treatment Period and within 4 weeks of any dose in the and Treatment/Follow-up Period)

4.7. Packaging and Labeling

NIVOLUMAB and/or ipilimumab will be packaged and labeled according to current good manufacturing practice requirements. The labels for NIVOLUMAB and/or ipilimumab will be supplied by BMS and will bear BMS's name and address, the storage conditions, lot number, the quantity of investigational product, and the standard caution statement, as follows: "Caution: New Drug - Limited by Federal Law to Investigational Use."

4.8. Storage

NIVOLUMAB and/or ipilimumab vials must be stored at a temperature of 2 degrees Celsius to 8 degrees Celsius in a refrigerator in a locked facility. NIVOLUMAB and/or ipilimumab solution should be stored in the carton, protected from light, and must not be frozen. Recommended safety measures for preparation and handling of NIVOLUMAB and/or ipilimumab include the use of laboratory coats and gloves. Care must be taken to assure sterility of the prepared solutions as the products do not contain any anti-microbial preservative or bacteriostatic agent. Discard unused portions according to institutional procedures.

Stability data supports the storage of diluted or undiluted (removed from the vial and prepared for administration) NIVOLUMAB and/or ipilimumab for 18 hours at 2 degrees Celsius to 8 degrees Celsius and/or 6 hours at room temperature and normal room light. Note: once NIVOLUMAB and/or ipilimumab has been prepared for administration, the total storage time (combination of refrigeration and room temperature) is not to exceed 24 hours.

4.8.1. Drug Accountability

Study drug supplies must be kept in an appropriate, secure area (eg, locked) and stored in accordance with the conditions specified on the labels and in Section 5.8.

The Investigator or designated study person must maintain a log of study drug disposition including the amount of each study drug received, dosages prepared, doses dispensed, and doses and/or vials used or destroyed.

At the conclusion of the study, and as appropriate during the course of the study, the Investigator will destroy all other used and partially used study drugs in accordance with the site's Standard Operating Procedures (SOPs). The Investigator will discard all unused NIVOLUMAB and/or ipilimumab with a copy of the completed NIVOLUMAB and ipilimumab drug disposition forms sent to BMS.

4.9. Replacement of Subjects

Subjects enrolled and those not treated will be replaced. A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will also be replaced.

5. STUDY PROCEDURES/EVALUATIONS

The study is divided into 4 periods: Screening (up to 4 weeks), Induction Treatment (a 12-week cycle), Treatment/Follow-up (cycles 2-5, up to 48 additional weeks), and Survival Follow-up with associated evaluations and procedures that must be performed at specific time points. The follow-up period has been extended indefinitely to include the Survival Follow-up period for overall survival, post-study treatment modalities, time to relapse, and site of relapse. The Screening Period is defined as the 28 days following initiation of screening assessments and before administration of any study drug, during which subjects are evaluated for study eligibility.

The schedule of study procedures and dosing frequency are shown in the Time and Events Schedule (Table 1). A description of individual study procedures is provided in the following subsections. For details of the procedures for assessment and reporting of adverse events, see Section 8.

5.1. Screening Procedures

After providing informed consent, subjects will undergo screening for eligibility to participate in the study.

5.1.1. Physical Examination

A physical examination will be performed at all visits. All abnormal findings at baseline will be recorded as medical history. Any physical examination finding that is judged by the Investigator as a clinically significant change (worsening) compared to a baseline value will be considered an adverse event, and will be recorded and monitored as described in Section 9.

5.1.2. Vital Signs

Vital sign measurements include:

- Temperature (°C)
- Pulse (beat/minute)
- Resting systolic and diastolic blood pressure (mmHg)
- Height (cm)
- Weight (kg)

Before pulse and blood pressure are measured, the subject should be in a sitting position and resting for at least 5 minutes. Vital signs are to be measured in accordance with the schedule of procedures shown in the Time and Events Schedule (Table 1).

In the event of an infusion reaction, the infusion may be temporarily stopped, slowed or discontinued, during which time vital signs should be monitored and recorded every 15 minutes until the infusion is completed, or if study drug is discontinued, the subject is stable. The frequency of vital sign measurements necessary to monitor an adverse event will be determined by the Investigator.

Any vital sign value that is judged by the Investigator as a clinically significant change (worsening) compared to a baseline value will be considered an adverse event, recorded and monitored as described in Section 8.

5.1.3. Performance Status Assessment

An assessment of performance status will be performed using the ECOG performance status scale of 0 to 5 (Appendix 2).

5.1.4. Safety

The overall safety and tolerability of NIVOLUMAB in combination with ipilimumab will be evaluated through an ongoing review of the incidence and severity of adverse events, clinical laboratory tests (blood and urine sampling for clinical laboratory parameters), physical examination results including vital sign measurements, ECOG evaluation, ECG, and chest radiography. Evaluations of immune safety tests and immunogenicity will also be performed

5.1.5. Adverse Events and Concomitant Medications

Adverse events and concomitant medication use will be collected throughout the study. See Section 8, Adverse Event Reporting, and Section 5.6, Concomitant Therapy for details.

5.1.6. Clinical Laboratory Tests

Samples for chemistry, hematology, and urinalysis will be taken at the times indicated on the Time and Events Schedule (Table 1) and results must be reviewed before dosing to evaluate whether or not a subject should be treated at that visit. Minimum required laboratory testing prior to each dose in all cycles: Within 72 hrs prior to re-dosing to include CBC w/ differential, LFTs, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase, TSH (with reflexive Free T4 and Free T3

if needed). A laboratory abnormality is considered an adverse event if it results in discontinuation from the study drugs, necessitates therapeutic medical intervention, or if the Investigator assesses the abnormality as an adverse event as described in Section 8.

5.1.6.1. Chemistry

Chemistry tests, including the following, will be performed:

- albumin
- alkaline phosphatase
- ALT
- AST
- bicarbonate
- bilirubin (total)
- calcium
- amylase
- chloride
- creatinine
- glucose
- potassium
- sodium
- total protein
- urea nitrogen
- lipase

5.1.6.2. Hematology

Hematology tests, including the following, will be performed:

- complete blood counts
- hemoglobin
- differential counts
- absolute lymphocyte count
- hematocrit
- direct platelet count

5.1.6.3. Urinalysis

The urinalysis will include testing for the following:

- protein
- specific gravity
- glucose
- blood (hemoglobin)
- microscopic (If gross findings are positive, then a microscopic examination including WBCs/high power field (HPF), and red blood cells/HPF, will be performed.)

5.1.6.4. Other

Hepatitis Test

Test for HBV SAg and HCV antibody will be conducted at Visit 1. Results indicating active or chronic infection will result in study exclusion. HCV RNA assay will be carried out if the antibody assay is positive and will determine if a HCV antibody assay is a true positive.

