BMS Protocol #: CA184-187

Local Protocol #: 2011-0919

Protocol Version/Date: Version 13: 08 October 2018

TITLE: Phase II Study of Nivolumab in combination with Ipilimumab for Uveal Melanoma

Coordinating Center: The University of Texas MD Anderson Cancer Center

Principal Investigator: Sapna P. Patel, MD
1515 Holcombe Blvd Unit 0430
Houston, TX 77030
Telephone: 713-792-2921
Fax: 713-745-1046
sppatel@mdanderson.org

Statistician: Roland L. Bassett, Jr., MS
1515 Holcombe Blvd Unit 1411
Houston, TX 77030
Telephone: 713-563-4272
rlbassett@mdanderson.org

Study Coordinator: Suzanne Cain, BSN, RN, OCN
1515 Holcombe Blvd Unit 0430
Houston, TX 77030
Telephone: 713-792-8874
Fax: 713-745-1046
scain@mdanderson.org

Research Nurse: Michael Shephard, RN
1515 Holcombe Blvd Unit 0430
Houston, TX 77030
Telephone: 713-745-1674
Fax: 713-745-1046
MPShephard@mdanderson.org

Data Manager: Liberty Posada
1515 Holcombe Blvd Unit 0430
Houston, TX 77030
Telephone: 713-792-2923
Fax: 713-745-1046
lposada@mdanderson.org

DOCUMENT HISTORY
Summary of Changes

SECTION	**SUMMARY OF CHANGE**
Cover Page	Updated Version/Date
Exclusion Criteria p. 48	Updated exclusion criteria to state concomitant palliative radiation for the purposes of symptom management is allowed.

TABLE OF CONTENTS 3
PROTOCOL SYNOPSIS 8
1 INTRODUCTION 13
1.1 Research Hypothesis 13
1.2 Product Development Rationale 13
1.2.1 CTLA-4 and T Cell Activation 13
1.3 Summary of Results of Investigational Program 17
1.3.1 Pharmacology of Ipilimumab 17
1.3.2 Animal Toxicology of Ipilimumab 17
1.3.3 Clinical Pharmacology 19
1.3.4 Mechanism of Action 19
1.3.5 Pharmacokinetics 20
1.3.6 Clinical Safety 21
1.3.7 Clinical Efficacy: Melanoma Program 24
1.3.7.a Rationale for Using Immune-Related Tumor Assessment Criteria (irRC) 26
1.3.7.b MDX010-20 (Phase 3, 3 mg/kg, previously treated melanoma) 26
1.3.7.c CA184024 (Phase 3, previously untreated melanoma, 10 mg/kg) 28
1.3.7.d 10 mg/kg Dosing with Ipilimumab 31
1.3.7.e Advanced Melanoma 32
1.3.7.f Rationale for combining Nivolumab with ipilimumab 34
1.3.7.g Rationale for Permitting Continued Treatment in Select Cases of Progressive Disease 37
1.4 Overall Risk/Benefit Assessment 37
1.5 Uveal Melanoma 38
1.6 Study Rationale 39
2 STUDY OBJECTIVES 40

2.1 Primary Objective 40
2.2 Secondary Objectives 40
2.3 Exploratory Objectives 40
3 STUDY DESIGN 40
3.1 Screening and registration 40
3.2 Study Schema 40
3.3 Treatment 42
3.3.1.a Induction Phase 42
3.3.1.b Maintenance Phase 42
3.3.1.c General Treatment Instructions 43
3.4 Follow-up (duration of study) 43
4 SUBJECT SELECTION CRITERIA 44
4.1 Inclusion Criteria 44
4.2 Exclusion Criteria 47
4.3 Data Safety Monitoring Plan 48
5 STUDY THERAPY 49
5.1 Nivolumab (BMS 936558) 49
5.2 Ipilimumab 49
5.2.1 Dose Calculations 50
5.2.2 Dose Delay Criteria 51
5.2.3 Discontinuation of Study Therapy 52
5.2.4 Permanent Discontinuation of Ipilimumab 53
5.2.4.a Permanent Discontinuation for Related Adverse Events 53
5.2.4.b Exceptions to Permanent Discontinuation 54
5.2.5 Immune-Related Adverse Events (irAEs)Reactions and Immune-mediated Adverse Reactions: Definition, Monitoring, and Treatment 56
5.2.6 Other Guidance 56
5.2.6.a Treatment of Nivolumab or Ipilimumab-Related Isolated Drug Fever 58

5.2.6.b Monitoring and Management of Immune-mediated Adverse Reactions 57
5.2.6.c Liver Function Test (LFT) Assessments Required Before Administration of Nivolumab or Ipilimumab 58
5.3 Prohibited and Restricted Therapies During the Study 59
5.3.1 Prohibited Therapies 59
5.3.2 Restricted Therapies 58
5.3.3 Precautions 58
6 STUDY PROCEDURES AND OBSERVATIONS 59
6.1 Time and Events Schedule 60
6.2 Procedures by Visit 62
6.2.1 Study Procedures by Visit and Treatment Cycle 62
6.2.1.a Screening/Baseline Visit 62
6.2.1.b Treatment Visits 62
6.2.2 Tissue Biopsies for Immune Biomarker Studies 63
6.2.3 Exploratory Correlative Studies 63
6.2.4 Study Completion or Early Discontinuation Visit 63
6.2.5 Study Drug Discontinuation 63
6.3 Details of Procedures 63
6.3.1 Study Materials 63
6.3.2 Safety Assessments 63
6.4 Criteria for Evaluation 64
6.4.1 Safety Evaluation 64
6.4.2 Efficacy Evaluation 64
6.4.2.a Definition of Measurable and Non-Measurable Lesions 64
6.4.2.b Definition of Index/Non-Index Lesions 64
6.4.3 *Definition of Tumor Response Using irRC* 65
6.4.3.a Definition of Index Lesions Response Using irRC 65
6.4.3.b Definition of Non-Index Lesions Response Using irRC 65
6.4.3.c Impact of New Lesions on irRC 66

6.4.3.d Definition of Overall Response Using irRC 66
6.4.3.e Immune-Related Best Overall Response Using irRC (irBOR) 67
6.4.4 Response Endpoints 68
7 INVESTIGATIONAL PRODUCT 68
7.1 Identification 68
7.2 Packaging and Labeling 69
7.3 Storage, Handling, and Dispensing 69
7.3.1 Storage 69
7.3.2 Handling and Disposal 70
7.3.3 Dispensing 70
7.4 Drug Ordering and Accountability 70
7.4.1 Initial Orders 70
7.4.2 Re-Supply 71
7.5 Investigational Product Accountability 71
7.6 Investigational Product Destruction 71
8 ADVERSE EVENT REPORTING 72
8.1 Collection of Safety Information 72
8.1.1 Definition of Serious Adverse Events 72
8.1.2 Definition of Nonserious Adverse Event 73
8.2 Assignment of Adverse Event Intensity and Relationship to Investigational Product 73
8.3 Collection and Reporting 74
8.3.1 Serious Adverse Events 74
8.3.2 Reporting to FDA 77
8.3.3 Handling of Expedited Safety Reports 77
8.3.4 Nonserious Adverse Events 77
8.3.5 Pregnancy 77
8.3.6 Other Safety Considerations 79
9 STATISTICAL METHODOLOGY 79

9.1 Efficacy Analysis 82
9.2 Secondary Analysis 82
10 ADMINISTRATIVE SECTION 82
10.1 Compliance with the Protocol and Protocol Revisions 82
10.2 Informed Consent 83
10.3 Records and Reports 83
10.4 Good Clinical Practice 83
10.5 Institutional Review Board/Independent Ethics Committee (IRB/IEC) 84
10.6 Records Retention 84
APPENDIX A – MANAGEMENT ALGORITHMS 86
LIST OF ABBREVIATIONS 94
REFERENCES 95

PROTOCOL SYNOPSIS

Protocol Title:	Nivolumab in combination with Ipilimumab for uveal melanoma
Site Numbers & Names:	The University of Texas MD Anderson Cancer Center
Research Hypothesis:	Among patients with metastatic uveal melanoma, treatment with nivolumab plus ipilimumab will demonstrate safety, tolerability, and efficacy in improving overall response
Study Schema: **Drugs / Doses /** **Length of Treatment)**	Metastatic uveal melanoma patients with at least one measureable lesion will be treated with nivolumab plus ipilimumab until disease progression or until unmanageable toxicity occurs. The doses used will be nivolumab 1 mg/kg and ipilimumab 3 mg/kg, both intravenous (IV). During the induction phase, patients will be treated with nivolumab 1 mg/kg IV plus ipilimumab 3 mg/kg IV every 3 weeks (+/- 7 days) for a total of four doses (week 1, 4, 7, 10). Treatment then continues at week 13 in the maintenance phase with nivolumab 480 mg IV every 4 weeks until disease progression or unacceptable toxicity.
Study Objectives: **Primary:** **Secondary:** **Exploratory:**	PRIMARY OBJECTIVE: Overall response rate SECONDARY OBJECTIVES: Progression-free survival, median overall survival, one-year overall survival EXPLORATORY OBJECTIVES: Exploratory objectives include tissue and blood correlates to define immune infiltration and signatures as a result of treatment with nivolumab plus ipilimumab.
Study Design:	Phase II study of nivolumab plus ipilimumab for metastatic uveal melanoma.

Accrual Goal: **(Total number of patients)**	Metastatic uveal melanoma: Up to 39 patients to achieve 27 evaluable patients
Accrual Rate: **(Number of patients expected per month)**	2-4 patients per month
FPFV: **LPFV:** **Follow Up:** **(dd-mmm-yy)**	01-Aug-2014 05-Jan-2018 Until death or alternate treatment

Inclusion Criteria:	1. Willing and able to give written informed consent. 2. History of uveal melanoma and documented metastatic disease with at least one measurable lesion is required, which is $\geq$ 1 cm x 1 cm (on spiral CT or equivalent). 3. Any number of prior therapies is allowed. 4. Required values for initial laboratory tests: WBC $\geq$ 2000/uL, ANC $\geq$ 1000/uL, Platelets $\geq$ 100 x 10^3/uL, Hemoglobin $\geq$ 9 g/dL, Creatinine $\leq$ 1.5 x ULN, or creatinine clearance (CrCl $\geq$ 40mL/min (using the Cockcroft-Gault formula) AST/ALT $\leq$ 3 x ULN for patients without liver metastasis, $\leq$ 5 x ULN for liver metastases, Bilirubin $\leq$ 1.5 x ULN, (except patients with Gilbert's Syndrome, who must have a total bilirubin less than 3.0 mg/dL) 5. In suspected patients, no active or chronic infection with HIV, Hepatitis B, or Hepatitis C. 6. Performance status ECOG 0-1. 7. Men and women $\geq$ 18 years of age. 8. Baseline imaging in the form of CT chest, abdomen, pelvis with oral and intravenous contrast within 28 days of study entry. For patients with a contrast allergy, choice of alternative body imaging will be at the discretion of the investigator or his designee. MRI of the brain is only needed if clinically indicated. 9. More than 21 days elapsed from surgery, radiation therapy, or prior chemotherapy. More than 42 days elapsed from prior immune therapy including vaccines. 10. Women of childbearing potential (WOCBP) and fertile men with partners of childbearing potential must be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 26 weeks after the last dose of investigational product, in such a manner that the risk of pregnancy is minimized.

Exclusion Criteria:	1. Untreated primary uveal melanoma except in cases where metastatic disease is diagnosed at the time of primary disease. 2. Metastatic uveal melanoma patients with bone-only disease. 3. Any other malignancy from which the patient has been disease-free for less than 2 years, with the exception of adequately treated and cured basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix, breast, or prostate. 4. Autoimmune disease: Patients with a history of inflammatory bowel disease, including ulcerative colitis and Crohn's Disease, are excluded from this study, as are patients with a history of symptomatic disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, autoimmune vasculitis [e.g., Wegener's Granulomatosis]); motor neuropathy considered of autoimmune origin (e.g. Guillain-Barre Syndrome and Myasthenia Gravis). 5. Any underlying medical or psychiatric condition, which in the opinion of the investigator will make the administration of ipilimumab hazardous or obscure the interpretation of AEs, such as a condition associated with frequent diarrhea. 6. Any non-oncology vaccine therapy used for prevention of infectious diseases for up to 1 month before or after any dose of ipilimumab. 7. Concomitant therapy with any of the following: tamoxifen, toremifene, IL-2, interferon, or other non-study immunotherapy regimens; cytotoxic chemotherapy; immunosuppressive agents; other investigation therapies; or chronic use of systemic corticosteroids greater than physiologic replacement doses. Ocular steroid use is acceptable. 8. Women of childbearing potential (WOCBP), defined above in Section 4.1, who: a. are unwilling or unable to use an acceptable method of contraception to avoid pregnancy for their entire study period and for up to 26 weeks after cessation of study drug, or b. have a positive pregnancy test at baseline, or c. are pregnant or breastfeeding. 9. Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (e.g., infectious) illness.

Criteria for Evaluation: **(Efficacy, safety, stopping rules, etc.)**	Efficacy will be evaluated at week 12 and then every 12 weeks until progression or treatment discontinuation. Safety will be assessed at every treatment visit.
Statistics:	A single-stage trial design will be employed. • Type I error rate of 5%, power of 80% • Null hypothesis of 5% response rate • Alternate hypothesis of 20% response rate • Response will be defined as those patients who achieve RECIST CR + PR. • Accounting for attrition (inevaluable patients, 25%) and screen fails (5%), up to 39 patients are needed to achieve a target enrollment of 27 evaluable patients.

1. INTRODUCTION

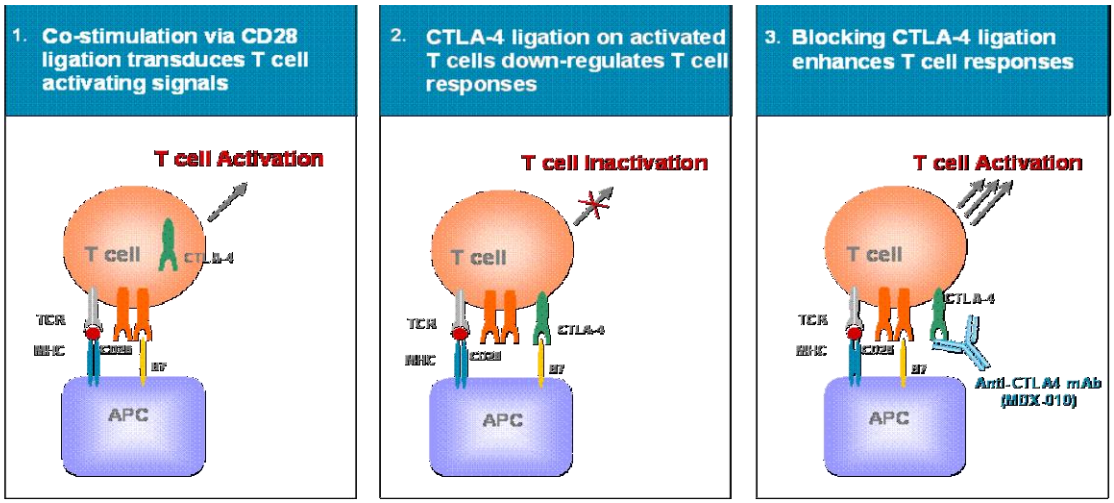
1.1 RESEARCH HYPOTHESIS

Among patients with metastatic uveal melanoma, treatment with nivolumab plus ipilimumab will demonstrate safety, tolerability, and efficacy in improving response rate compared with ipilimumab alone.

1.2 Product Development Rationale

1.2.1 CTLA-4 and T Cell Activation

Figure 1 Mechanism of Action



Advances in the understanding of the mechanisms that regulate T cell activation have allowed the rational design of new strategies for immunotherapy of tumors, including melanoma. It has been known for some time that engagement of the T cell antigen receptor by itself is not sufficient for full T cell activation; a second co-stimulatory signal is required for induction of IL-2 production, proliferation and differentiation to effector function of naive T cells. Abundant data now indicate that the primary source of this costimulation is mediated by engagement of CD28 on the T cell surface by members of the B7 family on the antigen-presenting cell (APC).[1] (Figure 1.)