Pregnancy Test

For female subjects of child bearing potential only. Pregnancy Test: WOCBP prior to dosing nivolumab. A serum or urine pregnancy testing is required within 24 hrs of study [treatment] enrollment or randomization, then every 6 weeks. [more frequently if required by local standard]. After discontinuation from nivolumab these should be repeated at approximately 30 days and approximately 70 days [or more frequently if required by local standard]. Pregnancy tests prior to dosing must be negative.

Immunogenicity Testing

Blood will be collected for immunogenicity testing. Sample preparation and storage instructions are provided in Appendix 4.

Immune Safety Assays

Blood samples for measurement of immune safety parameters will be taken at the times indicated on the Time and Events Schedule (Table 1), and the following parameters will be measured:

- Rheumatoid Factor
- Thyroid Stimulating Hormone
- Free T4 level[1]
- Adrenocorticotropic hormone
- C-Reactive Protein
- Antinuclear Antibody

[1] If abnormal, the sample should be analyzed for free T3 and free T4

The following tests may also be performed on selected stored samples. Samples will be stored up to 10 years

- anti-DNA antibody
- anti-phospholipid antibody
- anti-thyroid receptor antibodies
- anti-islet cell antibody
- anti-neutrophil cytoplasm antibody
- anti-thyroglobulin antibody
- anti-thyroid peroxidase

Additional tests and repeat tests to evaluate abnormal endocrine results may be obtained at the Investigator's discretion if deemed clinically significant. This may include follow up with prolactin and a.m. cortisol tests, and may require an endocrine consult.

All research samples will be labeled with a unique code. The PI and research staff will have access to the linking key. All research samples will be stored for up to 10 years at NYU Langone Medical Center – 1310 Smillow. All research samples will be stored only for research related to this protocol. Genetic tests will be performed only related to the subject's cancer and potential use of Nivolumab and Ipilumumab and will not be used to predict an individual's risk for developing disease or passing it ot their children. Subjects will not receive results of this testing.

5.1.7. Electrocardiogram

A 12-lead ECG will be performed. The subject should be relaxed and should be in a resting position at least 5 minutes before recording the ECG. The ECGs will be reviewed by the Investigator (paper or electronic tracing) and will be available for comparison with subsequent ECGs by the Investigator. A copy of the ECG tracing must be available in the subject's medical record for review and monitoring. The following will be recorded:

- PR interval (msec)
- QRS duration (msec)
- QT interval (msec)

- Heart rate (BPM)
- P axes
- R axes
- T axes

The clinical interpretation (normal, abnormal not clinically significant, or abnormal, clinically significant) will also be recorded. Any ECG finding that is judged by the Investigator as a clinically significant change (worsening) compared to a baseline value will be considered an adverse event, recorded and monitored as described in Section 9.

5.2. Chest Radiograph

The Screening chest radiograph may be substituted with a chest radiograph that had been performed as part of the subject's previous routine care in the 3 months prior to the initiation of Screening testing. There should be no evidence of significant abnormalities or clinical pulmonary signs or symptoms on the Screening physical examination. The chest radiograph report must be available in the subject's medical records for review and monitoring.

The clinical interpretation (normal, abnormal not related to malignant disease, or abnormal, related to malignant disease) will be recorded. Any finding on a repeat chest radiograph that is judged by the Investigator as a clinically significant change (worsening) compared to a baseline value will be considered an adverse event, recorded and monitored as described in Section 9.

5.3. Immunology

Evaluations of immunology assessments (below) are summarized in Appendix 4.

- Flow cytometry : Parameters include but may not be limited to the following:
- Blood and peripheral blood mononuclear cell samples will be collected and evaluated by leukapheresis or peripheral blood draw for flow cytometry (T cell, B cell, NK, monocytes, CD3, CD4, CD8, CD4/CD8, CD11b, CD11c, CD14, CD20, CD25, CD33, CD56, CD69, CD71, CD73, CD80, CD127, FOXp3, LAG3, TIGIT, BTLA, Tim3, CTLA-4, PD-1, PD-L1, CD244, OX-40, 41-BB, CD40, CD4/MHC Class II positive cells, and CD8/MHC Class II positive cells), serum cytokines (IL-6, IL-10, TNF-β, ING-gamma, TGF-β, neopterin and sIL-2R), cellular immune function (tetramer and/or ELIspot assays utilizing melanoma and other control antigens).
  - Percent and absolute CD4 and CD8 counts and CD4/CD8 ratio
  - Two color analyses to determine percent and absolute numbers for: CD4/MHC Class II positive cells
  - Two color analyses to determine percent and absolute numbers of: CD8/MHC Class II positive cells

- Serum samples will be collected and cryopreserved to study molecules that may be implicated in regulating anti-melanoma immune responses and/or NIVOLUMAB or ipilimumab activity such as soluble MICA, compounds detected by mass spectroscopy including those associated with wound healing, complement and the acute phase response, chemokines or cytokines, or antibodies to melanoma antigens.
- Cellular Immune Function Assays that may include, but will not be limited to proliferation and/or ELIspot assays utilizing melanoma and other control antigens (Appendix 4).
- Serum samples will be collected and cryopreserved to study molecules that may be identified based on prior analyses of acute phase reactants and may be implicated in regulating anti-melanoma immune responses and/or NIVOLUMAB with ipilimumab activity.

5.4. Efficacy

Using imaging results (ie, computed tomography/magnetic resonance imaging of the chest, abdomen, pelvis, and brain; and photography of lesions), efficacy defined as relapse free survival will be evaluated and treatment decisions will be made by the Investigator. CT of the neck will be performed in patients with prior disease of the head and neck.

At the Sponsor-investigator's discretion, scans and measurements may be reviewed by independent radiologists using irRC and/or standard RECIST 1.1 criteria at a later date or any time during the study.

Because immunotherapy may cause a delayed onset of tumor response, there will be cases that warrant confirmation of progressive disease (eg, borderline progression, apparent radiologic progression with improving clinical status).

Only subjects without relapse will receive additional doses of the study drugs, until confirmed relapse, development of a DLT, or other intolerability to therapy. Subjects with a confirmed relapse will not receive additional doses, and will complete all of the remaining evaluations without dosing. Subjects who discontinue treatment with the study drugs prematurely will complete the remaining visits and assessments except for the study drug infusions and pharmacokinetic sample collection, which will only be done at the visit following discontinuation of the study drugs.

Imaging will be performed as outlined in Table 1 and Appendix 1.

5.5. Subject Completion/Early Discontinuation

It will be documented whether or not each subject completed the Treatment and the Treatment/Follow-up Period, how long they followed, and the reason for withdrawal from the study.

5.6. Research Specimen Procedures

5.6.1. Tumor Tissue Specimens

If available, pre-treatment tumor tissue specimens in the form of a paraffin embedded block or a minimum of 10 unstained slides from the most recent tumor resection or biopsy will be submitted for central PD-L1 immunohistochemistry (IHC) assessment, and determination of other tumor microenvironment biomarkers such as CD8 T cell infiltrate and other biomarkers by IHC based on emerging science. In addition, patients will be asked to consent to have any post-relapse specimens previously resected as standard of care analyzed in a similar manner by immunohistochemistry. These biopsy samples should be excisional, incisional, punch or core needle. Fine needle aspirates or other cytology specimens are insufficient for downstream biomarker analyses. PD-L1 stained tissue sections will be assessed by a pathologist and scored as PD-L1 positive if membrane staining is observed in >5% tumor cells among a minimum of a hundred (100) evaluable tumor cells. Samples with < 5% tumor cell membrane staining in a minimum of a hundred (100) evaluable tumor cells will be scored as PD-L1 negative and samples where membrane staining is obscured by high cytoplasmic staining or melanin content, but contain the minimum number of evaluable tumor cells will be deemed PD-L1 indeterminate.

5.6.2. Research Blood Samples

Research blood samples will be taken at timepoints outlined in Table 1. Refer to Appendix 4 for specific processing and handling procedures for research blood specimens. All subjects will have blood samples collected.

5.6.3. Analysis of Immunological Response

For each time point (at baseline and Weeks 7 and 13) the percent of subjects with a response will be calculated – for T-cell proliferation response, along with an exact confidence interval.

Cryopreserved Serum

Serum samples will be analyzed to evaluate molecules that may be identified and implicated in regulating anti-melanoma immune responses and/or NIVOLUMAB/ipilimumab activity such as soluble MICA, and antibodies to melanoma antigens

6. STATISTICAL PLAN

6.1. Sample Size Determination

The sample size of up to approximately 25 subjects (total of 20 including screening failures and drop-outs) is based on the study design for safety and immune assays.

6.2. Study Population

The subject populations are defined below.

6.2.1. Safety Population

The Safety Population includes all subjects in the study who received at least 1 dose or any partial dose of NIVOLUMAB and/or ipilimumab.

6.2.2. Evaluable Population

The Evaluable Population includes subjects in the Safety Population who have the correct disease diagnosis, do not have any major protocol or inclusion/exclusion violations, have no major dosing violations, and who have a valid baseline and at least one post-baseline tumor assessment.

6.3. Statistical Analysis

The data collected in this study will be analyzed by the Biostatistics group at the Perlmutter Cancer Center at NYU.

All data will be listed individually by subject. For quantitative parameters, descriptive statistics will include the mean, standard deviation, minimum, median, and maximum. For qualitative parameters, descriptive statistics will include frequency and percentage.

Unless otherwise indicated, the statistical significance will be declared if the two-sided p-value is ≤ 0.05.

6.3.1. Demographics and Baseline Characteristics

Subject demographics and baseline characteristics including age, sex, race, height, weight, tumor information, medical conditions, etc. will be summarized using descriptive statistics

6.3.2. Concomitant Medication

Concomitant medications and significant non-drug therapies will be summarized using descriptive statistics.

6.3.3. Safety

The safety analysis will be conducted on the Safety Population. The following safety parameters will be evaluated: adverse events, clinical laboratory tests, physical examinations, vital signs, ECOG performance status, ECGs, chest radiographs, immune safety, and immunogenicity. All safety parameters will be summarized using descriptive statistics.

- **Adverse Events**

  Treatment-emergent adverse events (TEAEs) are defined as signs or symptoms that emerge during treatment or within 100 days of the last dose of study drug, including those signs and symptoms that have been absent pre-treatment or that have worsened relative to the pre-treatment assessment. Any adverse event considered related to treatment will also be considered a treatment-emergent adverse event (TEAE), regardless of the elapsed time since the last dose of study drug.

  An irAE, a subset of adverse events, is defined as a clinically significant adverse event of any organ that is associated with study drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism.

  All adverse events recorded during the study will be summarized using descriptive statistics. The incidence of TEAEs will be summarized by body system, preferred term, verbatim of adverse event, intensity (based on CTCAE Version 4.0 grade), and relationship to each study drug (NIVOLUMAB and/or the ipilimumab).

- **Vital Signs**

  The observed vital signs at each visit and the change from baseline to each post-baseline visit will be summarized by cohort using descriptive statistics.

- **Physical Examination**

  Abnormal findings in physical examination will be summarized using descriptive statistics.

- **Clinical Laboratory Tests**

  Clinical laboratory test values outside the normal range and clinically significant abnormal range will be flagged in the data listing.

  Laboratory data will be summarized using shift tables (baseline to notable post-baseline visit). The change from baseline will be summarized using descriptive statistics.

- **ECOG**

  The data observed from ECOG performance status will be summarized appropriately.

- **Other Safety Evaluations**

The results of ECGs, chest radiographs, immune safety tests, and immunogenicity will be summarized appropriately.

6.3.4. Immunology Parameters

The data from each of the assays and assessments described in Appendix 4 will be summarized by week of study, using standard descriptive statistical methods – preferably parametric if the distribution of the continuous assay data (possibly after transformation) is compatible with the assumptions of a normal distribution, and non-parametric otherwise. For each immunological marker studied, one of the following 4 transformations will be used: identity (ie, no transformation), square-root, cube root, or log transformation. Choice of the transformation will be made by computing the Anderson-Darling statistic based on the regression model residues using the pooled data. Then the transformation with the lowest Anderson-Darling statistic will be selected as the most normal-like and used in the mixed model analysis.

Scatterplots of the data for the individual subjects, over time, will be constructed to display the patterns; means (or geometric means or medians) with confidence intervals will also be plotted; contingency tables will be used for the categorical assay responses. For baseline and weeks 7 and 13, regression methods (linear or logistic) that accommodate random effects will be used to evaluate the effect of the treatment regimen on the overall levels and on the trends over time – with subject as the random effect and week as the fixed effects. These analyses will be used to evaluate the quantitative effects of the NIVOLUMAB + ipilimumab regimen on immunologic and pharmacodynamic changes due to treatment. While formally proving that the addition of NIVOLUMAB to ipilimumab will increase the probability of clinical benefit is beyond the scope of this trial, the data obtained will be used to test the hypothesis that the magnitude of the proliferating T-cells (as continuous) will increase with NIVOLUMAB added to ipilimumab compared to the prior cohorts of protocol 15651 at Moffitt Cancer Center with NIVOLUMAB alone. Note that the pre and post treatment assays from any given subject that are used in the analysis are always performed on the same plate, thus eliminating a potential confounding factor due to plate-to-plate assay variation.