Expression of B7 has been shown to be limited to "professional" antigen presenting cells; that is, specialized cells of the hematopoietic lineage, including dendritic cells, activated macrophages, and activated B cells. It has been suggested that this sharply-defined restriction of B7 expression is a fail-safe mechanism for maintenance of peripheral T cell tolerance, insuring that T cell activation can only be stimulated by appropriate APCs.[2] The

fact that tumor cells do not express B7 contributes to their poor capacity to elicit immune responses.[3,4]

The demonstration that induction of expression of B7 on many tumor cells by transfection, transduction, or other mechanisms can heighten tumor immunogenicity led to great interest in pursuing this as an approach to tumor immunotherapy. As demonstrated in vivo in murine tumor models, the utility of B7 expression as a vaccination approach is limited by the following factors: (1) B7-expressing tumor cell vaccines are only effective when the tumor cells have a high degree of inherent immunogenicity; (2) while B7-expressing vaccines have been shown in many cases to be effective in inducing protective immune responses, they have demonstrated only limited utility in inducing responses to established tumors; and (3) inactivation of tumor cells by radiation has been shown to destroy the immuno-enhancing activity of the B7 gene product.[5,6]

In the past few years it has become apparent that co-stimulation is even more complex than originally thought. After activation, T cells express CTLA-4, a close homologue to CD28. CTLA-4 binds members of the B7 family with a much higher affinity than CD28.[7]Although there was initially some controversy as to the role of CTLA-4 in regulating T cell activation, it has become clear that CTLA-4 down-regulates T cell responses.[8]

This was initially suggested by the following in vitro observations: (1) blockade of CTLA-4/B7 interactions with antibody enhanced T cell responses; (2) cross-linking of CTLA-4 with CD3 and CD28 inhibited T cell responses; and (3) administration of antibodies to CTLA-4 in vivo enhanced the immune response to peptide antigens or superantigens in mice.[9,10,11,12] Blocking CTLA-4-B7 interaction while preserving signaling via CD28 resulted in enhanced T cell responses in vitro.[10]

Perhaps the most convincing demonstration of the down-regulatory role of CTLA-4 came from examination of mice with a null mutation.[13,14,15] CTLA-4 knockout mice appear to have spontaneously activated T cells evident at approximately 1 week after birth, followed by rampant lymphoproliferation and lymphadenopathy. These mice die at approximately 3 weeks of age, either as a result of polyclonal T cell expansion and tissue destruction or as a result of toxic shock resulting from lymphokine production by the T cells. Since thymocyte differentiation and selection proceed normally in CTLA-4-deficient mice, the rampant T cell expansion that occurs in the mice indicates that CTLA-4 plays a critical role in down-regulating T cell responses in the periphery.[12]

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. This functions by aborting the emergence of tumors as they arise and/or causing tumor shrinkage where it is present. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immune surveillance and an effective immune response. This evasion may occur by exploiting any of the checkpoints that control the regulatory immune response, including display of antigens and control of co-stimulatory pathways that affect the proliferation of cells involved in immunity. Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system - either directly by stimulation of immune cells by antibodies directed to receptors on T and B cells or indirectly by cytokine manipulation. T-cell stimulation is a complex process involving the integration of numerous positive, as well as negative, costimulatory signals in addition to antigen recognition by the T-cell receptor (TCR).2 Collectively, these signals govern the balance between T-cell activation and tolerance to antigens.1

Programmed death receptor-1 (PD-1, CD279), a 55 kD type I transmembrane protein, is a member of the CD28 family of T-cell costimulary receptors that also includes CD28, CTLA-4, ICOS, and BTLA.2 PD-1 contains an intracellular membrane proximal immunoreceptor tyrosine inhibitory motif (ITIM) and a membrane distal immunoreceptor tyrosine-based switch motif (ITSM). Two ligands specific for PD-1 have been identified: PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273). PD-L1 and PD-L2 have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems.3,4 PD-1 delivers a negative signal by the recruitment of a protein tyrosine phosphatase SHP-2 to the phosphorylated tyrosine residue in the ITSM in its cytoplasmic region.5,6 PD-1 is primarily expressed on activated T cells, B cells and myeloid cells.7

Further evidence for a negative regulatory role of PD-1 comes from studies of PD-1-deficient mice. PD-1-deficient mice develop various autoimmune phenotypes, including dilated cardiomyopathy, a lupus-like syndrome with arthritis and nephritis, and accelerated diabetes mellitus.8,9,10 The emergence of these autoimmune phenotypes is dependent upon the genetic background of the mouse strain and many of these phenotypes emerge at

different times and show variable penetrance. In addition to the phenotypes of null mutations, PD-1 inhibition by antibody-mediated blockade in several murine models has been found to play a role in the development of autoimmune diseases such as encephalomyelitis, graft-versus-host disease, and type I diabetes.11,12 Taken together, these results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self antigens.

Preclinical animal models of tumors have shown that blockade by PD-1 by monoclonal antibodies (mAbs) can enhance the anti-tumor immune response and result in tumor rejection. Antitumor activity by PD-1 blockade functions in PD-L1+ tumors as well as in tumors that are negative for the expression of PD-L1.13,14,15,16,17,18 This suggests that host mechanisms (ie, expression of PD-L1 in antigen-presenting cells) limit the antitumor response. Consequently, both PD-L1 positive and negative tumors may be targeted using this approach. In humans, constitutive PD-L1 expression is normally limited to macrophage-lineage cells, although expression of PD-L1 can be induced on other hematologic cells as well, including activated T cells. However, aberrant expression of PD-L1 by tumor cells has been reported in a number of human malignancies.19,20,21,22,23,24,25 PD-L1 expressed by tumor cells has been shown to enhance apoptosis of activated tumor-specific T cells in vitro.7 Moreover, the expression of PD-L1 may protect the tumor cells from the induction of apoptosis by effector T cells.26 Retrospective analyses of several human tumor types suggest that tumor over-expression (as measured by IHC) of PD-L1 may permit immune evasion by tumors. In renal cell carcinoma, high surface expression levels of PD-L1 on tumor cells are related to tumor aggressiveness.20,24 Subjects with high tumor and/or lymphocyte PD-L1 levels are 4.5 times more likely to die from their cancer than subjects exhibiting low levels of PD-L1 expression. In addition, in multivariate analysis, high expression of PD-L1 is correlated to have a worse overall survival rate compared to low expression levels of PD-L1.27

Nivolumab is a fully human, IgG4 (kappa) isotype, mAb that binds PD-1. Blockade of the PD-1 pathway by nivolumab was studied using the mixed lymphocyte reaction (MLR). PD-1 blockade resulted in a reproducible enhancement of both proliferation and IFN-α release in the MLR.28 The effect of nivolumab on antigen-specific recall response was investigated using a CMV-restimulation assay with human peripheral blood mononuclear

cells (PBMCs), and was evaluated by ELISA.

These data indicated that nivolumab, versus an isotype-matched control antibody, augmented IFN-α secretion from CMV-specific memory T-cells in a dose-dependent manner. PD-1 blockade by nivolumab is therefore considered a promising immunotherapeutic option.

1.3 Summary of Results of Investigational Program

1.3.1 Pharmacology of Ipilimumab

Ipilimumab is a human immunoglobulin G (IgG1)κ anti-CTLA-4 monoclonal antibody (mAb). In vitro studies were performed with ipilimumab to demonstrate that it is specific for CTLA-4, actively inhibits CTLA-4 interactions with B7.1 and B7.2, does not show any cross-reactivity with human B7.1, B7.2 negative cell lines, and stains the appropriate cells without non-specific cross-reactivity in normal human tissues, as demonstrated by immunohistochemistry. Ipilimumab does cross-react with CTLA-4 in non-human primates including cynomolgus monkeys.

1.3.2 Animal Toxicology of Ipilimumab

The effects of ipilimumab on prenatal and postnatal development in monkeys have not been fully investigated. Preliminary results are available from an ongoing study in cynomolgus monkeys. Pregnant monkeys received ipilimumab every 21 days from the onset of organogenesis in the first trimester through delivery, at dose levels either 2.6 or 7.2 times higher than the clinical dose of 3 mg/kg of ipilimumab (by AUC). No treatment-related adverse effects on reproduction were detected during the first two trimesters of pregnancy. Beginning in the third trimester, the ipilimumab groups experienced higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth weight), and higher incidences of infant mortality in a dose-related manner compared to controls.

Genetically engineered mice heterozygous for CTLA-4 (CTLA-4+/-), the target for ipilimumab, appeared healthy and gave birth to healthy CTLA-4+/- heterozygous offspring. Mated CTLA-4+/- heterozygous mice also produced offspring deficient in CTLA-4 (homozygous negative, CTLA-4-/-). The CTLA-4-/- homozygous negative offspring appeared healthy at birth, exhibited signs of multiorgan lymphoproliferative

disease by 2 weeks of age, and all died by 3–4 weeks of age with massive lymphoproliferation and multiorgan tissue destruction.

Complete information on the pre-clinical toxicology studies can be found in the Ipilimumab Investigator Brochure (IB). Non-clinical toxicity assessments included in vitro evaluation for the potential of ipilimumab to mediate complement-dependent cellular cytotoxicity (CDCC) or antibody-dependent cellular cytotoxicity (ADCC), and toxicology assessments in cynomolgus monkeys alone and in the presence of vaccines.

The in vitro studies demonstrated that ipilimumab did not mediate CDCC of PHA- or (CD)3-activated human T cells. However, low to moderate ADCC activity was noted at concentrations up to 50 ug/mL. These data are consistent with the requirement of high levels of antigen expression on the surface of target cells for efficient ADCC or CDCC. Since ipilimumab is a human IgG1, an isotype generally capable of mediating CDCC and ADCC, the lack of these activities is likely due to a very low expression of CTLA-4 on activated T cells. Therefore, these data suggest that ipilimumab treatment would not result in depletion of activated T cells in vivo. Indeed, no depletion of T cells or T cell subsets were noted in toxicology studies in cynomolgus monkeys.

No mortality or signs of toxicity were observed in three independent 14-day intravenous toxicology studies in cynomolgus monkeys at multiple doses up to 30 mg/kg/dose. Furthermore, ipilimumab was evaluated in sub-chronic and chronic toxicology studies in cynomolgus monkeys with and without Hepatitis B (HepB) Vaccine and Melanoma Vaccine. Ipilimumab was well tolerated alone or in combination in all studies. There were no significant changes in clinical signs, body weight values, clinical pathology values or T cell activation markers. In addition, there were no significant histopathology changes in the stomach or colon.

Preclinical Summary of Nivolumab combined with Ipilimumab

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

effector cells and decreased intratumoral T regulatory cells, as compared to either agent alone.

Preclinically, a 4-week toxicity study of nivolumab in combination with ipilimumab conducted in cynomolgus monkeys demonstrated that the combination of nivolumab and ipilimumab resulted in dose-dependent gastrointestinal (GI) toxicity. Histologic findings included inflammatory changes in the large intestine, which increased in incidence and severity in a dose-dependent manner. GI toxicity/colitis was not observed in cynomolgus monkeys administered nivolumab alone, but was observed in monkeys receiving ipilimumab. Nivolumab in combination with ipilimumab was also associated with lymphoid hypocellularity of the cortex and/or medulla of the thymus and with acinar cell degranulation in the pancreas. Additional findings included interstitial mononuclear cell infiltrates in the kidneys, portal mononuclear cell infiltrates in the liver and myeloid hypercellularity in the bone marrow. Nivolumab in combination with ipilimumab at the high-dose level (ie, 50 mg/kg and 10 mg/kg, respectively) was associated with the death of 1 animal, attributed to acute gastric dilatation without histopathological evidence of colitis upon pathology evaluation of the GI tract.

1.3.3 Clinical Pharmacology

1.3.4 Mechanism of Action

CTLA-4 is a negative regulator of T-cell activation. Ipilimumab binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation. The mechanism of action of ipilimumab's effect in patients with melanoma is indirect, possibly through T-cell mediated anti-tumor immune responses.

Nivolumab is a fully human, IgG4 (kappa) isotype, mAb that binds PD-1. Blockade of the PD-1 pathway by nivolumab was studied using the mixed lymphocyte reaction (MLR). PD-1 blockade resulted in a reproducible enhancement of both proliferation and IFN-α release in the MLR.28 The effect of nivolumab augmented IFN-α secretion from CMV-specific memory T-cells in a dose-dependent manner. PD-1 blockade by nivolumab is therefore considered a promising immunotherapeutic option.

1.3.5 Pharmacokinetics

Ipilimumab Monotherapy

Ipilimumab has a terminal half life of approximately 15.4 days. The expected in vivo degradation of monoclonal antibodies is to small peptides and amino acids via biochemical pathways that are independent of cytochrome P450 enzymes.

The population PK of ipilimumab was studied with 785 subjects and demonstrated that PK of ipilimumab is linear and exposures are dose proportional across the tested dose range of 0.3 to 10 mg/kg, and the model parameters are time invariant. Upon repeated dosing of ipilimumab, administered every three weeks, minimal systemic accumulation was observed by an accumulation index of 1.5-fold or less and ipilimumab steady-state concentrations were achieved by the third dose. The ipilimumab clearance of 16.8 mL/h from population PK analysis is consistent with that determined by PK analysis. The terminal half-life (T-HALF) and Vss of ipilimumab calculated from the model were 15.4 days, and 7.47 L, which are consistent with that determined by non-compartmental analysis (NCA). Volume of central (Vc) and peripheral compartment were found to be 4.35 L and 3.28 L, respectively, suggesting that ipilimumab first distributes into plasma volume and subsequently into extracellular fluid space. Clearance of ipilimumab and Vc were found to increase with increase in body weight. Nevertheless, there was no significant increase in exposure with increase in body weight when dosed on a mg/kg basis, supporting dosing of ipilimumab based on a weight normalized regimen. Additional details are provided in investigator brochure.

Nivolumab Monotherapy

Single-dose pharmacokinetics (PK) of nivolumab was evaluated in subjects with multiple tumor types in MD1106-01 whereas multiple dose PK is evaluated in subjects in CA209003. In addition, a preliminary population pharmacokinetic (PPK) model has been developed with data from · 350 subjects from MDX1106-01, MDX1106-02 and CA209003.

Single-dose PK of nivolumab was evaluated in 39 subjects with multiple tumor types in study MDX1106-01 in the dose range of 0.3 to 10 mg/kg. The median Tmax across single doses ranged from 1.6 to 3 hours with individual values ranging from 0.9 to 7 hours. The PK of nivolumab is linear in the range of 0.3 to 10 mg/kg with dose proportional increase in Cmax and AUC(INF) with low to moderate inter-subject variability observed at each dose level (ie, CV ranging from 7 to 45%). Geometric mean clearance (CL) after a single

intravenous (IV) dose ranged from 0.13 to 0.19 mL/h/kg, while mean volume of distribution (Vz) varied between 83 to 113 mL/kg across doses. The mean terminal T-HALF of nivolumab is 17 to 25 days, which is consistent with half life of endogenous IgG4, indicating that the elimination mechanism of nivolumab may be similar to IgG4. Both elimination and distribution of nivolumab appear to be independent of dose in the dose range studied. Additional details are provided in the Investigator Brochure.

A preliminary PPK model was developed by nonlinear mixed effect modeling using data from 350 subjects from MDX1106-01, MDX1106-02 and CA209003. The body weight normalized dosing produces approximately constant trough concentrations over a wide range of body weight, and hence is appropriate for future clinical trials of nivolumab. Clearance of nivolumab is similar in all tumor types studied and is independent of dose range studied (0.1 to 10 mg/kg).

1.3.6 Clinical Safety

Ipilimumab Monotherapy

In MDX010-20, the ipilimumab monotherapy arm was administered 3 mg/kg ipilimumab every 3 weeks for four doses. In this arm, there were 79% drug related adverse events, with 21% being Grade 3/4 and 3/131 (2%) Grade 5. The most frequent adverse events of interest were rash (30%), pruritis (33%), diarrhea (33%), colitis (8%), endocrine disorders (9%), AST/ALT increased (2%), and hepatitis (1%). Any grade immune related adverse events were 60% and the Grade 3/4 immune related adverse events for the same cohort was 13% with the most frequent adverse events being diarrhea (5%), colitis (5%), rash (2%), and endocrine disorders (3%).

Additional details on the safety profile of ipilimumab, including results from other clinical studies, are also available in the ipilimumab IB.

Nivolumab Monotherapy

One study has contributed most to the clinical experience with nivolumab monotherapy in subjects with melanoma and other solid malignancies. CA209003 is an ongoing Phase 1 open label, multiple dose escalation study in 304 subjects with select previously treated advanced solid tumors, including melanoma, RCC, NSCLC, colorectal cancer, and hormone-refractory prostate cancer. Subjects received nivolumab at doses of 0.1, 0.3, 1, 3 or 10 mg/kg intravenously every 2 weeks, up to a maximum of 2 years of total therapy. As of 03-Jul-2012, a total of 107 melanoma subjects were treated with nivolumab in the dose

range of 0.1-10 mg/kg.

No maximal tolerated dose was identified in CA209003. The incidence, severity and relationship of AEs were generally similar across dose levels and tumor types. Nivolumab related AEs of any grade occurred in 72.4% of subjects. The most frequent nivolumab related AEs occurring in 5% of subjects included: fatigue (25.7%), rash (13.5%), diarrhea (11.8%), pruritis (10.2%), nausea (7.9%), decreased appetite (7.9%), hemoglobin decreased (5.9%) and pyrexia (5.3%). The majority of events were low grade, with grade 3-4 drug related AEs observed in 14.8% of subjects. The most common Grade 3-4 drug-related AEs occurring in ・ 1% of subjects were: fatigue (1.6%), lymphopenia (1.3%), abdominal pain (1%), diarrhea (1%), hypophosphatemia (1%) and pneumonitis (1%). At least one SAE was reported for 150 (49.3%) of the 304 subjects at all dose levels. Grade 3-4 SAEs were reported for 23 subjects (7.6%). Drug-related SAEs occurred in 11.5% of subjects. Grade 3-4 drug-related SAEs reported in at least 2 subjects included: diarrhea (3 subjects, 1.0%), pneumonitis (3 subjects, 1.0%), pneumonia (2 subjects, 0.7%) and lipase increased (2 subjects, 0.7%). Additional select treatment-related AEs have occurred with low frequency (< 5%) but are considered clinically meaningful, as they require greater vigilance for early recognition and prompt intervention. These AEs include: ALT increased (4.3%), AST increased (3.6%), pneumonitis (3.3%), hypothyroidism (3.0%), hyperthyroidism (1.3%), renal failure (1.0%), adrenal insufficiency (0.7%) and colitis (0.7%). Grade 3-4 events of pneumonitis were reported in 3 subjects (1.0%) as described above (1 event was Grade 4). Grade 3 events of colitis, ALT increased, and AST increased were reported in 2 subjects (0.7%) each. Grade 3 events of adrenal insufficiency, hyperthyroidism, and hypothyroidism were reported in 1 subject (0.3%) each. Treatment-related AEs leading to discontinuation were reported in 18 (5.9%) of the 304 treated subjects on CA209003. The only events reported in more than 1 subject were pneumonitis (4 subjects; 1.3%) and hepatitis (2 subjects; 0.7%). There were 3 (1%) drug related deaths; each occurred after development of pneumonitis.