Due to the exploratory nature of this trial, there will be no formal adjustments made to account for the multiple statistical testing performed on the 11 surface and intracellular biomarkers under investigation. However, to guard against having a possibly over-inflated overall type I error rate, result sensitivity will be high if 3 or more phenotypic changes occur with addition of ipilimumab at an individual α level of 0.05 each for further studying these phenotypic changes in NIVOLUMAB + ipilimumab treated cells. In the case of doing 11 independent hypothesis testings with an α level of 0.05 each, the probability of having 3 or more significant results by chance will be only about 0.015, whereas, the probability of having at least 1 or 2 significant results is 0.43 or 0.10, respectively

In addition to analyzing the results of these assays as continuous variables, the T-cell proliferation assay results will be classified as "response" or "non-response" to further explore the relationship of immunologic changes with treatment.

6.3.4.1. T-cell Proliferation

The definition of augmented proliferation for the purposes of this trial will be a 20% increase, at Week 12, in the absolute proportion of CD107a positive CD8+ T cells that stain with the Ki-67 marker.

6.4. Missing Data Handling

Unresolved missing data may be imputed when the analysis integrity is affected. The conservative principle will be used for data imputation. For example, if an adverse event onset day is missing but the adverse event onset year and month cannot exclude this adverse event as a TEAE, the adverse event will be flagged as a TEAE.

6.5. Statistical Software

All statistical analyses will be performed using SAS® Version 8.2 or higher.

SAFETY AND ADVERSE EVENT REPORTING

6.6. Definitions

An **Adverse Event (AE)** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product. A laboratory abnormality is considered an adverse event if it results in discontinuation from the study drugs, necessitates therapeutic medical intervention, or if the Investigator assesses the abnormality as an adverse event.

6.7. Serious Adverse Events

A **serious adverse event (SAE)** is any untoward medical occurrence that:

- results in death

- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see "note" below for exceptions)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- Suspected transmission of an infectious agent (eg, any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Although overdose and cancer are not always serious by regulatory definition, these events should be reported on an SAE form and sent to BMS in an expedited manner. An overdose is defined as the accidental or intentional ingestion or infusion of any dose of a product that is considered both excessive and medically important.

NOTE: The following hospitalizations are <u>not</u> considered SAEs in BMS clinical studies:

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

Note that all pregnancies, regardless of outcome, must be reported to the sponsor-investigator on a Pregnancy Surveillance Form, not an SAE form. All pregnancies must be reported and followed to outcome, <u>including pregnancies that occur in the female partner of a male study subject.</u> **See Section 8.4 for instructions on reporting pregnancies.**

Nonserious Adverse Events

<u>A **non-serious adverse event** is an AE not classified as serious.</u>

6.7.1. Assignment of Adverse Event Intensity and Relationship to Investigational Product

Describe how adverse events (AEs and SAEs) will be graded, for example:

For oncology studies:

Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. Version 4.0 of the CTCAE is identified and located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of Version 4.0 of CTCAE.

The following categories and definitions of causal relationship to investigational product as determined by a physician should be used:

- **Related:** There is a reasonable causal relationship to investigational product administration and the adverse event.
- **Not Related:** There is not a reasonable causal relationship to investigational product administration and the adverse event.

The expression "reasonable causal relationship" is meant to convey in general that there are facts (eg, evidence such as de-challenge/re-challenge) or other arguments to suggest a positive causal relationship.

6.7.2. Collection and Reporting

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

If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. The following information should be captured for all AEs: onset, duration, intensity, seriousness, relationship to investigational product, action taken, and treatment required. If treatment for the AE was administered, it should be recorded in the medical record.

The sponsor-investigator shall supply the ethics Committee with any additional requested information, notably for reported deaths of subjects.

6.8. Reporting of Serious Adverse Events and Unanticipated Problems

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 100 days of discontinuation of dosing. CTCAE version 4.03 terms should be used.

The collection of nonserious AE information should begin at initiation of study drug. All nonserious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment. Additionally, any SAE or other AE of concern that the investigator believes may be related to study treatment and that occurs later than 30 days after last study treatment should be reported. Information for any non-serious AE that starts during the treatment period or within 70 days after last treatment will be collected from the time of the event until resolution of the event, or until the patient's last study visit, whichever comes first. Serious adverse event information will be collected until the event is considered chronic and/or stable.

All fatal or life-threatening adverse events must be immediately reported to the Sponsor-investigator by telephone or e-mail. Within 24 hours of the event, the Serious Adverse Event (SAE) Form supplied by NYULMC must be faxed to the Sponsor-investigator and BMS, who must then inform the NYULMC IRB, PCC CTO, and DSMC within 24 hours of the event whether full information regarding the event is

known or not. Additional follow-up by the investigator will be required if complete information is not known. De-identified source documentation of all examinations, diagnostic procedures, etc. which were completed with respect to the event should be included with the SAE form. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers (as assigned at the time of study enrollment) are properly mentioned on any copy of source document provided to the Sponsor-investigator. For laboratory results, include the laboratory normal ranges.

In case of accidental or intentional overdose of study drug, even if asymptomatic or not fulfilling a seriousness criterion, the overdose is to be reported to the Sponsor-investigator and BMS immediately (within 1 working day) using the AE and SAE forms supplied by NYULMC. Overdose of study drug will be defined as at least 2 times the intended dose of study drug within the intended therapeutic window.

All serious adverse events (SAEs) will be evaluated by the DSMC If meeting the requirements for expedited reporting, the Sponsor-investigator will report the adverse event to all regulatory authorities with jurisdiction over ongoing trials with the study drug and to all other investigators involved in clinical trials with the study drug. The investigator is responsible for reporting all SAEs to the appropriate IRB, DSMC, Sponsor-investigator, BMS and FDA.

6.8.1. Investigator reporting: notifying the IRB

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The IRB requirements reflect the current guidance documents released by the Office of Human Research Protection (OHRP), and the Food and Drug Administration (FDA) and are respectively entitled "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events" and "Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting-Improving Human Subject Protection." The following describes the NYULMC IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record. The NYU IRB address is:

NYULMC IRB
1 Park Avenue, 6th Floor
New York, NY 10016

6.8.2. Serious Adverse Events

The following information is provided to investigators for either inclusion in protocol documents or other related study documents. It will also be contained in the Study Agreement:

Following the subject's written consent to participate in the study, all SAEs must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 100 days of discontinuation of dosing of the investigational product. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy). The investigator should notify BMS of any SAE occurring after this time period that is believed to be certainly, probably, or possibly related to the investigational product or protocol-specified procedure.

All SAEs should be followed to resolution or stabilization.

The Sponsor/Investigator will ensure that all SAEs in the clinical database are reported to BMS and any applicable health authority during the conduct of the study. This reconciliation will occur at least quarterly and be initiated by the sponsor/investigator. Sponsor/investigator will request a reconciliation report from: aepbusinessprocess@bms.com. During reconciliation, any events found to not be reported previously to BMS must be sent to Worldwide.Safety@BMS.com.