Preliminary new non-clinical safety findings of adverse pregnancy outcomes and infant losses in the absence of overt maternal toxicity have been reported.44 The findings of increased late stage pregnancy loss and early infant deaths/euthanasia in nivolumab exposed pregnant monkeys suggest a potential risk to human pregnancy if there is continued treatment with nivolumab during pregnancy.

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the BMS-936558 (nivolumab) IB.

Nivolumab Combined with Ipilimumab

In the Phase 1 study CA209004, ascending doses of nivolumab have been studied concomitantly with ascending doses of ipilimumab in subjects with unresectable or metastatic melanoma. In each arm in this multi-arm study, ipilimumab was administered once every 3 weeks for 4 doses with nivolumab administered once every 3 weeks for 8 doses. Starting at week 24, ipilimumab and nivolumab were administered once every 12 weeks for 8 doses. The three initial dose-escalation cohorts consisted of Cohort 1 (nivolumab 0.3 mg/kg plus ipilimumab 3 mg/kg; n=14), Cohort 2 (nivolumab 1.0 mg/kg plus ipilimumab 3 mg/kg; n=17) and Cohort 3 (nivolumab 3.0 mg/kg plus ipilimumab 3 mg/kg; n=6). Later, the study was amended to include Cohort 2a which evaluated nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (n-16). The following DLTs were observed in Cohort 1 - Grade 3 elevated AST/ALT (1 subject); in Cohort 2 - Grade 3 uveitis (1 subject) and Grade 3 elevated AST/ALT (1 subject) and in Cohort 3 - Grade 4 elevated lipase (2 subjects) and Grade 3 elevated lipase (1 subject). Based on these data, Cohort 2 was identified as the maximum tolerated dose (MTD) and Cohort 3 exceeded the MTD.

As of 15-Feb-2013, a total of 53 melanoma subjects were treated with nivolumab combined with ipilimumab in CA209004 across cohorts 1, 2, 2a, and 3. At least one AE regardless of causality has been reported in 98% of subjects treated. The most common (reported at > 10% incidence) treatment related AEs (any Grade %; Grade 3-4 %: 93; 53) are rash (55; 4), pruritus (47; 0), vitiligo (11; 0), fatigue (38; 0), pyrexia (21, 0), diarrhea (34; 6), nausea (21, 0), vomiting (11, 2), ALT increased (21; 11), AST increased (21; 13), lipase increased (19; 13), amylase increased (15, 6), headache (11, 0), and cough (13, 0).

The majority of AEs leading to discontinuation (regardless of causality) were Grade 3 or 4 (reported in 11 of 53 subjects, 21%). Grade 3 events included lipase increased, ALT increased, AST increased, troponin I increased, colitis, diverticular perforation, pancreatitis, tachycardia, renal failure acute, choroiditis, autoimmune disorder, and pneumonitis. One subject each discontinued due to Grade 4 events of blood creatinine increased and AST increased. No drug-related deaths were reported.

Adverse Event Management Algorithms

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 renal toxicity. Prompt interventions are recommended

according to the management algorithms and in addition include ophthalmologic evaluations for any visual symptoms in order to evaluate for nivolumab or ipilimumab related uveitis.

Given the nature of the study and in order to standardize the management of adverse events the recommendations are to follow the BMS-936558 (nivolumab) adverse event algorithms and not the ipilimumab IB algorithms.

The algorithms recommended for utilization in CA209067 are contained in Appendix B.

As of 03-Apr-2013, three subjects out of approximately 1200 patients on nivolumab clinical trials have developed opportunistic infections (2 cases of Aspergillus pneumonia, and 1 case of Pneumocystis jiroveci pneumonia) after receiving prolonged treatment with high dose steroids for nivolumab-related adverse events. Details of these cases are available in the Investigator Brochure. Because of the potential for opportunistic infections with prolonged high dose corticosteroids administration, the following recommendations should be considered for subjects with inflammatory events expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage the adverse event:

・Antimicrobial/antifungal prophylaxis per institutional guidelines to prevent opportunistic infections such as Pneumocystis jiroveci and fungal infections.

・Early consultation with an infectious disease specialist should be considered. Depending on the presentation, consultation with a pulmonologist for bronchoscopy or a gastroenterologist for endoscopy may also be appropriate.

・In patients that develop recurrent adverse events in the setting of ongoing or prior immunosuppressant use, an opportunistic infection should be considered in the differential diagnosis.

Additional details on the safety of nivolumab, including results from other clinical studies, are available in the IB.

1.3.7 Clinical Efficacy: Melanoma Program

Ipilimumab Monotherapy

In melanoma, a completed Phase 3 study (MDX010-20) has demonstrated a clinically meaningful and statistically significant survival benefit in pre-treated advanced melanoma. The study compared the overall survival (OS) of ipilimumab plus a melanoma-specific vaccine (gp100) to that of gp100 alone. A second comparison defined the OS of ipilimumab

alone vs. gp100 alone. Both comparisons demonstrated statistically significant improvements in OS (p = 0.0004 and 0.0026, respectively). The 1-year survival for the two ipilimumab-containing groups, respectively, was 44% and 46% respectively, compared to 25% for the gp100 control group. The 2-year survival was 22%, 24% and 14% respectively. The median survival was 10, 10.1, and 6.4 months, for ipilimumab plus gp100, ipilimumab monotherapy, and gp100 monotherapy, respectively.

Nivolumab Monotherapy

In CA209003, the clinical activity of nivolumab was demonstrated in a variety of tumor types, including melanoma, RCC, and NSCLC. Clinical activity was noted across a range of doses (0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg).

In CA209003, as of the clinical cut-off date of 03-Jul-2012, a total of 304 subjects with melanoma, RCC, and NSCLC have been evaluated for clinical activity. A response of either CR or PR, as determined by investigator assessed tumor evaluations based on modified irRC, has been reported at all dose levels. No responses (CR or PR) have been reported in subjects with colorectal carcinoma or castrate-resistant prostate cancer.

Among 106 patients with advanced melanoma who received nivolumab and were evaluable for response, the preliminary objective response rates were 6/17 (35%), 5/18 (28%), 11/34 (32%), 7/17 (41%), and 4/20 (20%) for melanoma subjects treated at 0.1, 0.3, 1, 3, and 10 mg/kg, respectively. Duration of response range from 3.6 to 11.2, 1.8 to 9.2, 1.9 to 24.9, 9.2 to 22.4, and 17.0 to 25.7 months in the melanoma subjects treated at 0.1, 0.3, 1, 3, and

10 mg/kg, respectively. Stable disease · 24 weeks occurred in an additional 1/18 (6%), 4/34 (12%), 1/17(6%) melanoma subjects at 0.3, 1, and 3 mg/kg, respectively. Finally, the PFS-24 week was 41%, 33%, 48%, 55%, and 30% in melanoma subjects treated at 0.1, 0.3, 1, 3, and 10 mg/kg, respectively.

Nivolumab Combined with Ipilimumab

As of the 15-Feb-2013 clinical cut-off in CA209004, of the 52 subjects evaluable for response, 21 subjects (40%) had an objective response by modified World Health Organization (mWHO) criteria. 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).

1.3.7.a Rationale for Using Immune-Related Tumor Assessment Criteria (irRC)

Ipilimumab is an immuno-stimulating antibody with evidence of anti-cancer activity (durable objective response and stable disease) in subjects with advanced melanoma, including subjects with established brain disease. Observations of clinical activity defined by tumor response endpoints defined by conventional criteria (eg, mWHO) may be inadequate to realize the kinetics and magnitude of clinical benefit achieved with ipilimumab.

Histopathologic evidence has demonstrated ipilimumab can produce an influx or expansion of tumor infiltrating lymphocytes. Therefore, early increases in lesion size detected radiologically or upon gross examination could be misinterpreted as progressive tumor growth and precede objective tumor shrinkage. In addition the appearance of new lesions may have categorized a subject to have progressive disease using conventional tumor assessment criteria despite the concurrent observation of objective tumor responses in pre-existing lesions and a net reduction in global tumor burden that includes the new lesions.

Hence the appearance of new lesions in and of themselves may not necessarily constitute progressive disease. The immune-related response criteria (irRC) were developed as a tool to gauge tumor response using the changes in global tumor burden. In addition, the irRC may be useful to inform a physician's decision to continue dosing in subjects who may receive benefit from additional ipilimumab therapy. The ir-response assessment is based solely on objective measurements (SPD) of index and new lesions. Non-index lesions are not considered.

1.3.7.b MDX010-20 (Phase 3, 3 mg/kg, previously treated melanoma)

MDX010-20, a randomized (3:1:1), double-blind, double-dummy study included 676 randomized subjects with unresectable or metastatic melanoma previously treated with one or more of the following: aldesleukin, dacarbazine, temozolomide, fotemustine, or carboplatin. Of these 676 subjects, 403 were randomized to receive ipilimumab at 3 mg/kg in combination with an investigational peptide vaccine with incomplete Freund's adjuvant (gp100), 137 were randomized to receive ipilimumab at 3 mg/kg, and 136 were randomized to receive gp100 alone. The study enrolled only subjects with HLA A2*0201 genotype; this HLA genotype facilitates the immune presentation of the investigational peptide vaccine. The study excluded subjects with active autoimmune disease or those receiving

systemic immunosuppression for organ transplantation. Ipilimumab/placebo was administered at 3 mg/kg as an intravenous infusion every 3 weeks for 4 doses. Gp100/placebo was administered at a dose of 2 mg peptide by deep subcutaneous injection every 3 weeks for four doses. Assessment of tumor response was conducted at Weeks 12 and 24, and every 3 months thereafter. Subjects with evidence of objective tumor response at 12 or 24 weeks had assessment for confirmation of durability of response at 16 or 28 weeks, respectively.

The major efficacy outcome measure was overall survival (OS) in the ipilimumab + gp100 arm compared to that in the gp100 arm. Secondary efficacy outcome measures were OS in the ipilimumab + gp100 arm compared to the ipilimumab arm, OS in the ipilimumab arm compared to the gp100 arm, best overall response rate (BORR) at Week 24 between each of the study arms, and duration of response.

Of the randomized subjects, 61%, 59%, and 54% in the ipilimumab + gp100, ipilimumab, and gp100 arms, respectively, were men. Twenty-nine (29%) percent were ≥ 65 years of age, the median age was 57 years, 71% had M1c stage, 12% had a history of previously treated brain metastasis, 98% had ECOG performance status of 0 and 1, 23% had received aldesleukin and 38% had elevated LDH level. Sixty-one (61%) percent of subjects randomized to either ipilimumab -containing arm received all 4 planned doses. The median duration of follow-up was 8.9 months.

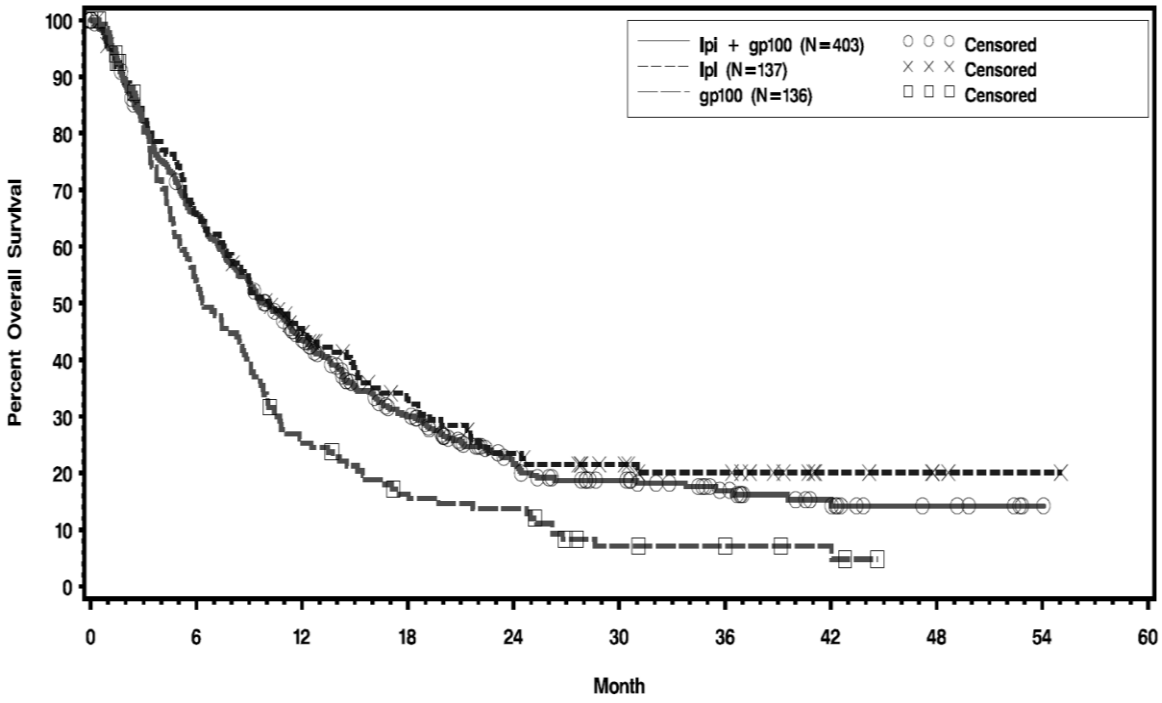
The OS results are shown in Table 5 and Figure 2.

Table 5: MDX010-20 Overall Survival Results

	Ipilimumab n = 137	**Ipilimumab + gp100 n = 403**	**gp100 n = 136**
Hazard Ratio (vs gp100) (95% CI)	0.66 (0.51, 0.87)	0.68 (0.55, 0.85)	
p-value	p = 0.0026[a]	p = 0.0004	
Hazard Ratio (vs ipilimumab) (95% CI)		1.04 (0.83, 1.30)	
Median (months) (95% CI)	10 (8.0, 13.8)	10 (8.5, 11.5)	6 (5.5, 8.7)

[a] Not adjusted for multiple comparisons.

Figure 2: MDX010-20 - Overall Survival by Treatment (ITT Population)



The best overall response rate (BORR) as assessed by the investigator was 5.7% (95% CI: 3.7%, 8.4%) in the ipilimumab + gp100 arm, 10.9% (95% CI: 6.3%, 17.4%) in the ipilimumab arm, and 1.5% (95% CI: 0.2%, 5.2%) in the gp100 arm. The median duration of response was 11.5 months in the ipilimumab + gp100 arm and has not been reached in the ipilimumab or gp100 arm.

1.3.7.c CA184024 (Phase 3, previously untreated melanoma, 10 mg/kg)

CA184024 evaluated the addition of 10 mg/kg ipilimumab to dacarbazine in patients with previously untreated, metastatic melanoma. A total of 502 patients were randomized to receive up to 8 cycles of dacarbazine 850 mg/m^2 q3w, with either ipilimumab 10 mg/kg or placebo cycles 1-4, and as maintenance after completion of chemotherapy.

The two arms were well balanced regarding most baseline characteristics, as shown in Table 6.

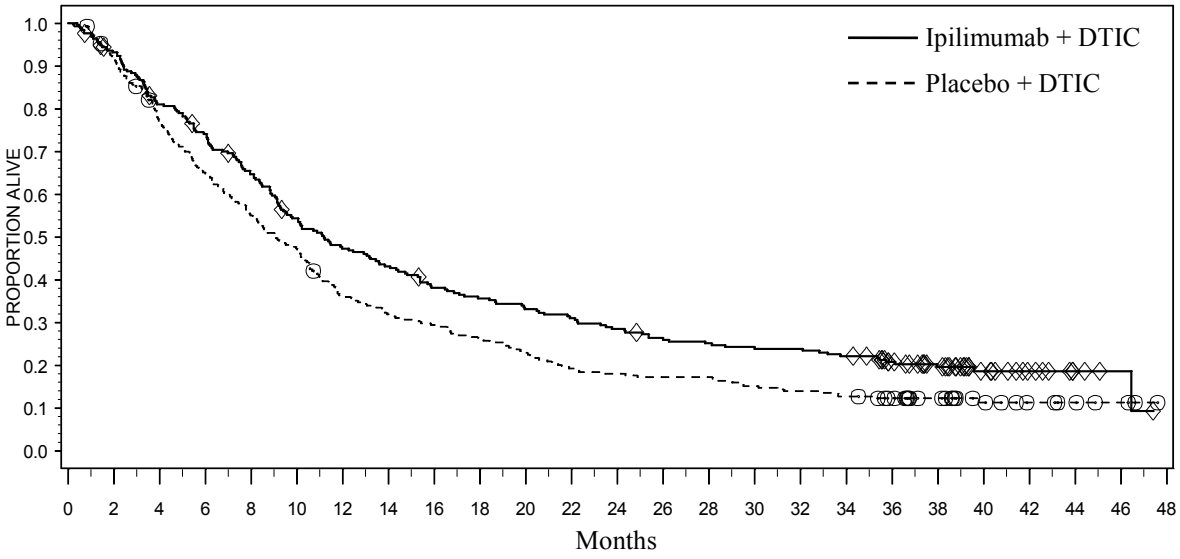
Table 6: CA184024 Baseline Characteristics

	Ipilimumab + DTIC n = 250	**Placebo + DTIC n = 252**
Age (years)		
Mean	57.5	56.4
Gender (%)		
Male	60.8	59.1
Female	39.2	40.9
M Stage (%)		
M0	2.4	3.2
M1a	14.8	17.1
M1b	25.6	24.6
M1c	57.2	55.2
ECOG PS (%)		
0	70.8	71.0
1	29.2	29.0
LDH (%)		
≤ ULN	62.8	55.6
> ULN	37.2	43.7
≤ 2x ULN	86.4	85.3
> 2x ULN	13.6	13.9
Prior adjuvant therapy (%)	26.4	26.6
Prior therapy for advanced disease (%)	0	0

Patients on the ipilimumab arm received a median of 3 ipilimumab induction doses, versus 4 placebo induction doses on the placebo arm. A total of 17.4% and 21.1% of patients continued to receive maintenance ipilimumab or placebo, for a median of 4 and 2 doses, respectively. The number of patients who received all 8 dacarbazine doses was 12.2% in the ipilimumab arm, and 21.5% in the placebo arm.

The study met its primary end-point of prolonging overall survival in patients treated with ipilimumab (HR 0.72 (95% CI, 0.59 – 0.87), median OS 11.2 vs 9.1 months, p = 0.0009). The OS Kaplan-Meier curve is presented in Figure 3.

Figure 3: CA184024 Kaplan-Meier Plot of Overall Survival - All Randomized Subjects



One, two and three year survival rates were 47.3%, 28.5% and 20.8% in the ipilimumab arm, and 36.3%, 17.9% and 12.2% in the placebo arm.

PFS, a secondary end-point, was also prolonged by the addition ipilimumab, HR 0.76 (95% CI, 0.63 - 0.93). The median PFS was 2.8 months in the ipilimumab and vs 2.6 months in the placebo arm, p = 0.006.

BORR was increased from 10.3% in the placebo arm to 15.2% in the ipilimumab arm (Table 7). More importantly, duration of response was more than twice as long in the ipilimumab arm (19.3 months) than in the placebo arm (8.1 months).

Table 7: CA184024 Tumor Response

	Ipilimumab + DTIC n = 250	Placebo + DTIC n = 252
Disease Control Rate, n (%)	83 (33.2)	76 (30.2)
BORR (CR + PR), n (%)	38 (15.2)	26 (10.3)
Complete response	4 (1.6)	2 (0.8)
Partial response	34 (13.6)	24 (9.5)
Stable disease	45 (18.0)	50 (19.8)
Progressive disease	111 (44.4)	131 (52.0)
Duration of response, months	19.3	8.1

1.3.7. d 10 mg/kg Dosing with Ipilimumab

In melanoma, Phase 3 studies show improved survival at both 3 mg/kg (study MDX010-20) as well as with 10 mg/kg (study CA184024). Several additional conducted trials studied the efficacy and safety of 10 mg/kg dosing, and additional information gained from these trials is listed below:

- A dose of 10 mg/kg is necessary to ensure a blockade of the CTLA-4 pathway: *in vitro* a concentration of 20 μg/mL of ipilimumab was the minimal concentration able to fully abrogate the binding of CTLA-4 to B7.1 and B7.2. With a dose of 3 mg/kg q3w 30% achieved a trough concentration of ipilimumab greater than 20 μg/mL, compared to 95% of subjects treated at 10 mg/kg q3w.
- In addition, in all ipilimumab trials examined to date, mean Absolute Lymphocyte Count (ALC) increased after ipilimumab treatment throughout the 12-week induction-dosing period, in a dose-dependent manner. In an analysis of ipilimumab at 0.3, 3, or 10 mg/kg in melanoma studies CA184007, CA184008, and CA184022 combined, the rate of change in ALC after ipilimumab treatment was significantly associated with dose ($p = 0.0003$), with the largest rate at 10 mg/kg ipilimumab. Moreover, the rate of change in ALC over the first half of the induction-dosing period was significantly associated with clinical activity in these studies ($p = 0.009$), where clinical activity was defined as CR, PR, or prolonged SD (ie, SD lasting at least 6 months from first dose). Although these analyses alone could not determine whether the rate of change in ALC was specifically associated with clinical activity in response to ipilimumab treatment, as opposed to being generally prognostic, these results do suggest a potential benefit to higher rates of ALC increase after ipilimumab treatment. Among the 3 doses evaluated, 10 mg/kg ipilimumab led to the greatest such rates.
- In the 3 primary studies conducted in advanced melanoma (CA184007, CA184008, and CA184022), subjects treated with 10 mg/kg during the induction period had the

highest response, disease control rates, median OS as well as 1-year and 2-year survival rates compared to other doses. The CA184022 data are summarized in Table 8.

Table 8: Summary of Phase 2 Response Data in Melanoma (CA184022)

	10 mg/kg (n = 72)	3 mg/kg (n = 72)	0.3 mg/kg (n = 73)
BORR (mWHO) – % (95% CI)	11.1 (4.9 - 20.7)	4.2 (0.9 - 11.7)	0 (0.0 - 4.9)
DCR (mWHO) – % (95% CI)	29.2 (19.0 - 41.1)	26.4 (16.7 - 38.1)	13.7 (6.8 - 23.8)
Survival rate at 1 year - % %, 95% CI	48.64 (36.84, 60.36)	39.32 (27.97, 50.87)	39.58 (28.20, 51.19)
Survival rate at 2 year - % %, 95% CI	29.81 (19.13, 41.14)	24.20 (14.42, 34.75)	18.43 (9.62, 28.22)
Overall median survival 95%CI (months)	11.43 (6.90, 16.10)	8.74 (6.87, 12.12)	8.57 (7.69, 12.71)

Finally, the dose and schedule in study CA184156 is the one that was evaluated in the signal finding study CA184041, with an acceptable safety profile and improvement of irPFS and OS.

Treatment with ipilimumab has demonstrated clinically important and durable tumor responses in several malignancies including melanoma, prostate cancer, and renal cell carcinoma.

1.3.7.e Advanced Melanoma

Ipilimumab prolonged survival in subjects with pre-treated advanced melanoma are based on results from MDX010-20 (Phase 3) supported by data from Phase 2 studies; the primary efficacy and safety studies are summarized in Table 9.[16-23] The primary endpoint in MDX010-20 was OS, which was also a key secondary endpoint in Phase 2 studies.

Table 9: Studies Supporting the Efficacy and Safety of Ipilimumab in Subjects with Advanced Melanoma

				# Randomized or Enrolled/Treated		
Study No. (Phase)	Populations	Primary Efficacy Endpoint	Doses Studies	3 mg/kg	10 mg/kg	Total

Table 9: Studies Supporting the Efficacy and Safety of Ipilimumab in Subjects with Advanced Melanoma

				# Randomized or Enrolled/Treated		
MDX010-20 (Phase 3)	HLA-A2*0201-positive, previously treated, unresectable Stage III or IV melanoma	OS	3 mg/kg q3 wk x 4 ± gp100 (induction) followed by re-induction	540/512	--/--	676/643[a]
CA184022 (Phase 2)	Previously treated, unresectable Stage III or IV melanoma	BORR	0.3, 3, or 10 mg/kg q3 wk x 4 (induction) followed by maintenance dosing q12 wk	72/71	72/71	217/214
CA184004 (Phase 2) Biomarker Study	Unresectable Stage III or IV melanoma	BORR	3 or 10 mg/kg q3 wk x 4 (induction) followed by maintenance dosing q12 wk	40/40	42/42	82/82
CA184008 (Phase 2)	Previously treated unresectable State III or IV melanoma	BORR	10 mg/kg q3 wk x 4 (induction) followed by maintenance dosing q12 wk	--/--	155/155	155/155
CA184007	Unresectable Stage III or IV melanoma	BORR	10 mg/kg q3 wk x 4 ± budesonide (induction) followed by maintenance dosing q12 wk	--/--	115/115	115/115
Additional Studies						
MDX010-08(Phase 2)	Chemotherapy-naive advanced melanoma	ORR	3 mg/kg q4 wk x 4 ± DTIC (induction)	78/74	--/--	78/74
CA184042 (Phase 2)	Stage IV melanoma with brain metastases	DCR	10 mg/kg q3 wk x 4 (induction) followed by maintenance dosing q12 wk	--/--	28/28[b]	28/28[b]

Table 9: Studies Supporting the Efficacy and Safety of Ipilimumab in Subjects with Advanced Melanoma

				# Randomized or Enrolled/Treated		
MDX010-28 (Phase 2) Survival Follow-up Study	Subjects enrolled in earlier Medarex studies, including MDX010-08 and MDX010-15[c]	OS	N/A	--/N/A	--/NA	--/N/A

BORR = best overall response rate; DCR = disease control rate; DTIC = dacarbazine; N/A = not applicable; ORR = overall response rate; OS = overall survival; PK = pharmacokinetics.

[a] Total includes 136 randomized/131 treated subjects in the gp100 treatment group.

[b] Information is presented only for subjects enrolled in MDX010-20, Arm A.

[c] MDX010-15 was primarily a PK study that evaluated ipilimumab at single and multiple doses.

Source: Reference 16-23

1.3.7.f Rationale for combining Nivolumab with ipilimumab

The combination of nivolumab and ipilimumab was chosen as an experimental arm because of preclinical and preliminary clinical evidence suggesting synergy between nivolumab and ipilimumab. While PD-1 and CTLA-4 are both co-inhibitory molecules, evidence suggests that they use distinct mechanisms to limit T cell activation. Preliminary indirect data from peripheral T cell assessments suggest that a given T-cell checkpoint inhibitor may modulate host immune cell phenotype rendering them more susceptible to alternate checkpoint inhibitors and thereby enhancing anti-tumor activity. Specifically, nivolumab increased peripheral CTLA-4+ and regulatory T cells in subjects without clinical response in CA209006.48 In a preclinical melanoma model, anti-CTLA-4 therapy increased PD-1+, PD-L1+ and CTLA-4+ tumor infiltrating T cells.49 In addition, in the Phase 2 ipilimumab monotherapy study CA184004, increases in tumor infiltrating lymphocytes (TILs) and interferon-α-inducible genes were observed following treatment with ipilimumab, and PD-L1 positive tumor cells co-localize with both TILs and IFN-α expression in metastatic melanoma.50, 51,52

The preliminary clinical evidence has demonstrated a higher frequency of patients with substantial tumor burden reduction for the combination of nivolumab and ipilimumab.

Improved overall survival associated with substantial tumor burden reduction has been noted with immunotherapies. For instance, improved overall survival has been noted in metastatic melanoma subjects obtaining a complete response to IL-2.53 If this observation is also applicable to treatment with nivolumab combined with ipilimumab then there could also be the potential for large improvements in overall survival compared to ipilimumab.

Dose and Schedule Rationale

In CA209004, the 3 mg/kg nivolumab and 3 mg/kg ipilimumab cohort exceeded the maximum tolerated dose per protocol. In CA209004, while both Cohort 2 (1 mg/kg nivolumab + 3 mg/kg ipilimumab) and Cohort 2a (3 mg/kg nivolumab + 1 mg/kg ipilimumab) had similar clinical activity, a dose of 3 mg/kg of ipilimumab every 3 weeks for a total of four doses and 1 mg/kg nivolumab every 3 weeks for four doses followed by nivolumab 3mg/kg every 2 weeks until progression was chosen. Exposure-response analysis of nivolumab monotherapy across dose ranges of 1 mg/kg to 10 mg/kg reveals similar clinical activity while exposure-response analysis of 0.3 mg/kg, 3 mg/kg, and 10 mg/kg of ipilimumab monotherapy have demonstrated increasing activity with increase in dose in the phase 2 study CA184022.54 Therefore, theoretically the selection of 3 mg/kg of ipilimumab (Cohort 2) may be more clinically impactful than selection of 3 mg/kg of nivolumab (Cohort 2a).

The combination arm has a similar dose and schedule as that in CA209004 for the first 12 weeks, increasing the likelihood of replicating the clinical activity seen in the CA209004 study. Based on the clinical activity in CA209004, the majority of responses to the combination of nivolumab and ipilimumab occur in the first 12 weeks. Given the uncertainty of whether the ipilimumab administered past week 12 contributes to the clinical benefit and the fact that the approved schedule for ipilimumab is every 3 weeks for a total of four doses in the FDA and EMA approved label dosing section, ipilimumab will only be administered every 3 weeks for a total of 4 doses. Nivolumab monotherapy treatment every two weeks until progression was studied in CA209003 and is implemented program-wide across the nivolumab monotherapy Phase 3 registrational trials.

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 populationpharmacokinetic (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.

1.3.7. g Rationale for Permitting Continued Treatment in Select Cases of Progressive Disease

Accumulating clinical evidence indicates some subjects treated with immune system stimulating agents may develop progression of disease (by conventional response criteria) before demonstrating clinical objective responses and/or stable disease. This phenomenon was observed in approximately 10% of subjects in the Phase 1 study of nivolumab and also with ipilimumab monotherapy. Two hypotheses have been put forth to explain this phenomenon. First, enhanced inflammation within tumors could lead to an increase in tumor size which would appear as enlarged index lesions and as newly visible small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease leading to overt signs of clinical improvement. Alternatively, in some individuals, the kinetics of tumor growth may initially outpace anti-tumor immune activity. With sufficient time, the anti-tumor activity will dominate and become clinically apparent. Therefore, subjects will be allowed to continue study therapy after initial investigator-assessed RECIST 1.1 defined progression if they are assessed to be deriving clinical benefit and tolerating study drug.

1.4 Overall Risk/Benefit Assessment

There continues to be a significant unmet need for patients with previously untreated, **unresectable or metastatic uveal melanoma.**

Nivolumab monotherapy has demonstrated clinical activity across several tumor types, including advanced prior treated melanoma, with objective response rates of 20 - 41% in 106 melanoma subjects treated at various dose levels in CA209003. Nivolumab has also demonstrated a manageable safety profile. The most common AEs included fatigue, rash, pruritis, diarrhea, and nausea.

The combination of nivolumab and ipilimumab has the potential for increased benefit compared to both ipilimumab monotherapy and nivolumab monotherapy. Preliminary analysis of the evaluable CA209004 subjects revealed that approximately 33% of the subjects had >80% tumor reductions in target lesions by week 12. This compares favorably to < 2% for 3 mg/kg ipilimumab monotherapy based on the CA184020 (N=540) and <3% for nivolumab monotherapy based on the CA209003. However, the combination of nivolumab and ipilimumab also has the potential for increased frequencies of adverse events. The most common (reported at > 10% incidence) treatment related AEs 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 sequalae and adverse events have been manageable and reversible following intervention dose delays or with systemic steroid treatment.

Evaluating the combination of nivolumab and ipilimumab will provide clinical data allowing clinicians to select the appropriate treatment for each patient based on the individual risk-benefit ratio. The robust clinical activity demonstrated by nivolumab monotherapy and the promising clinical activity of nivolumab combined with ipilimumab in subjects with advanced melanoma in combination with the manageable safety profile and the lack of approved survival-prolonging agents for a large segment of the previously untreated population supports the further development of nivolumab and nivolumab combined with ipilimumab in subjects with previously untreated, unresectable or metastatic melanoma.

1.5 Uveal Melanoma

Uveal melanoma is the most common primary intraocular malignant tumor in adults and the second most common type of primary malignant melanoma in the body. It represents five to six percent of all melanoma diagnoses. The incidence of uveal melanoma in the world is approximately 4,800 persons per year with nearly 2,000 cases diagnosed in North America annually. Metastasis is via vascular spread, and approximately 40-50% of patients with uveal melanoma will ultimately develop distant disease. The liver is involved in up to 95% of individuals who develop metastatic disease. The clinical course of patients with uveal melanoma is determined by progression of the disease in the liver. Once metastatic disease is identified, the median survival of patients with liver metastases is six

to seven months, despite therapy, with a dismal one-year survival of approximately 10-15%.[25, 26, 33]

Immunotherapy using checkpoint blockade inhibitors have made significant headway in cutaneous melanoma but their relevance in melanomas of rare subtypes, including uveal melanoma, remains unstudied in a prospective fashion. Anecdotal reports from expanded access programs and case reports of uveal melanoma patients treated with ipilimumab at both 3 mg/kg and 10 mg/kg demonstrate modest clinical activity at best with responses no more than 6%, CA184-187 was the first prospective ipilimumab trial in the world dedicated solely to uveal melanoma patients. After enrollment of 20 patients however, no documented responses were noted at both 3 mg/kg and 10 mg/kg.

Because of rationale behind combination checkpoint blockade inhibition and the notable clinical activity in cutaneous melanoma with a 1-year overall survival approaching that of targeted therapies (69% 1-year OS presented by Sznol et al. ASCO 2014), it is possible that monotherapy checkpoint blockade may not be enough to overcome tumor progression in uveal melanoma and that combination immunotherapy is in fact the necessary approach. Indeed, reports of small series of uveal melanoma patients on monotherapy anti-PD-1 clinical trials to date have failed to demonstrate any responses (nivolumab, MK-3475). Combination checkpoint blockade with nivolumab and ipilimumab at doses established in cutaneous melanoma warrant investigation in a prospective fashion for metsatatic uveal melanoma patients.

The overall risk-benefit ratio for patients entering this protocol is therefore at least comparable to and possibly better than alternative options, specifically for uveal melanoma, where no standard therapies exist. Therefore, this protocol is at least comparable to the consensus recommendations for this population to enroll on some form of a clinical trial.

1.6 Study Rationale

Metastatic uveal melanoma is uniformly fatal and median overall survival with current therapies remains poor (6 months) with 10-15% of patients surviving at one year. Ipilimumab has been safely used in uveal melanoma patients in the expanded access program both in the United States and in Europe. Anti PD-1 early clinical trials have enrolled few uveal melanoma patients with no notable responses, although administration was safe and tolerable. Combination nivolumab plus ipilimumab in cutaneous melanoma is marked by early tumor responses with significant regression in tumor burden. However,

uveal melanoma patients were not enrolled on this combination study. As noted in cutaneous melanoma, the combination of two checkpoint inhibitors may result in early and deep tumor responses for the population of patients with advanced uveal melanoma.