All SAEs should be faxed or emailed to BMS at:

Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
Email: Worldwide.safety@bms.com

For studies conducted under an Investigator IND, any suspected adverse event that is both serious and unexpected must be reported to the FDA as soon as possible and, in no event, later than 7 days (death or life-threatening event) or 15 days (all other SAEs) after the investigator's or institution's initial receipt of the information. BMS will be provided with a simultaneous copy of all adverse events filed with the FDA. SAEs should be reported on the MedWatch Form 3500A, which can be accessed at: http://www.accessdata.fda.gov/scripts/medwatch/.

MedWatch SAE forms should be sent to the FDA at:

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

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

Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
Email: Worldwide.safety@bms.com

The contact information for submitting IND safety reports is noted below:

Email: NYUPCCsafety@nyumc.org

Tel: 212-263-4427

Serious adverse events, whether related or unrelated to investigational product, must be recorded on the SAE page and reported expeditiously to BMS (or designee) to comply with regulatory requirements. An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

All SAEs must be immediately reported by confirmed facsimile transmission (fax) and mailing of the completed SAE page. In some instances where a facsimile machine is not available, overnight express mail may be used. If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.) In selected circumstances, the protocol may specify conditions that require additional telephone reporting.

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

If an ongoing SAE changes in its intensity or relationship to the investigational product, a follow-up SAE report should be sent immediately to the Sponsor--investigator. As follow-up information becomes available it should be sent immediately using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.

6.8.3. Handling of Expedited Safety Reports

In accordance with local regulations, BMS will notify investigators of all SAEs that are suspected (certainly, probably, or possibly related to the investigational product) and unexpected (ie, not previously described in the Investigator Brochure). In the European Union (EU), an event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of an expedited safety report (ESR).

Other important findings which may be reported by the sponsor-investigator as an ESR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor-investigator decision to end or temporarily halt a clinical study for safety reasons.

Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the Investigator Brochure. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor-investigator will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

6.8.3.1. Non-serious Adverse Events

The collection of nonserious AE information should begin at initiation of investigational product. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

If an ongoing non-serious AE worsens in its intensity, or if its relationship to the investigational product changes, a new non-serious AE entry for the event should be completed. Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of investigational product, or those that are present at the end of study participation. Subjects with non-serious AEs at study completion should receive post-treatment follow-up as appropriate.

All identified non-serious AEs must be recorded and described in the medical record.

6.9. Pregnancy

Sexually active WOCBP must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized. Before enrolling WOCBP in this clinical study, the investigator must review the guideline about study participation for WOCBP which can be found in the GCP Manual for Investigators. The topics include the following:

- General Information
- Informed Consent Form
- Pregnancy Prevention Information Sheet
- Drug Interactions with Hormonal Contraceptives
- Contraceptives in Current Use
- Guidelines for the Follow-up of a Reported Pregnancy.

Before study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

All WOCBP MUST have a negative pregnancy test within 72 hours before receiving NIVOLUMAB. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. If the pregnancy test is positive, the subject must not receive NIVOLUMAB and must not be enrolled in the study.

In addition, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). The investigator must immediately notify BMS of this event and record the pregnancy on the Pregnancy Surveillance Form (not an SAE form). Initial information on a pregnancy must be reported immediately to BMS, and the outcome information provided once the outcome is known. Completed Pregnancy Surveillance Forms must be forwarded to BMS according to SAE reporting procedures.

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

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

PCC, and follow-up on information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants should be followed for a minimum of 8 weeks.

6.9.1. Follow-up

For female subjects, protocol-required procedures for study discontinuation and follow-up must be performed (Section 8) unless contraindicated by pregnancy (eg, radiograph studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome should be reported where possible.

For male subjects, follow-up information regarding the course of the partner's pregnancy, including perinatal and neonatal outcome, should be reported where possible.

Infants should be followed for a minimum of 8 weeks and the outcome reported where possible.

6.10. Immune-related Adverse Events

An irAE, a subset of adverse events, is defined as a clinically significant adverse event of any organ that is associated with study drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

Given the intended mechanism of action of NIVOLUMAB and/or ipilimumab, namely disinhibition of cellular immune responses, it is possible that syndromes may develop that are most consistent with an underlying enhanced immune response as the driving factor. Such events may consist of persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, or cardiomyopathy. The spectrum of irAEs is currently hypothetical, as very few human subjects have been treated to date, and are based upon preclinical studies in mice deficient in PD-1, as well as experience with other monoclonal antibodies that act by disinhibiting the immune response. Such irAEs may resolve with time, or may require institution of counteracting immunosuppressive therapies.

BMS has observed irAEs in another development program with the immunostimulatory antibody, ipilimumab (anti-CTLA-4). Ipilimumab-induced irAEs are typically low grade and self limited, more often occur after multiple doses, and most frequently involve the gastrointestinal tract (diarrhea/colitis), skin (rashes), liver (hepatitis), and endocrine systems (a variety of endocrinopathies). In addition, the known animal and human toxicity profiles of anti-CTLA-4 antibodies such as ipilimumab include colitis as an expected adverse event. Based on these considerations, NIVOLUMAB may also cause immune-mediated colitis. Uveitis and visual changes may also be seen.

Colitis is characterized by new onset of diarrhea, which may be accompanied by abdominal pain and or gastrointestinal bleeding. Events of Grade 3 or Grade 4 diarrhea as well as Grade 2 diarrhea with blood in stool should be evaluated for colitis. All adverse events of colitis $\geq$ Grade 2 are deemed to be of special interest, and should be reported to BMS within 24 hours of occurrence using the serious adverse event reporting procedures (Described in Section 8.3), even if the adverse event itself is not deemed as serious.

Management Algorithms for High Grade irAEs

Management algorithms for high-grade irAEs have been established for ipilimumab, where timely application of defined immunosuppressive regimens appear to be effective in limiting the morbidity and mortality from such events without compromising therapeutic efficacy. A general management algorithm with recommended guidelines for the treatment and monitoring of suspected irAEs, as well as algorithms for specific irAEs (ie, diarrhea/colitis, endocrinopathy, hepatotoxicity, and neuropathy) are provided in the NIVOLUMAB Investigator Brochure. **All incidents of diarrhea should be managed according to the diarrhea/colitis algorithm.** Additional clinical experience will be required to define the spectrum of irAE-like events that may emerge in the NIVOLUMAB program, and these algorithms are useful guides towards establishing an effective management approach as experience accumulates.

In all cases, study drug-related ≥ Grade 2 diarrhea/colitis will be managed with regular communication between the Investigator and BMS, and with a minimum of at least 1 in-person visit per week until the diarrhea/colitis is < Grade 2. Any Grade 2 adverse event of colitis (per Version 4.0 CTCAE) that also results in additional medical requirements, such as more than 2 weeks of immunosuppressive doses of steroids (> 10 mg/day of prednisone or equivalent), blood transfusion, or i.v. hyperalimentation, will be defined as a Grade 3 adverse event. Subjects are to be carefully monitored until recovery of the colitis to ≤ Grade 1.