Metastatic uveal melanoma patients with at least one measureable lesion will be treated with nivolumab plus ipilimumab until disease progression or until unmanageable toxicity occurs.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is overall response rate

2.2 Secondary Objectives

Secondary objectives include Safety and tolerability of combination, progression-free survival, median overall survival, and one-year overall survival.

2.3 Exploratory Objectives

Exploratory Objectives include tissue and blood correlates to define immune infiltration and signatures as a result of treatment with nivolumab plus ipilimumab.

3. STUDY DESIGN

3.1 Screening and registration

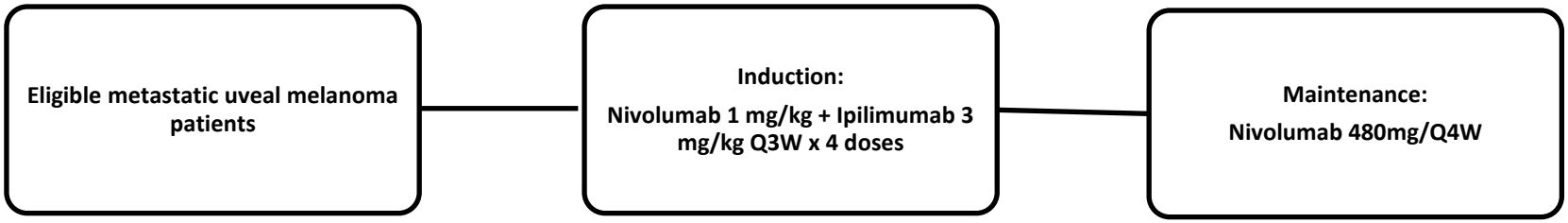
Interested patients with uveal melanoma will be screened for eligibility as defined in Section 4. If all criteria are met, the patient will sign consent and be registered into the central database, Clinical Oncology Research System (CORe).

3.2 Study Schema

This is a Phase II study of nivolumab combined with ipilimumab for metastatic uveal melanoma.

See illustrated schema on the following page.

STUDY SCHEMA:



3.3 Treatment

Nivolumab is to be administered as a 60-minute IV infusion, using a volumetric pump with a 0.2/0.22 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline for delivery but the total drug concentration of the solution cannot be below 0.35 mg/ml. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

Ipilimumab is to be administered as a 90-minute IV infusion, using a volumetric pump with a 0.2 to 1.2 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline or 5% Dextrose Injection to concentrations between 1 mg/mL and 4 mg/mL. It is not to be administered as an IV push or bolus injection. Care must be taken to assure sterility of the prepared solutions, since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents. At the end of the infusion, flush the line with a sufficient quantity of normal saline or 5% dextrose solution.

When both study drugs are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion.

Baseline weight will be used to calculate all induction doses unless weight varies by +/- 10% from baseline. In that case, actual weight will be used.

3.2.1.a Induction Phase

During the induction phase, patients will be treated with nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (+/- 7 days) for a total of four doses (week 1, 4, 7, 10). The induction phase continues through week 12.

During the induction phase, patients will also have a mandatory biopsy of tumor tissue for exploratory immune biomarker studies. This biopsy can occur any time after cycle 1 until the end of cycle 4 (weeks 4-12).

3.2.1.b Maintenance Phase

For patients who have not experienced disease progression, or unmanageable toxicity by week 12, a maintenance phase will begin. Maintenance treatment consists of nivolumab

monotherapy 480 mg/ every 4 weeks for up to 104 weeks or until disease progression or unmanageable toxicity as deemed by the clinical investigator.

During the maintenance phase and at the end of the study, patients have the option to undergo an additional biopsy of tumor tissue for exploratory biomarker studies.

3.2.1.c General Treatment Instructions

- As durable disease stabilization and/or objective tumor response can be seen after early progression before week 12, it is recommended that, in the absence of dose-limiting toxicities (eg, serious immune-mediated adverse reactions), all four doses of nivolumab plus ipilimumab be administered over the initial 12 weeks even in the setting of apparent clinical progression, providing the subject's performance status remains stable.
- All metastatic subjects who enter the induction period, including those who may have discontinued treatment for drug-related AEs and/or who have evidence of clinical progression during the induction period, should obtain a 12-week tumor assessment.
- Based on clinical experience in the ongoing and completed melanoma studies, the following recommendations apply for subject management in light of the week 12 or later tumor assessments:
  - The appearance of new lesions in subjects with other stable or shrinking baseline tumor burden may be experiencing clinical benefit and should continue in follow-up and/or maintenance therapy before alternative anti-cancer agents are considered. These subjects can be seen to have continued tumor shrinkage in follow-up scans.
  - As long as overall tumor burden is stable or decreasing, subjects should remain in follow-up and/or maintenance (see below), even in the presence of new lesions.
  - Clinical progression warranting alternative anti-cancer treatment should be considered only in subjects whose overall tumor burden appears to be substantially increased and/or in subjects whose performance status is decreased.

3.4 Follow-up (duration of study)

- Subjects who are no longer receiving treatment and are removed from the study because of unacceptable toxicity (refractory Grade > 3 immune-mediated adverse reactions) or due to investigator or his designee judgment are managed in follow-up. Efficacy assessments for these subjects during follow-up are as per the standard of care. Date of death is recorded.
- Subjects who discontinue treatments should be followed until death or the closure of the study (whichever is first).

- Subjects who are no longer receiving treatment because of clinical progression or who have switched to alternative treatment are not followed formally except to record the date of death.
- All subjects who come off study for any reason will be followed for at least 60 days, which is equal to 4 half –lives of the longest drug.

4 SUBJECT SELECTION CRITERIA

For entry into the study, the following criteria MUST be met. Any exceptions from the protocol-specific selection criteria must be approved by the Principal Investigator, the IND office medical monitor and/or the Institutional Review Board (IRB) before enrollment.

4.1 Inclusion Criteria

1. Willing and able to give written informed consent.
2. History of uveal melanoma and documented metastatic disease with at least one measurable lesion is required defined as ≥ 1 cm x 1 cm (on spiral CT or equivalent).
3. Any number of prior therapies is allowed.
4. Required values for initial laboratory tests:
   - WBC ≥ 2000/uL
   - ANC ≥ 1500/uL
   - Platelets ≥ 100 x 10^3/uL
   - Hemoglobin ≥ 9 g/dL
   - Creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥ 40 mL/min (using the Cockcroft-Gault formula):
     - Female CrCl = (140 - age in years) x weight in kg x 0.85
     72 x serum creatinine in mg/dL
     - Male CrCl = (140 - age in years) x weight in kg x 1.00
   - 72 x serum creatinine in mg/dL AST/ALT ≤ 3 x ULN for patients without liver metastasis, ≤ 5 x ULN for liver metastases
   - Bilirubin ≤ 1.5 x ULN, (except patients with Gilbert's Syndrome, who must have a total bilirubin less than 3.0 mg/dL)
5. In suspected patients, no active or chronic infection with HIV, Hepatitis B, or Hepatitis C.
6. Performance status ECOG 0-1.

7. Men and women, ≥ 18 years of age. Because no dosing or adverse event data are currently available on the use of ipilimumab in patients <18 years of age, minors are excluded from this study.
8. Baseline imaging in the form of CT chest, abdomen, pelvis with oral and intravenous contrast within 28 days of study entry. For patients with a contrast allergy, choice of alternative body imaging will be at the discretion of the investigator or his designee. MRI of the brain is only needed if clinically indicated.
9. Prior to start of treatment must be more than 21 days elapsed from surgery, radiation therapy, or prior chemotherapy. More than 42 days elapsed from prior immune therapy including vaccines.
10. Women of childbearing potential (WOCBP) and fertile men with partners of childbearing potential must be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 26 weeks after the last dose of investigational product, in such a manner that the risk of pregnancy is minimized.

    WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not post-menopausal. Post-menopause is defined as:

    - Amenorrhea ≥ 12 consecutive months without another cause, or
    - For women with irregular menstrual periods and taking hormone replacement therapy (HRT), a documented serum follicle stimulating hormone (FSH) level ≥ 35 mIU/mL.

    Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or are practicing abstinence or where their partner is sterile (e.g., vasectomy) should be considered to be of childbearing potential.

    WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of βHCG) within 72 hours before the start of ipilimumab.

    Men of fathering potential must be using an adequate method of contraception to avoid conception throughout the study (and for up to 26 weeks after the last dose

of investigational product) in such a manner that the risk of pregnancy is minimized.

Sexually active WOCBP must use an effective method of birth control during the course of the study, in a manner such that the risk of failure is minimized. Before enrolling women of childbearing potential in this clinical trial, investigators must review the guideline about study participation for WOCBP, which can be found in the Good Clinical Practice (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

Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. This discussion will be documented on the informed consent form required for study participation.

In addition, all WOCBP or fertile men with partners of childbearing potential should be instructed to contact the investigator immediately if they suspect they or their partner might be pregnant (e.g., missed or late menstrual period) at any time during study participation. If following initiation of study treatment, it is subsequently discovered that a trial patient is pregnant or may have been pregnant at the time of exposure to ipilimumab, including during at least 6 half-lives after product administration, ipilimumab will be permanently discontinued in an appropriate manner. Exceptions to ipilimumab discontinuation may be considered for life-threatening conditions only after consultation with the Medical Monitor or as otherwise specified in this protocol.

Protocol-required procedures for study discontinuation and follow-up must be performed on the patient 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 Bristol-Myers Squibb follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants should be followed for a minimum of 8 weeks.

4.2 Exclusion Criteria

1. Melanomas other than uveal melanoma (i.e. cutaneous, acral lentiginous, mucosal).
2. Metastatic uveal melanoma patients with bone-only disease.
3. Any other malignancy from which the patient has been disease-free for less than 2 years, with the exception of adequately treated and cured basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix, breast, or prostate.
4. Autoimmune disease: Patients with a history of inflammatory bowel disease, including ulcerative colitis and Crohn's Disease, are excluded from this study, as are patients with a history of symptomatic disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, autoimmune vasculitis [e.g., Wegener's Granulomatosis]; motor neuropathy considered of autoimmune origin (e.g. Guillain-Barre Syndrome and Myasthenia Gravis).
5. Any underlying medical or psychiatric condition, which in the opinion of the investigator will make the administration of ipilimumab hazardous or obscure the interpretation of AEs, such as a condition associated with frequent diarrhea.
6. Any non-oncology vaccine therapy used for prevention of infectious diseases (for up to 1 month before or after any dose of ipilimumab).
7. Concomitant therapy with any of the following: tamoxifen, toremifene, IL-2, interferon, or other non-study immunotherapy regimens; cytotoxic chemotherapy; immunosuppressive agents; other investigation therapies; or chronic use of systemic corticosteroids greater than physiologic replacement doses. Ocular steroid use is acceptable.
    a. Concomitant palliative radiation for the purposes of symptom management is allowed.

8. Women of childbearing potential (WOCBP), defined above in Section 4.1, who:
    d. are unwilling or unable to use an acceptable method of contraception to avoid pregnancy for their entire study period and for up to 26 weeks after cessation of study drug, or
    e. have a positive pregnancy test at baseline, or
    f. are pregnant or breastfeeding.

9. Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (e.g., infectious) illness.

4.3 Data Safety Monitoring Plan

MD Anderson Cancer Center (MDACC) will monitor the progress of all clinical investigations being conducted under its IND and remain compliant under 21CFR312.56(b). The clinical research monitor, who has not had a prior role in the conduct of the study, will be assigned to monitor the study and will discuss the frequency of the chart review with the PI and the study manager. For all studies, eligibility and informed consent documentation will be reviewed following enrollment of selected subjects. With the exception of eligibility and informed consent review, the PI and the study manager will receive notification from the clinical research monitor approximately 2 weeks prior to each monitoring visit. The study coordinator or research nurse will be responsible for providing the monitor with any additional supporting documents and regulatory binders.

The frequency of the monitoring visits will occur every 8-12 weeks or more or less frequently as determined by the activity of the clinical trial.

Source documentation will be reviewed and used to independently verify study data. Data quality will be assessed by measuring it against the standards for optimal data as delineated in the research protocol. Investigator compliance with regulatory requirements and guidelines for Good Clinical Practice (GCP) will be assessed.

The clinical research monitor will complete a written monitoring report following each monitoring visit. The report will include a summary of what the monitor reviewed, any significant findings, identified actions taken or to be taken by the research team, and/or actions recommended securing compliance. Emphasis will be placed on clear and complete reporting of the findings. Comments will be made regarding problems or concerns affecting the validity or accuracy of the data.

The final report will be submitted to the MDACC IND Medical Monitor for review. The original signed report will be kept in the IND folder within the IND Office. A follow-up letter identifying unresolved issues will be sent to the PI to be kept in the regulatory binder. In order to remain compliant with 21CFR312.56(b) any trial that is being conducted under an MDACC-sponsored IND and is discontinued due to investigator noncompliance will have official notification set to the FDA.

5 STUDY THERAPY

5.1 Nivolumab (BMS 936558)

Nivolumab (BMS-936558) vials must be stored at a temperature of 2or for review. The ori protected from light and freezing. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) and 40 mg/4 mL (10 mg/mL)
Vials of nivolumab injection must be stored at 2°-8°C (36°-46°F) and protected from light, freezing, and shaking.

Undiluted Nivolumab Injection and Diluted Nivolumab Injection in the IV Bag
The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°-8°C, 36°-46°F) for up to 24 hours, and a maximum of 4 hours of the total 24 hours can be at room temperature (20°-25°C, 68°-77°F) and room light. The maximum 4-hour period under room temperature and room light conditions includes the product administration period.

Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between nivolumab and polyolefin bags have been observed.Nivolumab is to be administered before ipilimumab as a 60-minute IV infusion, using a volumetric pump with a 0.2/0.22 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline for delivery but the total drug concentration of the solution cannot be below 0.35 mg/ml. It is not to be administered as an IV push or bolus.

When the combination of nivolumab and ipilimumab are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The second infusion will always be ipilimumab and will start no sooner than 30 minutes after completion of the nivolumab infusion. Ipilimumab may be diluted in 0.9% Sodium Chloride Solution or 5% Dextrose solution. Nivolumab may be diluted in 0.9% Sodium Chloride Solution.

The dosing calculations should be based on body weight. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded up to the nearest milligram per institutional standard. There will be no dose modifications allowed.

5.2 Ipilimumab

Ipilimumab injection can be used for IV administration without dilution after transferring

to a PVC (polyvinyl chloride), non-PVC/non-DEHP (di-(2-ethylhexyl)phthalate) or glass containers and is stable for 24 hours at 2-8containersrsistration without dilution after transferring storage instructions, refer to ipilimumab IB and/or pharmacy reference sheets.

Recommended safety measures for preparation and handling include protective clothing, gloves, and safety cabinets.

Ipilimumab is to be administered as a 90-minute IV infusion, using a volumetric pump with a 0.2 to 1.2 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline or 5% Dextrose Injection to concentrations between 1 mg/mL and 4 mg/mL. It is not to be administered as an IV push or bolus injection. Care must be taken to assure sterility of the prepared solutions, since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents. At the end of the infusion, flush the line with a sufficient quantity of normal saline or 5% dextrose solution.

When both study drugs are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion.

Ipilimumab infusion will start no sooner than 30 minutes after completion of the nivolumab infusion. During **the induction phase**, subjects may be dosed no less than 19 days between doses. If dosing is delayed, both nivolumab and ipilimumab must be delayed together. If dosing is resumed after a delay, both nivolumab and ipilimumab must be resumed on the same day.

During the **maintenance phase**, subjects may be dosed no less than 24 days between doses. Subjects may be dosed up to 3 days after the scheduled date if necessary. Subsequent dosing should be based on the actual date of administration of the previous dose of drug. Ipilimumab may be diluted in 0.9% Sodium Chloride Solution or 5% Dextrose solution. Nivolumab may be diluted in 0.9% Sodium Chloride Solution.

5.2.1 Dose Calculations

Premedications should not be routinely administered prior to dosing of study drugs. See Section 4.5.6 for subsequent premedication recommendations following a nivolumab or ipilimumab-related infusion reaction.

The dosing calculations should be based on body weight. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be

recalculated. All doses should be rounded up to the nearest milligram per institutional standard. There will be no dose modifications allowed.

5.2.2 Dose Delay Criteria

Dose reductions or dose escalations are not permitted.

Dose delay criteria apply for all drug-related adverse events (regardless of whether or not the event is attributed to nivolumab, ipilimumab, or both). All study drugs must be delayed until treatment can resume (see Section 4.3.4.)

Nivolumab and ipilimumab administration should be delayed for the following:

During Induction, subjects may be dosed no less than 19 days between doses. If dosing is delayed, both nivolumab and ipilimumab must be delayed together. If dosing is resumed after a delay, both nivolumab and ipilimumab must be resumed on the same day.

During Maintenance, subjects may be dosed no less than 24 days between doses. Subjects may be dosed up to 3 days after the scheduled date if necessary. Subsequent dosing should be based on the actual date of administration of the previous dose of drug.

Criteria to Resume Treatment

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

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 4.3.5)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 are 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 > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in Section 5.2.3.

5.2.3 Discontinuation of Study Therapy

Subjects MUST be discontinued from study therapy AND withdrawn from the study for the following reasons:

 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 discontinuation:

  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

 Any dosing interruption lasting > 6 weeks with the following exceptions:

 Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the PI will discuss feasibility with the sponsor.. 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 ipilimumab dosing.

- Withdrawal of informed consent (subject's decision to withdraw for any reason).
- Any clinical adverse event, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued treatment with study therapy is not in the best interest of the subject.
- Pregnancy
  - 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. Institutional policy and local regulations should determine the frequency of on study pregnancy tests for WOCBP enrolled in the study.
  - The investigator must immediately notify BMS in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by Bristol-Myers Squibb (BMS).
- Imprisonment or the compulsory detention for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

5.2.4 Permanent Discontinuation of Ipilimumab

5.2.4.a Permanent Discontinuation for Related Adverse Events

Refer to Appendix B for algorithms recommended for utilization in CA184-187. Permanently discontinue treatment for any of the following:

- Persistent moderate adverse reactions or inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day.
- Severe or life-threatening adverse reactions, including any of the following:
  - Radiographic or histologic diagnosis of colitis with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency (7 or more over baseline) or incontinence unable to be mitigated with corticosteroids, gastrointestinal hemorrhage, or gastrointestinal perforation
  - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5 times the upper limit of normal or total bilirubin >3 times the upper limit of normal
  - Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations
  - Severe motor or sensory neuropathy, Guillain-Barré syndrome, or myasthenia gravis
  - Severe immune-mediated reactions involving any organ system (eg, nephritis, pneumonitis, pancreatitis, non-infectious myocarditis)
  - Immune-mediated ocular disease that is unresponsive to topical immunosuppressive therapy (eg, ocular steroids)
  - Any adverse event, laboratory abnormality or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the patient with continued dosing.
  - The development of progression (irPD) in the global tumor burden confirmed by serial imaging 4-6 weeks later and/or clinical deterioration of subject's condition such that further benefit from ipilimumab dosing is unlikely or requires a change of therapy.

Please refer to section 5.1.7 and the IB for specific AE management algorithms.

The following neurological adverse event requires permanent discontinuation of ipilimumab and defines unacceptable neurotoxicity:

- Any motor neurologic toxicity >/= Grade 3 regardless of causality
- Any >/= Grade 3 treatment related sensory neurologic toxicity

Please refer to section 5.1.7 and the IB for specific AE management algorithms.

5.2.4.b Exceptions to Permanent Discontinuation

- Potentially reversible inflammation (< Grade 4), attributable to a local anti-tumor reaction and a potential therapeutic response. This includes inflammatory reactions at

sites of tumor resections or in draining lymph nodes, or at sites suspicious for, but not diagnostic of metastasis.

- Hospitalization for ≤ Grade 2 adverse events where the primary reason for hospitalization is to expedite the clinical work-up.
- Patients with the following conditions where in the investigator's opinion continuing study drug administration is justified:
  - Ocular toxicity that has responded to topical therapy (eg, ocular steroids).
  - Endocrinopathies where clinical symptoms are controlled with appropriate hormone replacement therapy. **Note:** Ipilimumab may not be restarted while the patient is being treated with systemic corticosteroids except for patients on stable doses of hormone replacement therapy such as hydrocortisone.

5.2.5 Immune-Related Adverse Events (irAEs)Reactions and Immune-mediated Adverse Reactions: Definition, Monitoring, and Treatment

Blocking CTLA-4 and PD-1 function may permit the emergence of auto-reactive T cells and resultant clinical autoimmunity. Rash/vitiligo, diarrhea/colitis, uveitis/episcleritis, hepatitis, and hypopituitarism were drug-related, presumptive autoimmune events, now termed immune-mediated adverse reactions, noted in previous ipilimumab studies.

For the purposes of this study, an immune-related adverse reaction is defined as an adverse reaction of unknown etiology associated with drug exposure and consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an event an immune-related adverse reactions. Serologic, immunologic, and histologic (biopsy) data should be used to support the diagnosis of an immune-related toxicity. Suspected immune-related adverse reactions must be documented on an AE or SAE form. Another term for an irAE is an immune-mediate adverse reaction, as it is termed in the Ipilimumab US Prescribing Information. Both terms may be used in this protocol document.

Patients should be informed of and carefully monitored for evidence of clinically significant systemic immune-mediated adverse reactions (e.g., systemic lupus erythematosus-like diseases) or organ-specific immune-mediated adverse reaction (e.g., rash, colitis, uveitis, hepatitis or thyroid disease). If an immune-mediated adverse reaction is noted, appropriate work-up (including biopsy if possible) should be performed, and steroid therapy may be considered if clinically necessary.

It is unknown if systemic corticosteroid therapy has an attenuating effect on ipilimumab activity. However, clinical anti-tumor responses have been maintained in patients treated with corticosteroids and discontinued from ipilimumab. If utilized, corticosteroid therapy

should be individualized for each patient. Prior experience suggests that colitis manifested as ≥ Grade 3 diarrhea requires corticosteroid treatment.

Specific treatment algorithms for immune-mediated adverse reactions adverse events are included as appendices B.

5.2.6 Other Guidance

Treatment of Nivolumab or Ipilimumab Related Infusion Reactions Since nivolumab and ipilimumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (version 4.0) guidelines.

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

For mild symptoms, Grade 1 (Mild reaction; infusion interruption not indicated; intervention not indicated) Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations.For moderate symptoms, Grade 2

- (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours). Stop the nivolumab or ipilimumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further nivolumab or ipilimumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30

minutes before additional nivolumab or ipilimumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

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

- Immediately discontinue infusion of nivolumab or ipilimumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab or ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

5.2.6.a Treatment of Nivolumab or Ipilimumab-Related Isolated Drug Fever

In the event of isolated drug fever, the investigator must use clinical judgment to determine if the fever is related to the ipilimumab or to an infectious etiology. If a patient experiences isolated drug fever, for the next dose, pre-treatment with acetaminophen or non-steroidal anti-inflammatory agent (investigator discretion) should be instituted and a repeated antipyretic dose at 6 and 12 hours after ipilimumab infusion, should be administered. The infusion rate will remain unchanged for future doses. If a patient experiences recurrent isolated drug fever following premedication and post dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be decreased to 50% of the previous rate. If fever recurs following infusion rate change, the investigator should assess the patient's level of discomfort with the event and use clinical judgment to determine if the patient should receive further ipilimumab.

5.2.6.b Monitoring and Management of Immune-mediated Adverse Reactions

Refer to Appendix B for algorithms recommended for utilization in CA184-187.

5.2.6.c Liver Function Test (LFT) Assessments Required Before Administration of Nivolumab or Ipilimumab

Liver function tests (AST, ALT, T. bilirubin) will be evaluated for every subject prior to administration of nivolumab or ipilimumab. Blood samples must be collected and analyzed at local or central labs within 7 days prior to dosing. LFT results must be reviewed by the principal investigator (or designee) to meet dosing criteria specifications: ≤ 2.5 x ULN for AST, ALT and ≤ 2 x ULN for T. bilirubin unless liver metastases are present in which case LFT ≤ 5 x ULN for AST, ALT and T. bilirubin ≤ 3.0 x ULN) prior to dosing.

If, during the course of treatment abnormal LFT values are detected, the subject must be managed using the hepatotoxicity algorithm section in Appendix B.

5.3 Prohibited and Restricted Therapies During the Study

5.3.1 Prohibited Therapies

Patients in this study may not use vaccines for the treatment of cancer or prevention of disease unless indicated as a component of the protocol regimen (including those for common medical conditions) for up to one month pre and post dosing with ipilimumab. Concomitant systemic or local anti-cancer medications or treatments are prohibited in this study while receiving ipilimumab treatments.

Patients may not use any of the following therapies during the study:

- Any non-study anti-cancer agent (investigational or non-investigational)
- Any other investigational agents
- Any other (non-CA184024 related) CTLA-4 inhibitors or agonists
- Immunosuppressive agents
- Chronic systemic corticosteroids
- Any non-oncology vaccine therapies used for the prevention of infectious diseases (for up to 30 days prior to or after any dose of study drug).

5.3.2 Restricted Therapies

Not applicable.

5.3.3 Precautions

Caution is advised when considering treatment with high-dose IL-2 in patients who have previously been administered ipilimumab, particularly in patients who experienced ipilimumab-related diarrhea/colitis. Colonoscopy or sigmoidoscopy with biopsy may be advisable prior to IL-2 administration once the patient is no longer receiving ipilimumab.

6 STUDY PROCEDURES AND OBSERVATIONS

6.1 Time and Events Schedule

Table 10: Time and Events Schedule for Protocol

Procedure	Baseline[a]	Week 1, 4, 7, 10	Week 13 and every 4 weeks thereafter	Week 13 and every 12 weeks thereafter	End of Study
Eligibility					
Consent	x				
Inclusion/Exclusion	x				
Medical History	x				
Safety Assessments					
Interim History	x	x	x		x
Physical Examination	x	x	x		x
Vital signs, Height[c], Weight, Performance Status	x[c]	x	x		x
Adverse Events	x	x	x[b]		x
Concomitant Medications	x	x	x		x
Common Laboratory Tests	x	x	x[b]		x

Liver Function Tests	x	x	x[b]		x
Thyroid Function Tests	x	x		x	x
Pregnancy Test[e]	x	x			
Tumor Measurements[c]	x			x	
Correlative studies[d]		x	x		x
Nivolumab infusion		x	x[b]		
Ipilimumab infusion		x			

a. Baseline visit and Week 1 visit may occur simultaneously.

b. Patients will have adverse event assessments, common laboratory tests, liver function tests, and treatment every 4 weeks thereafter until removed from study.

c. Tumor assessments will occur at baseline, Week 13 and every 12 weeks thereafter until removed from study. Assessments will have a window of +/- 7 days and will be in the form of CT chest, abdomen, pelvis with oral and intravenous contrast or acceptable alternative body imaging at the discretion of the investigator. Brain imaging only at the discretion of the investigator.

d. Mandatory biopsy one-time during induction weeks 4-12, optional biopsy during maintenance and at the end of study

e. Pregnancy test will be every 4 weeks during Maintenance phase (every other visit).

6.2 Procedures by Visit

The Time and Events Schedule summarizes the frequency and timing of various measurements.

6.2.1 Study Procedures by Visit and Treatment Cycle

Note that results of all safety laboratory tests (that is, all chemistry and all hematology results) must be obtained and reviewed by the investigator or his designee before each ipilimumab administration. All induction period laboratory samples must be collected within a window of up to 7 days before administration of nivolumab or ipilimumab. The order set for infusion will require labs to be verified prior to administration. Hold and notify MD parameters will be given on the order set.

6.2.1.a Screening/Baseline Visit

Eligible patients will have a screening/baseline visit that may, in some instances, occur simultaneously with Treatment Visit 1. During this visit, the patient will have: a review of his/her medical history; physical examination including vital signs; assessment of signs, symptoms, concomitant medications, and adverse events; a review of common laboratory tests (CBC with differential, basic metabolic panel), a pregnancy test (within 72 hours of first dose) if applicable, liver function test (AST, ALT, T. bilirubin), and thyroid function test (TSH, free T4). In addition, study personnel will review inclusion/exclusion criteria, tumor assessments, and review and sign the informed consent document with the patient. All screening evaluations with the exception of pregnancy test should be completed within 28 days (+/- 7 days) of start of protocol treatment.

6.2.1.b Treatment Visits

At each treatment visit during the induction phase, the patient will have a physical examination including vital signs, assessment of signs, symptoms, and adverse events, review of laboratory data and a concomitant medication assessment. If the Baseline Visit occurs within 14 days of Treatment Visit 1, physical examination can be omitted from Treatment Visit 1. During the maintenance phase, patients will have adverse event assessment and treatment every 4 weeks, and physical examination including vital signs every 4 weeks.

6.2.2 Tissue Biopsies for Immune Biomarker Studies

During the induction phase, patients will have mandatory biopsy of tumor tissue for exploratory studies. This biopsy can occur any time after cycle 1 until the end of cycle 4 (weeks 4-12).

During the maintenance phase and at the end of study, patients have the option to undergo an additional biopsy of tumor tissue for exploratory biomarker studies.

6.2.3 Exploratory Correlative Studies

Tissues collected for exploratory correlates may be analyzed for immunological features using platforms included, but no limited to immunohistochemistry (IHC) for T cells (CD3, CD4, CD8, CD68). Molecular analytes (e.g. DNA, m RNA, protein) may be extracted as available tissue allows and characterized using a variety of analytic platforms, or the most efficacious method for a particular analyte at the time of analysis including whole transcriptomic profiling, RNASeg, Nanostring, Reverse Phase Protein Array, and next generation sequencing.

6.2.4 Study Completion or Early Discontinuation Visit

At the time of study early withdrawal, the reason for early withdrawal and any new or continuing adverse events should be documented. A concomitant medication assessment will also be performed.

6.2.5 Study Drug Discontinuation

If study drug administration is discontinued, the reason for discontinuation will be recorded.

6.3 Details of Procedures

6.3.1 Study Materials

Bristol-Myers Squibb (BMS) will provide nivolumab and ipilimumab at no cost for this study.

6.3.2 Safety Assessments

All patients who receive at least one dose of treatment will be considered evaluable for safety parameters. Additionally, any occurrence of non-SAE or SAE from time of consent forward, up to and including follow-up visits, will be reported. See Section 8: Adverse Event Reporting.

6.4 Criteria for Evaluation

6.4.1 Safety Evaluation

Safety will be evaluated for all treated patients using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (http://ctep.cancer.gov). Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, physical examinations, and clinical laboratory tests.

6.4.2 Efficacy Evaluation

All efficacy evaluations will be conducted by the investigator or their designee using the response criteria established by the World Health Organization (WHO). All subject's results will documented in the subject's eCRF.

6.4.2.a Definition of Measurable and Non-Measurable Lesions

- **Measurable Lesions** are lesions that can be accurately measured in two perpendicular diameters, with at least one diameter ≥ 20 mm and the other dimension ≥ 10 mm (10 mm x 10 mm for spiral CT). The area will be defined as the product of the largest diameter with its perpendicular. Skin lesions can be considered measurable.
- **Non-Measurable (evaluable) Lesions** are all other lesions, including unidimensionally measurable disease and small lesions (lesions without at least one diameter ≥ 20 mm), and any of the following:
  - Lesions occurring in a previously irradiated area (unless they are documented as new lesions since the completion of radiation therapy), bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitis cutis/pulmonis, abdominal masses that are not pathologically/cytologically confirmed and followed by imaging techniques and cystic lesions.
  - All measurable and non-measurable lesions should be measured at screening and at the defined tumor assessment timepoints (see Section 5, Table 2). Extra assessments may be performed, as clinically indicated, if there is a suspicion of progression.

6.4.2.b Definition of Index/Non-Index Lesions

All measurable lesions, up to a maximum of **five lesions per organ** and **ten lesions in total,** should be identified as *index* lesions to be measured and recorded on the medical record at Screening. The *index* lesions should be representative of all involved organs. In addition, *index* lesions should be selected based on their size (lesions with the longest diameters), their suitability for accurate repeat assessment by imaging techniques, and how

representative they are of the patient's tumor burden. At Screening, a sum of the products of diameters (SPD) for all *index* lesions will be calculated and considered the baseline sum of the products of diameters. Response criteria to be followed are listed below. The baseline sum will be used as the reference point to determine the objective tumor response of the *index* lesions at tumor assessment (TA).

Measurable lesions, other than *index* lesions, and all sites of non-measurable disease, will be identified as *non-index* lesions. *Non-index* lesions will be recorded on the medical record and should be evaluated at the same assessment time points as the *index* lesions. In subsequent assessments, *non-index* lesions will be recorded as "stable or decreased disease," "absent," or "progression."

6.4.3 Definition of Tumor Response Using irRC

The sum of the products of diameters at tumor assessment using the immune-related response criteria (irRC) for progressive disease incorporates the contribution of new measurable lesions. Each net Percentage Change in Tumor Burden per assessment using irRC criteria accounts for the size and growth kinetics of both old and new lesions as they appear.

6.4.3.a Definition of Index Lesions Response Using irRC

- **irComplete Response (irCR):** Complete disappearance of all *index* lesions. This category encompasses exactly the same subjects as "CR" by the mWHO criteria.
- **irPartial Response (irPR):** Decrease, relative to baseline, of 50% or greater in the sum of the products of the two largest perpendicular diameters of all *index* and all new measurable lesions (ie., Percentage Change in Tumor Burden). Note: the appearance of new measurable lesions is factored into the overall tumor burden, but does not automatically qualify as progressive disease until the SPD increases by ≥25% when compared to SPD at nadir.
- **irStable Disease (irSD):** Does not meet criteria for irCR or irPR, in the absence of progressive disease.
- **irProgressive Disease (irPD):** At least 25% increase Percentage Change in Tumor Burden (i.e., taking sum of the products of all *index* lesions and any new lesions) when compared to SPD at nadir.

6.4.3.b Definition of Non-Index Lesions Response Using irRC

- **irComplete Response (irCR):** Complete disappearance of all *non-index* lesions. This category encompasses exactly the same subjects as "CR" by the mWHO criteria.
- **irPartial Response (irPR) or irStable Disease (irSD):** *non-index* lesion(s) are not considered in the definition of PR, these terms do not apply.

- **irProgressive Disease (irPD):** Increases in number or size of *non-index* lesion(s) does not constitute progressive disease unless/until the Percentage Change in Tumor Burden increases by 25% (i.e., the SPD at nadir of the index lesions increases by the required amount).

6.4.3.c Impact of New Lesions on irRC

New lesions in and by themselves do not qualify as progressive disease. However their contribution to total tumor burden is included in the SPD which in turn feeds into the irRC criteria for tumor response. Therefore, new non-measurable lesions will not discontinue any subject from the study.