6.11. Rapid Notification of Adverse Events of Special Interest

In addition to serious adverse events, overdose, and pregnancy, the following adverse events will also be reported on an expedited basis to the designated email address: **Worldwide.safety@bms.com**

- Adverse events that potentially meet DLT criteria;
- ≥ Grade 2 study-drug related adverse events (including neurologic toxicity);
- Grade 3 or 4 infusion reactions;
- ≥ Grade 2 diarrhea/colitis;
- ≥ Grade 3 irAE other than diarrhea/colitis;
- ≥ Grade 4 study drug-related hepatic failure; and
- ≥ Grade 3 motor neurologic toxicity regardless of causality

6.12. Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Adverse events are evaluated monthly by the principal investigator in conjunction with the research team. The Data Safety and Monitoring Committee (DSMC) will review the study twice a year. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

6.12.1. Data and Safety Monitoring Committee

This investigator-initiated study will be monitored by the Data Safety Monitoring Committee (DSMC) of the New York University (NYU) Perlmutter Cancer Center (PCC). The DSMC operates based on the 2011 National Cancer Institute approved Charter. It is an existing and multidisciplinary committee (consisting of clinical investigators/oncologists, biostatisticians, nurses, and research administration staff knowledgeable of research methodology and design and in proper conduct of clinical trials) that is responsible for monitoring safety, conduct and compliance in accordance with protocol data monitoring plans for clinical trials conducted in the NYULMC Perlmutter Cancer Center that are not monitored by another institution or agency. The DSMC reports to the Director of the NYULMC PCC. Per the NYU PCC Institutional Data Safety and Monitoring Plan, this trial will be monitored by DSMC twice annually (from the date the first patient is enrolled), subsequent cohort activation, and at the completion of the study prior to study closure. This review includes accrual data, subject demographics and adverse events. Principal Investigators are required to attend the review of their studies. Additional reviews can be scheduled based on SAE reports, investigator identified issues, external information, etc. The DSMC will review safety data every 6-8 weeks..

6.12.2. Efficacy

Efficacy analyses will be conducted on the Safety and Evaluable populations.

6.13 Overdose

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

6.14 Other Safety Considerations

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

7. DATA HANDLING AND RECORD KEEPING

7.1. Confidentiality Regarding Study Subjects

Investigators must ensure that the privacy of subjects, including their personal identity and all personal medical information, will be protected at all times, as required by law. In CRFs and other study documents, subjects will be identified by their initials, subject number, date of birth, and/or gender.

Personal medical information may be reviewed and/or copied for research, quality assurance, and/or data analysis. This review may be conducted by the Sponsor-investigator, properly authorized persons on behalf of the Sponsor-investigator, an independent auditor, the IRB, or regulatory authorities. Personal medical information will always be treated as confidential. The study team will maintain clinical and laboratory data in a designed manner to ensure patient confidentiality. All study personnel have passed human subject protection courses. If applicable, tissue samples sent to collaborators outside of NYULMC will only be labeled with an assigned protocol-subject identification number without patient identifiers. Systems used for electronic data capture are compliant with HIPAA and applicable local

regulatory agency guidelines. All documents are kept in strictly confidential files and are only made accessible for specific study personnel, CTO quality assurance specialists, and authorized representatives of regulatory agencies as described in the informed consent document. The Investigator agrees to keep all information provided by BMS in strict confidence and to request similar confidentiality from his/her staff and the IRB. Study documents provided by BMS (eg, NIVOLUMAB Investigators' Brochure) will be stored appropriately to ensure their confidentiality. Such confidential information may not be disclosed to others without direct written authorization from BMS, Inc., except to the extent necessary to obtain informed consent from subjects who wish to participate in the study.

7.2. Confidentiality and HIPAA

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

7.3. Source Documentation

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

7.4. Data and Source Documentation

Velos, an electronic database capture system will be created to record the data for this trial. Research coordinators will input clinical trial data into the database. This database is password protected and only the PI, assigned research coordinator, and CTO quality assurance specialists will have access to the database. Velos is the primary data collection instrument for the study. All data requested in Velos must

be reported. All missing data must be explained. The quality assurance specialists will monitor this trial every 6-8 weeks for data entry accuracy.

7.5. Recording of Data and Retention of Documents

All information required by the protocol should be recorded in source documents and CRFs; any omissions or corrections should be explained.

All entries to the CRFs must be clear and must be completed in black ball-point pen to ensure the legibility of self-copying or photocopied pages. Corrections will be made by placing a single horizontal line through the incorrect entry, so that the original entry can still be seen, and placing the revised entry beside it. The revised entry must be initialed and dated by a member of the Investigator's research team authorized to make CRF entries. Correction fluid must not be used.

The Investigator must maintain source documents for each subject in the study. All information on CRFs will be traceable to these source documents, which are generally maintained in the subject's file. The source documents will contain all demographic and medical information (eg, laboratory data, ECGs, diagnostic test results, assessment of presence or absence of adverse events, changes in concomitant medications), and a copy of the signed ICF, which should indicate the study number and title of the study.

Essential documents, as listed below, will be retained by the Investigator for as long as needed to comply with national regulations.

Essential documents include:

1. Signed protocol and all amendments;
2. IRB approvals for the study protocol and all amendments;
3. All source documents and laboratory records;
4. CRF copies;
5. Signed ICF for both screened and enrolled subjects; and
6. Any other pertinent study document.

8. STUDY MONITORING, AUDITING AND INSPECTING

8.1. Study Monitoring Plan

This study will be monitored according to the monitoring plan detailed below. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit. A risk-based, data-driven monitoring approach will be used to verify data for this trial which will also include a centralized review of data for quality, trends, consistency and general safety review. A quality assurance specialist will make regularly scheduled trips to the investigational site to review the progress of the trial, study data and site processes. At each visit, the

monitor will review various aspects of the trial including, but not limited to: screening and enrollment logs; compliance with the protocol and study manual and with the principles of Good Clinical Practice; completion of case report forms; source data verification; study drug accountability and storage; facilities and staff.

During scheduled monitoring visits, the investigator and the investigational site staff must be available to meet with the quality assurance specialist in order to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests and respond to any other trial-related inquiries of the monitor. In addition to on-site monitoring visits, the Sponsor-investigator and/or representatives will also be routinely reviewing data. Any queries identified through this review will be managed within the systems established for query resolution and tracking. Inquiries related to study conduct, which require further information or action will be discussed within the study team for appropriate and documented escalation plans. It is expected that response to data clarification requests and other trial-related inquiries will occur throughout the course of the study through regular communication with the site monitor, the Sponsor-investigator or representatives, and review/entry of data into the electronic study database.