6.4.3.d Definition of Overall Response Using irRC

Overall response using irRC will be based on these criteria:

- **Immune-Related Complete Response (irCR):** Complete disappearance of *all* tumor lesions (index and nonindex together with no new measurable/unmeasurable lesions) for at least 4 weeks from the date of documentation of complete response.
- **Immune-Related Partial Response (irPR):** The sum of the products of the two largest perpendicular diameters of all index lesions is measured and captured as the SPD baseline. At each subsequent tumor assessment, the sum of the products of the two largest perpendicular diameters of all index lesions and of new measurable lesions are added together to provide the Immune Response Sum of Product Diameters (irSPD). A decrease, relative to baseline of the irSPD compared to the previous SPD baseline, of 50% or greater is considered an immune Partial Response (irPR).
- **Immune-Related Stable Disease (irSD):** irSD is defined as the failure to meet criteria for immune complete response or immune partial response, in the absence of progressive disease.
- **Immune-Related Progressive Disease (irPD):** It is recommended in difficult cases to confirm PD by serial imaging. Any of the following will constitute progressive disease:
  - At least 25% increase in the sum of the products of all index lesions over baseline SPD calculated for the index lesions.
  - At least a 25% increase in the sum of the products of all index lesions and new measurable lesions (irSPD) over the baseline SPD calculated for the index lesions.

Table 11: Immune-Related Response Criteria Definitions

Index Lesion Definition	Non-Index Lesion Definition	New Measurable Lesions	New Unmeasurable Lesions	Percent change in tumor burden (including measurable new lesions when present)	Overall irRC Response
Complete Response	Complete Response	No	No	-100%	irCR
Partial Response	Any	Any	Any	≥ -50%	irPR
				<-50% to <+25%	irSD
				>+25%	irPD
Stable Disease	Any	Any	Any	<-50% to <+25%	irSD
				>+25%	irPD
Progressive Disease	Any	Any	Any	≥+25%	irPD

6.4.3.e Immune-Related Best Overall Response Using irRC (irBOR)

irBOR is the best confirmed irRC overall response over the study as a whole, recorded between the date of first dose until the last tumor assessment before subsequent therapy (except for local palliative radiotherapy for painful bone lesions) for the individual subject in the study. For the assessment of irBOR, all available assessments per subject are considered.

irCR or irPR determinations included in the irBOR assessment must be confirmed by a second (confirmatory) evaluation meeting the criteria for response and performed no less than 4 weeks after the criteria for response are first met.

For metastatic patients, imaging of the chest, abdomen and pelvis is required at screening (ie, baseline) and at each tumor assessment visit, regardless of the location of known metastases. Refer to Section 6.1 Time and Events Schedule for further information. Similar methods of tumor assessment and similar techniques must be used to characterize each identified and reported lesion at screening and during subsequent tumor assessments. Imaging-based evaluation is preferred to clinical examination. For adjuvant patients, imaging of the chest, abdomen and pelvis is required at baseline and at Week 24 (+/- 7 days) and every 6 months thereafter (+/- 7 days) until removal from or completion of study.

6.4.4 Response Endpoints

Nivolumab and ipilimumab are expected to trigger immune-mediated responses, which require activation of the immune system prior to the observation of clinical responses. Such immune activation may take weeks to months to be evident. Some patients may have objective volume increase of tumor lesions or other disease parameters (based on study indication, ie, hematologic malignancies) within 12 weeks following the start of ipilimumab dosing. Such patients may not have had sufficient time to develop the required immune activation or, in some patients, tumor volume or other disease parameter increases may represent infiltration of lymphocytes into the original tumor or blood. In conventional studies, such tumor volume or relevant laboratory parameter increases during the first 12 weeks of the study would constitute PD and lead to discontinuation of imaging to detect response, thus disregarding the potential for subsequent immune-mediated clinical response.

Therefore, patients with tumor volume increase detected or lack of laboratory parameter response documentation prior to week 12 but without rapid clinical deterioration should continue to be treated and clinically observed with a stringent imaging schedule to allow detection of a subsequent tumor response. This will improve the overall assessment of the clinical activity or ipilimumab and more likely capture its true potential to induce clinical responses. Tumor assessments will be made using modified WHO criteria.

7 INVESTIGATIONAL PRODUCT

The investigational product is defined as a pharmaceutical form of an active ingredient being tested as a reference in the study,. In this study, the investigational products are nivolumab and ipilimumab.

Other medications used in the study as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, are considered noninvestigational products. In this protocol, noninvestigational product(s) is/are: acetaminophen, diphenhydramine, hydroxyzine, anti-emetics including but not limited to ondansetron, promethazine, prochlorperazine, and corticosteroids.

7.1 Identification

	Product Description: Treatment Period

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
BMS-936558-01 Solution for Injection(a)	100 mg (10 mg/mL)	10 mL vial/ Open-label	10 vials per carton/ Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect form light and freezing
Ipilimumab Solution for Injection	50 mg/10 mL and 200 mg/40 mL (5 mg/mL)	40 mL vial/Open-label	4 vials per carton/Open-label	Clear, colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect from light and freezing.

(a) Nivolumab is labeled as BMS-936558-01 Solution for Injection

7.2 Packaging and Labeling

BMS will provide drugs at no cost for this study. Nivolumab and ipilimumab will be provided in open-label containers. The labels will contain the protocol prefix, batch number, content, storage conditions, and dispensing instructions along with the Investigational New Drug (IND) caution statement.

7.3 Storage, Handling, and Dispensing

7.3.1 Storage

Both drugs must be stored in a secure area according to local regulations. The investigator must ensure that they are stored at a temperature ≥ 2°C and ≤ 8°C.

7.3.2 Handling and Disposal

As with all injectable drugs, care should be taken when handling and preparing nivolumab or ipilimumab. Whenever possible, nivolumab or ipilimumab should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents applying aseptic technique. Latex gloves are required. If drug concentrate or solution comes in contact with skin or mucosa, immediately and thoroughly wash with soap and water. After final drug reconciliation, unused drug solution should be disposed at the site following procedures for the disposal of anticancer drugs.

Please refer to the current version of the Investigator Brochure and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information for BMS-936558 (nivolumab) and ipilimumab.

7.3.3 Dispensing

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

7.4 Drug Ordering and Accountability

7.4.1 Initial Orders

Following submission and approval of the required regulatory documents, drug supply may be ordered from BMS. Investigators must complete a Drug Request Form. This order form will be provided by the BMS protocol manager.

Ipilimumab vials (40 mL) are shipped in quantities of five. The initial order should be limited to 25 vials (5 cartons of 5 vials each). Allow 5 business days for shipment of drug from BMS receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. All product will be shipped via Federal Express in a temperature-controlled container. Shipments will be made from Fisher Clinical Services on Monday through Thursday for delivery onsite Tuesday through Friday. There will be no weekend or holiday delivery of drugs.

It is possible that sites may have more than one nivolumab and/or ipilimumab clinical study ongoing at the same time. **It is imperative that only product designated for this protocol number be used for this study.** To help segregate product for this study from other

investigational or marketed product, stickers bearing the BMS protocol number will be provided and should be affixed to the front of the outer carton just above the company names so as not to obscure any marking.

7.4.2 Re-Supply

Reorders should be emailed directly to Fisher Clinical Services (distribution.allentown@thermofisher.com) for shipment within 5 business days. When assessing need for resupply, institutions should keep in mind the number of vials used per treatment dose, and that shipments may take 5 business days from BMS receipt of request. Drug is not patient specific. Be sure to check with your pharmacy regarding existing investigational stock to assure optimal use of drug on hand.

7.5 Investigational Product Accountability

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

- Amount received and placed in storage area.
- Amount currently in storage area.
- Label ID number or batch number and use date or expiry date.
- Dates and initials of person responsible for each ipilimumab inventory entry/movement.
- Amount dispensed to and returned by each subject, including unique subject identifiers.
- Amount transferred to another area/site for dispensing or storage.
- Non-study disposition (e.g., lost, wasted, broken).
- Amount destroyed at study site.

7.6 Investigational Product Destruction

If investigational product is to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for disposal and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures. BMS agrees to drug disposal and destruction per MDACC institutional policy. Appropriate records of the disposal must be maintained.

8 ADVERSE EVENT REPORTING

8.1 Collection of Safety Information

Adverse events will be documented in the medical record and entered into PDMS/CORe according to the following guidelines…

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. Any Adverse Events considered common for this disease process (uveal melanoma, metastatic uveal melanoma) or related to disease will be captured at the discretion of the attending MD.

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

8.1.1 Definition of Serious Adverse Events

A ***serious AE (SAE)*** is any untoward medical occurrence that at <u>any dose:</u>

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

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

Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- **Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.**
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB and BMS in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

8.1.2 Definition of Nonserious Adverse Event

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

8.2 Assignment of Adverse Event Intensity and Relationship to Investigational Product

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.

8.3 Collection and Reporting

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- **Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.**

- **Serious adverse events will be captured from the time of the first protocol-specific intervention, until 100 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.**
- **Additionally, any serious adverse events that occur after the 100 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.**

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Investigator Communication with Supporting Companies:

All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB and BMS in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

8.3.1 Serious Adverse Events

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 related to the investigational product or protocol-specified procedure.

All SAEs whether related or unrelated to the ipilimumab, must be immediately reported to BMS (by the investigator or designee) within 24 hours of becoming aware of the event. If

only limited information is initially available, follow-up reports are required. The original SAE form must be kept on file at the study site.

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 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. The MDACC "Internal SAE Report Form for Prompt Reporting" will be used for reporting to the IRB Office and to BMS.

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

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. 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.

The adverse events will be recorded in PDMS according to the following guidelines. The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

Recommended Adverse Event Recording Guidelines					
Attribution	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

8.3.2 Reporting to FDA

Serious adverse events will be forwarded to FDA by the IND Sponsor (Project Manager, IND office) according to 21 CFR 312.32.

8.3.3 Handling of Expedited Safety Reports

In accordance with local regulations, BMS will notify investigators of all SAEs that are suspected (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).

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

8.3.4 Nonserious Adverse Events

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

All identified nonserious AEs must be recorded and described in the medical record.

8.3.5 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 ipilimumab. 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 ipilimumab and must not be enrolled in the study.

Women of childbearing potential (WOCBP) and fertile men with partners of childbearing potential must be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 26 weeks after the last dose of investigational product.

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. 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, 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.

8.3.6 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 in the medical record.

9. Statistical Methodology

The trial originally used Simon's two-stage design to target a response rate of 15% vs. a historical rate of 5%. A total of 30 patients were to have been enrolled in the first stage, and if at least two had responded, an additional 22 patients would have been enrolled in the second stage. Given advancements in melanoma treatment, a 15% response rate is no longer considered interesting, and in 2017, the study has been changed to a single-stage design targeting a response rate of 20%. A total of 23 evaluable patients have been enrolled at the time of this change.

A single-stage trial design will be employed to enroll patients on the metastatic arm with the following assumptions:

- Type I error rate of 5%, power of 80%
- Null hypothesis of 5% response rate
- Alternate hypothesis of 20% response rate
- Response will be defined as those patients who achieve RECIST CR + PR.
- Accounting for attrition (inevaluable patients, 25%) and screen fails (5%), up to 39 patients are needed to achieve a target enrollment of 27 evaluable patients.
- If at least 4 of the 27 patients are responders, the null hypothesis of a 5% response rate will be rejected in favor of the alternative hypothesis.

If the true probability of response if 5%, this design has a 4.4% chance of incorrectly concluding that it is effective. If the true probability of response is 20%, the design has an 18.2 % chance of incorrectly concluding that it is not effective.

Safety Analysis at baseline, a medical history will be obtained to capture relevant underlying conditions. The baseline examinations should include weight, height, ECOG Performance Status, BP, HR, temperature and oxygen saturation by pulse oximetry at rest and after exertion and should be performed as noted in Table 10 Notes Baseline signs and symptoms are those that are assessed within 14 days prior to randomization. Concomitant medications will be collected from within 14 days prior to randomization through the study treatment period.

Baseline local laboratory assessments should be done within 14 days prior to treatment to include: CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH, Free T4, Free T3, and Hep B and C testing only as clinically indicated (HBV sAg, HCV Ab or HCV RNA). Pregnancy testing for WOCBP (done locally) must be performed within 24 hours prior to the initial administration of study drug at baseline and then within 24 hours of dosing at Week 1 and Week 4 of cycle 1 and , 3 and Week 1 and Week 5 starting from cycle 5 and at the safety follow up visits.

Subjects will be evaluated for safety if they have received any study drug. Toxicity assessments will be continuous during the treatment phase. During the safety follow-up phase, toxicity assessments should be done in person. Once subjects reach the survival follow-up phase either in person or documented telephone calls to assess the subject's status are acceptable.

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

On-study weight and ECOG Performance status should be assessed on Day 1 of Weeks 1, 3, 4 and 5 during cycles 1 and 2 (except Cycle 1 Day 1) and Day 1 of Weeks 1, 3 and 5 starting from Cycle 3 and vital signs should be assessed at each on-study visit (except Cycle 1 Day 1). Vital signs should also be taken as per institutional standard of care prior to, during and after dosing. Oxygen saturation by pulse oximetry at rest and after exertion should be assessed at each on-study visit prior to dosing. The start and stop time of the

nivolumab infusion should be documented. Physical examinations are to be performed as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse event page.

On study local laboratory assessments should be done within 72 hours of dosing to include; CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH with Free T4, Free T3 on Day 1 of Weeks 1, 4, 7, 10 and 13, then every 12 weeks. Additional measures including non-study required laboratory tests should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug inducted liver enzyme elevations) will be monitored during the follow-up phase via on site/local labs until all study drug related toxicities resolve, return to baseline or are deemed irreversible.

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

Some of the previously referred to assessments may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

9.1 Efficacy Analysis

Study evaluations will take place in accordance with the flow charts in Section 5.1. Baseline assessments should be performed within 28 days prior to randomization utilizing CT or MRI. In addition to chest, abdomen, pelvis, and brain, all known sites of disease should be assessed at baseline. Subsequent assessments should include chest, abdomen, and pelvis, and all known sites of disease and should use the same imaging method as was used at baseline. Subjects will be evaluated for tumor response beginning 12 weeks (+/ 1 week) from randomization and continuing every 6 weeks (± 1 week) for the first 12 months from randomization and every 12 weeks (+/ 1 week) thereafter, until disease progression is documented or treatment is discontinued (whichever occurs later). Tumor assessments for ongoing study treatment decisions will be completed by the investigator using RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 criteria.

9.2 Secondary Analysis

We will use the Kaplan-Meier method to assess the distribution of time-to-event variables, including overall survival, progression-free survival, and landmark analysis where possible. We will use Cox proportional hazards regression methodology to model the association between survival parameters and clinical, disease, and demographic factors of interest, including data from the immune biomarker studies.

10. ADMINISTRATIVE SECTION

10.1 Compliance with the Protocol and Protocol Revisions

The study must be conducted as described in the final approved protocol. Documentation of approval signed by the chairperson or designee of the IRB(s) must be sent to your BMS protocol manager.

All revisions (protocol amendments, administrative letters, and changes to the informed consent) must be submitted to your BMS protocol manager. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB of an Amendment, except where necessary to eliminate an immediate hazard(s) to study patients.

See also 21CFR for definitions of amendment and requirements.

10.2 Informed Consent

Investigators must ensure that subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representative, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. Freely given written informed consent must be obtained from every subject or, in those situations where consent cannot be given by subjects, their legally acceptable representative, prior to clinical study participation, including informed consent for any screening procedures conducted to establish subject eligibility for the study.

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

10.3 Records and Reports

Case histories will be collected and recorded on all study patients and all data will be entered in the computerized Protocol Data Management System (PDMS) of the Division of Medicine at MD Anderson Cancer Center. Patients must be registered in PDMS before a cycle of therapy can be given. A brief explanation for required but missing data should be recorded as a comment. The investigator is required to retain, in a confidential manner, the data pertinent to the study for the duration of the study or the maximum period required by applicable regulations and guidelines or institutional procedures. If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator or IRB). Documentation of such transfer must be provided to BMS.

10.4 Good Clinical Practice

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

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS and to the IND Sponsor-MD Anderson Cancer Center (Office of Research Education and Regulatory Management) immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s). This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

Systems with procedures that ensure the quality of every aspect of the study will be implemented.

10.5 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

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

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

10.6 Records Retention

The investigator must retain investigational product disposition records, source documents, and case histories designed to record all observations and other data pertinent to the investigation (e.g. medical record) for the maximum period required by applicable regulations and guidelines, or Institution procedures.

If the investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IRB). Documentation of such transfer must be provided to BMS.