At any time during the course of the study, representatives of the FDA and/or local regulatory agencies may review the conduct or results of the study at the investigational site. The investigator must promptly inform Bristol Myers Squibb of any audit requests by health authorities, and will provide BMS with the results of any such audits and with copies of any regulatory documents related to such audits.

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

At the NYU Perlmutter Cancer Center, all investigator-initiated protocols are subject to a standardized data and safety monitoring, which includes scientific peer review, IRB review and DSMC review as well as internal auditing.

The review of AEs and trial conduct for this trial occurs at several levels:

(1) Principal Investigator: Adverse events are evaluated monthly by the principal investigator in conjunction with the research nurses, data manager and research team.

(2) DSMC, twice annually

(3) Institutional Review Board (IRB): An annual report to the IRB is submitted by the trial PI for continuation of the protocol. It includes a summary of all AEs, total enrollment with demographics, protocol violations, and current status of subjects as well as available research data.

(4) In addition, the quality assurance unit will monitor this trial every 6-8 weeks, to verify adherence to the protocol; the completeness, accuracy and consistency of the data; and adherence to ICH Good Clinical Practice guidelines.

8.2. Auditing Procedure

In addition to the routine monitoring procedures at the Laura and Isaac Perlmutter Cancer Center which include annual audits of all patients treated on investigator initiated trials, or by NCI/CTEP or the FDA, BMS, Inc. or its designees may conduct audits of clinical research activities of this trial in accordance with internal Standard Operating Procedures to evaluate compliance with the principles of Good Clinical Practices. BMS, Inc., its designee, or a regulatory authority may wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority, the Investigator will inform BMS, Inc. immediately that this request has been made.

9. ETHICAL ASPECTS

9.1. Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and in accordance with the Sponsor-investigator's SOPs. These are designed to ensure adherence to Good Clinical Practice (GCP), as described in the International Conference on Harmonisation (ICH) GCP Guideline (1996) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50) and Title 21, Part 312 (21CFR312).

The protocol and any amendments and the subject informed consent will receive IRB approval/favorable opinion before initiation of the study. Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical license, debarment).

10. STUDY FINANCES

10.1. Funding Source

Funding for conducting the trial will be provided by BMS. The investigational agent will be provided to patients enrolled on this study by Bristol Myers Squibb.

10.2. Subject Stipends or Payments

No patient or subject will receive payments or stipends for participation in this research study. Bristol Myer Squibb may provide coverage for tests and/or procedures that are a part of the research study, if it is not covered by the subject's insurance.

11. PUBLICATION PLAN

Any formal presentation or publication of data collected from this study will be considered for a joint publication by the Investigator(s) and the appropriate personnel of BMS. Authorship will be determined by mutual agreement.

BMS, Inc. must receive copies of any intended public communications of study data or results (eg, manuscripts, posters, abstracts and oral presentations) at least thirty (30) days in advance of their submission. For abstracts, this requirement can be met by providing to BMS, Inc. details about the data and subject matter to be disclosed if a final draft of the abstract is not available 30 days in advance. BMS, Inc. will review the communications for accuracy (thus avoiding potential discrepancies with submissions to health authorities), verify that confidential information is not being inadvertently disclosed, and provide any relevant supplementary information and comments.

12. ADMINISTRATIVE REQUIREMENTS

12.1. Institutional Review Board

Before implementing this study, the protocol, the proposed ICF, and other information provided to subjects must be reviewed and approved by an IRB before study initiation. Any amendments to the protocol which need formal approval, as required by local law or procedure, will be approved by this committee. The IRB will also be notified of all other amendments (ie, administrative changes)

12.2. Protocol Amendments

Any change or addition to this protocol requires a written protocol amendment. Amendments affecting the safety of subjects, the scope of the investigation or the scientific quality of the study, as well as administrative amendments require additional approval by the IRB. All amendments that affect the safety of subjects, the scope of the investigation, or the scientific quality of the study must be approved by BMS and the NCI CTEP prior to implementation. Examples of amendments requiring such approvals are:

1. Increase in drug dosage or duration of exposure of subjects
2. Significant change in the study design (eg addition or deletion of a control group)
3. Increase in the number of invasive procedures to which subjects are exposed
4. Addition or deletion of a test procedure for safety monitoring

These requirements for approval should in no way prevent any immediate action from being taken by the Principal Investigator or by BMS, Inc. in the interests of preserving the safety of all subjects included in the trial. If an immediate change to the protocol is felt to be necessary by the Investigator and is implemented by him/her for safety reasons BMS, Inc. should be notified and the NYULMC IRB should be informed within 10 working days.

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14. APPENDICES

Appendix 1: Imaging Methodologies

Contrast enhanced CT or enhanced MRI are the preferred imaging modalities to be used. Chest radiographs performed during the screening phase (and repeated at anytime during the study if clinically indicated) may be used as supportive data, as an accessory to the CT chest scans.

The same imaging techniques used at screening MUST be used at all subsequent time points to permit accurate, comparable measurement of lesions. All imaging data are to be collected on film or in digital format.

CT/MRI of the Chest/Abdomen/Pelvis

CT/MRI imaging of the chest, abdomen and pelvis is required at Screening and at each tumor assessment visit as indicated in Table 1, regardless of the location of known prior metastases. In addition, CT/MRI scans must be obtained of anatomic regions not covered by the chest, abdomen and pelvic scans, in subjects where there is clinical suspicion of deep soft tissue metastases indicative of relapse (eg, lesions in the thigh). Such additional CT/MRIs will be required at Screening only when deep soft tissue disease was present and was resected and must be consistently repeated at all subsequent tumor assessment visits.

Brain MRI/CT

Brain scans (MRI or CT) are required at Screening. Brain scans should be conducted during the course of the study as clinically indicated.

Non-radiographic Assessments/Digital Photography

These should be made at the sites and recorded in the source documents. Visible skin lesions indicative of relapse should be measured clinically and documented digitally using standardized photographic images, including a ruler for scale as part of the image.

Image Acquisition Guidelines

Similar methods of tumor assessment and similar techniques must be used to characterize each identified and reported lesion at Screening and during the Induction and Maintenance Phases. Additional assessments may be performed, as clinically indicated, if there is a suspicion of relapse.). Imaging-based evaluation is preferred to physical examination. Helical (spiral) CT scans of neck, chest, abdomen and pelvis are preferred. If not available, conventional (non-helical, non-spiral CT) should be used. IV contrast should be used for all CT scans. If i.v. contrast is contraindicated, CT may be performed without contrast. Alternatively, MRI can be used to assess lesions that might be indicative of relapse. Subjects who develop contrast allergy after study enrollment may be followed by MRI for subsequent tumor measurements. Sections should be contiguous, similarly sized and consistent from visit-to-visit. Section thickness must be based on institutional standards (eg, from 5 to 8 mm; 10 mm cuts are not recommended). Chest radiograph, ultrasound, and PET scans are not acceptable methods to routinely assess patients for the presence of disease for the purposes of this study.

Appendix 2: ECOG Performance Status

ECOG PERFORMANCE STATUS	
Grade	**ECOG**
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, eg, light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

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Appendix 3: Pre-existing Autoimmune Diseases

Subjects should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Subjects with any history of immune deficiencies or autoimmune disease are excluded from participating in the study. Possible exceptions to this exclusion could be subjects with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (eg, acute Lyme arthritis). Please contact the BMS Medical Monitor regarding any uncertainty over autoimmune exclusions.

Diseases that may be autoimmune related include but are not limited to the following:

Acute disseminated encephalomyelitis
Addison's disease
Alopecia universalis
Ankylosing spondylitis
Antiphospholipid antibody syndrome
Aplastic anemia
Asthma
Autoimmune hemolytic anemia
Autoimmune hepatitis
Autoimmune hypoparathyroidism
Autoimmune hypophysitis
Autoimmune myocarditis
Autoimmune oophoritis
Autoimmune orchitis
Autoimmune thrombocytopenic purpura
Behcet's disease
Bullous pemphigold
Celiac disease
Chronic fatigue syndrome
Chronic inflammatory demyelinating polyneuropathy
Churg-Strauss syndrome
Crohn's disease
Dermatomyositis
Dysautonomia
Eczema
Epidermolysis bullosa acquista
Gestational pemphigoid
Giant cell arteritis
Goodpasture's syndrome
Graves' disease
Guillain-Barré syndrome
Hashimoto's disease
IgA nephropathy
Inflammatory bowel disease
Interstitial cystitis
Kawasaki's disease
Lambert-Eaton myasthenia syndrome
Lupus erythematosus
Lyme disease - chronic
Meniere's syndrome
Mooren's ulcer
Morphea
Multiple sclerosis
Myasthenia gravis
Neuromyotonia
Opsoclonus myoclonus syndrome
Optic neuritis
Ord's thyroiditis
Pemphigus
Pernicious anemia
Polyarteritis nodusa
Polyarthritis
Polygrandular autoimmune syndrome
Primary biliary cirrhosis
Psoriasis
Reiter's syndrome
Rheumatoid arthritis
Sarcoidosis
Scleroderma
Sjögren's syndrome
Stiff-Person syndrome
Takayasu's arteritis
Ulcerative colitis
Vogt-Kovanagi-Harada disease
Vulvodynia
Wegener's granulomatosis

Appendix 4: Description of Use of Blood Samples for Immune Analyses

Detection of Proliferating T cells After NIVOLUMAB + ipilimumab Treatment

Two different but complementary methods (Ki-67 and propidium iodide staining) will be used to detect proliferation of T cells in the peripheral blood of subjects on this trial. Pre-treatment (pheresis), and on weeks 5 and 9 (80 mL sample of blood in green top heparinized tubes on infusion days, prior to infusion) and week 12 follow-up (pheresis) during the trial, PBMC cells will be stained with PI, anti-CD3, anti-CD4, anti-CD8 (T cell markers) and anti-CD56 (NK marker). PI staining will define the proportion of cells in S-phase, and Ki-67 staining with anti-CD3/4/8/56 will define the proliferating compartment. Although it is felt that the proportion of proliferating Ki-67(+) cells and the proportion of cells in S phase will be identical (77), Ki-67 staining will be the "gold" standard to define the proliferating population in case the two parameters are in disagreement. A value of 1.0 % Ki-67 staining will be regarded as minimal evidence for proliferation in subjects based on data from HIV subjects (77). In a recent study in HIV infected subjects, Ki-67 staining was found to correlate closely (r=0.90) with an in vivo detection technique for T cell proliferation using deuterated glucose to label the DNA sugar backbone (78). Fresh PBMC will be stained with anti-CD3-PerCP, anti-CD4-APC and anti-CD8-PE (all from Becton-Dickinson). After washing, cells will be lysed at room temperature for 40 minutes, and stained with anti-Ki-67 (MIB-1 from B-D) in PBS with 0.5% NP-40 and 5% FCS at room temperature for 45 minutes. Cells will be washed and fixed with 1% paraformaldehyde and run directly using a FACscan flow cytometer (Beckman-Coulter). All tests will be batched and run simultaneously. The definition of augmented proliferation for the purposes of this trial will be a 20% increase in the absolute proportion of antigen-specific, tetramer positive CD8+ T cells that stain with the Ki-67 marker. We will also assess the phenotype of circulating CD8 and CD4+ T cells in this study using antibodies against markers including HLA-DR, CD25, CD44, CD45 RO/RA, CD62L, CD73, CD95, CD127, FOXp3, PD-1, CTLA-4, BTLA, CD160, Tim3, LAG3, VISTA, 41-BB, OX-40, and ICOS.

Polymorphism Analysis

The four single nucleotide polymorphisms known to be present in CTLA-4 (79-81) and at least six known for PD-1 (82, 83) will be measured by DNA PCR analysis, and a selection of 20% of the total samples will have the results verified by direct DNA sequencing of the relevant areas of DNA. All subjects will be used from the first, and the second trials and the data will be pooled to allow correlations, if any, to be drawn between the presence of a SNP, response, time to progression and development of autoimmunity.

Studies on Regulatory T cells

We propose to study the regulatory activity of $CD4^+CD25^{+\ high}$ cells before and after NIVOLUMAB +ipilimumab treatment. Peripheral blood $CD4^+$ T cells will be sorted into $CD4^+CD25^+$ and $CD4^+CD25^-$ populations by flow cytometry. The latter cell subset (responders) will be stimulated with anti-CD3 (10 μg/ml) alone or with anti-CD28 (2μg/ml) and with or without IL-2 (10 IU/ml) in the presence of increasing numbers of sorted $CD4^+CD25^+$cells. In addition, $CD4^+CD25^-$ will be stimulated with allogeneic mature myeloid dendritic cells (DC), generated from PBMC with GM-CSF and IL-4 and matured with a cytokine cocktail (IL-6, IL-1 beta, TNF-alpha and PGE-2), in the presence or absence of

$CD4^+CD25^+$. The ability of $CD4^+CD25^+$ to suppress the proliferation of $CD4^+CD25^-$ to polyclonal or allogeneic stimulation in a 3 to 5 day proliferation assay using tritiated thymidine incorporation will be determined. We anticipate that $CD4^+CD25^+$ cells will exhibit suppressor activity in vitro as has been previously described and that NIVOLUMAB + ipilimumab treatment will inhibit their suppressive activity in either polyclonal or allogeneic proliferation reaction. We will examine whether loss of suppressor activity of $CD4^+CD25^+$ cells, if found, following NIVOLUMAB + ipilimumab treatment correlates with the development of colitis or other autoimmune side effects. The suppression of allo MLR proliferation by isolated CD4+CD25+ is an established assay, and well-established in the principal investigator group.