APPENDIX A: MANAGEMENT ALGORITHMS

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

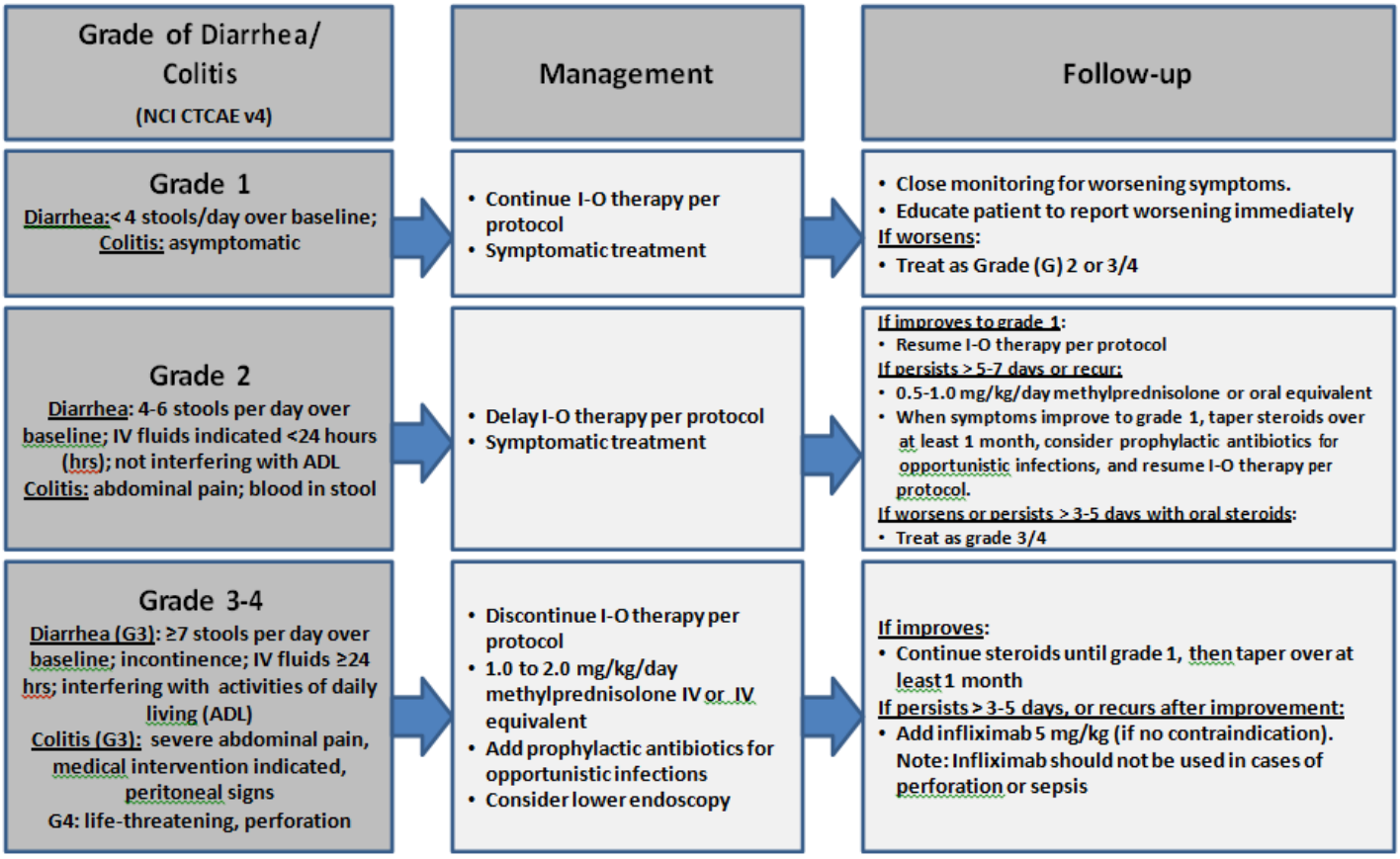
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

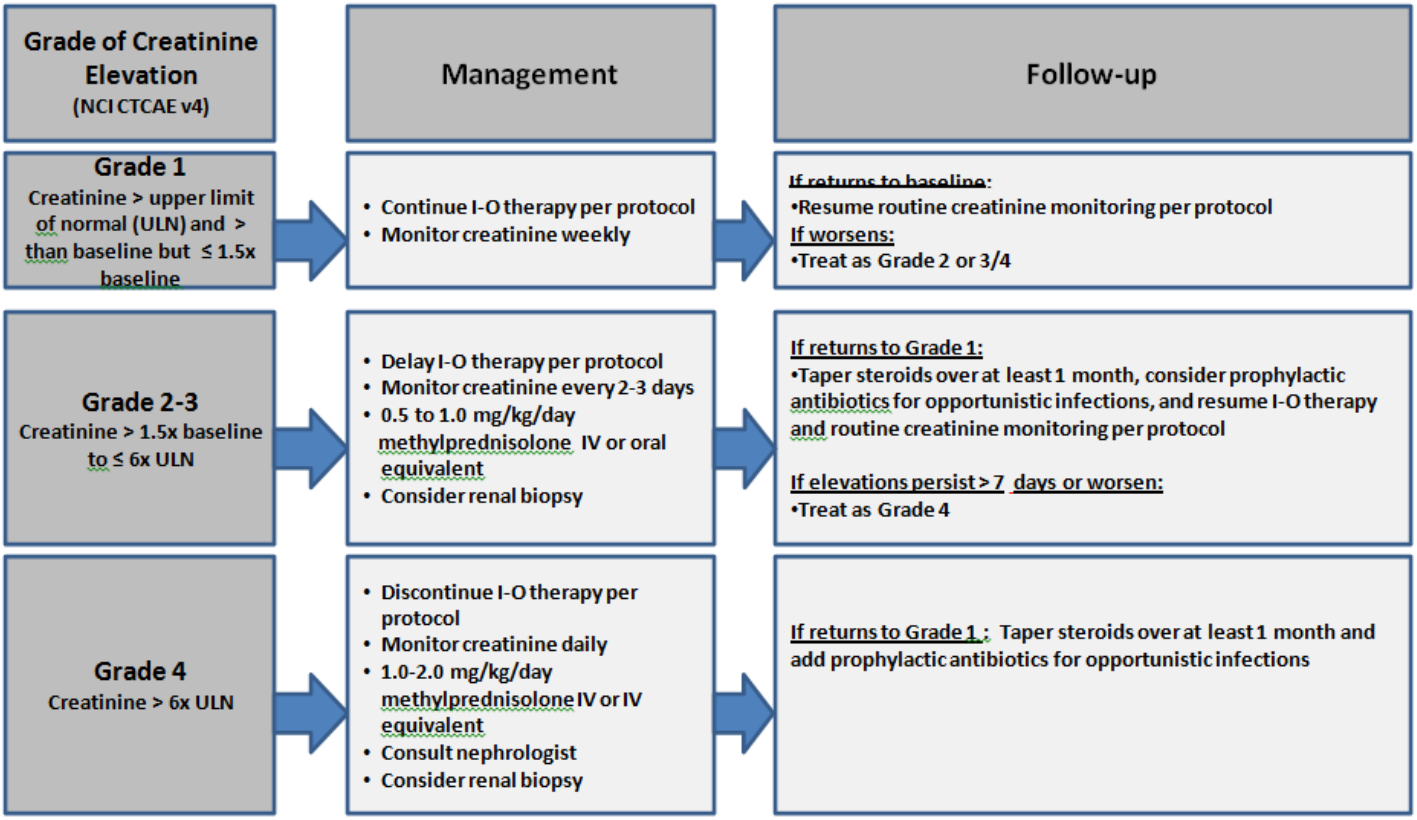
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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

Renal Adverse Event Management Algorithm

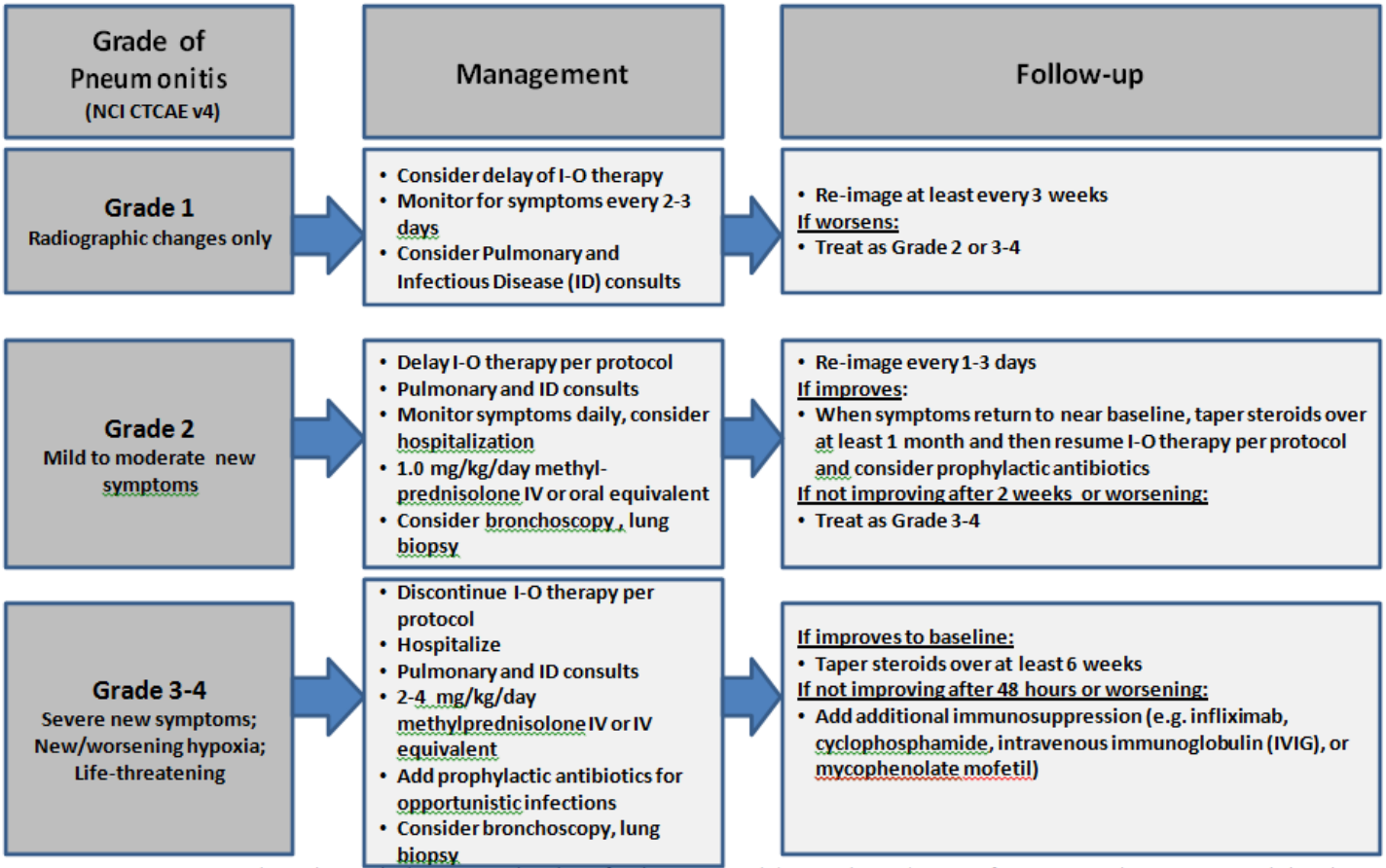
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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

Pulmonary Adverse Event Management Algorithm

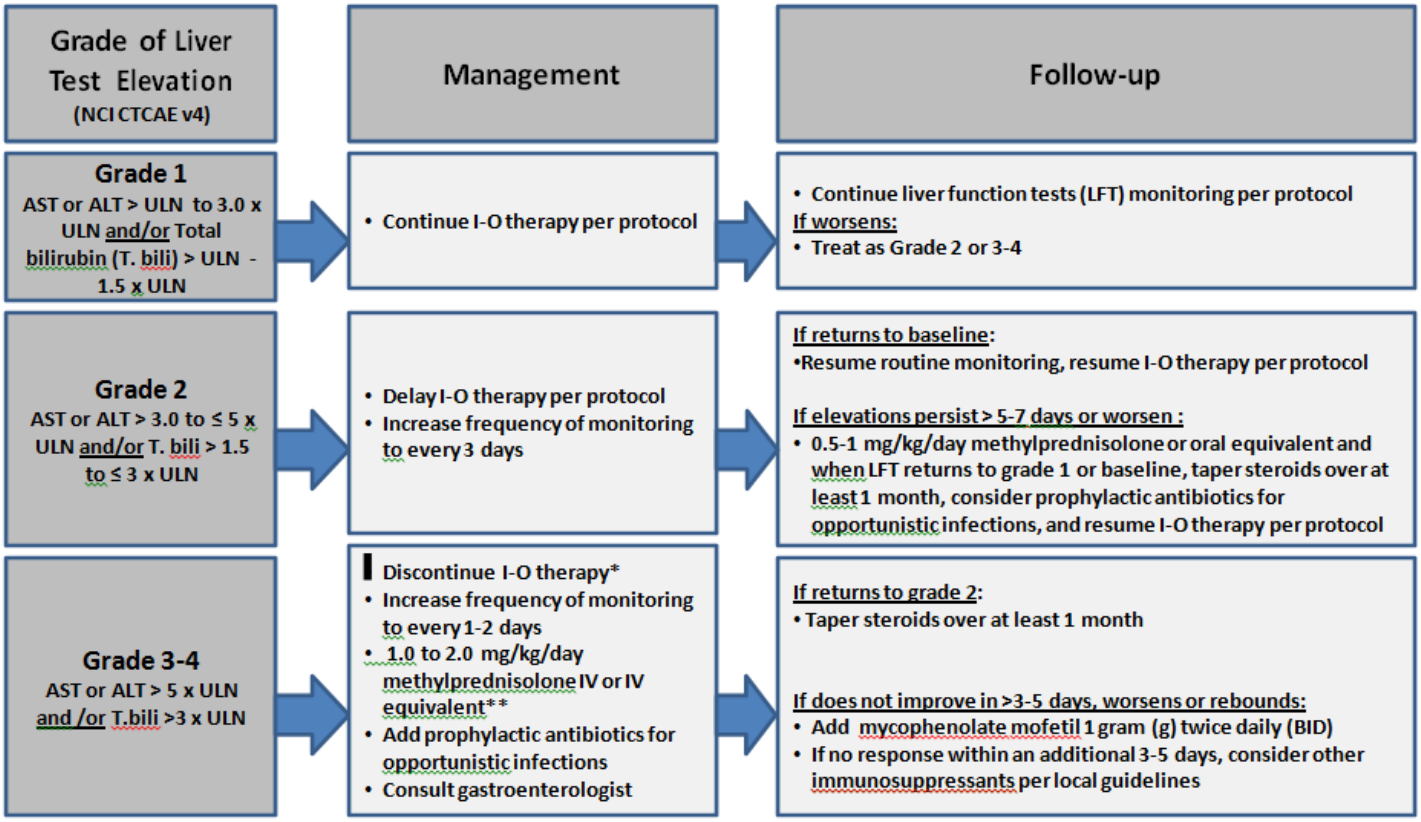
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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

Hepatic Adverse Event Management Algorithm

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



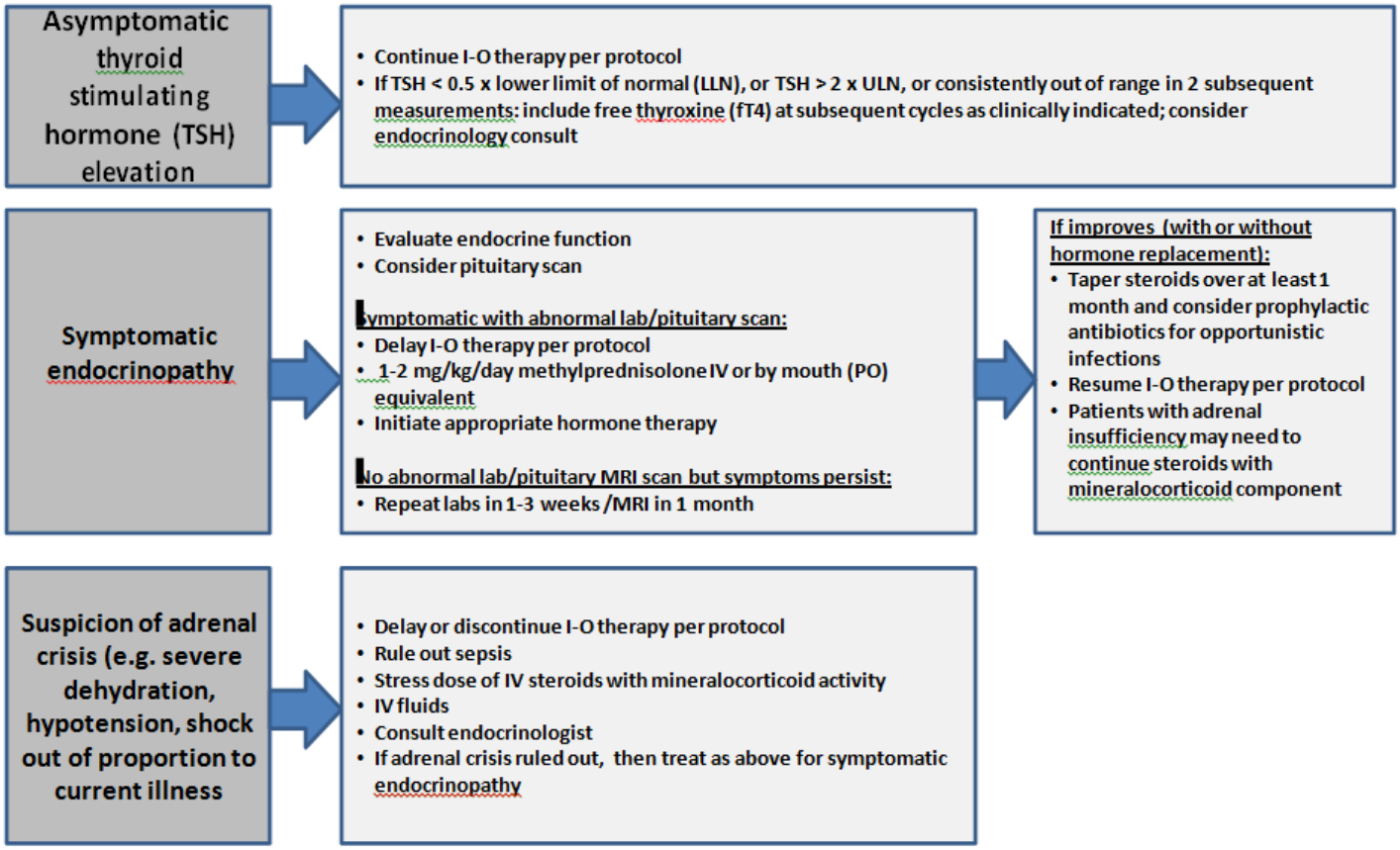
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

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

Endocrinopathy Management Algorithm

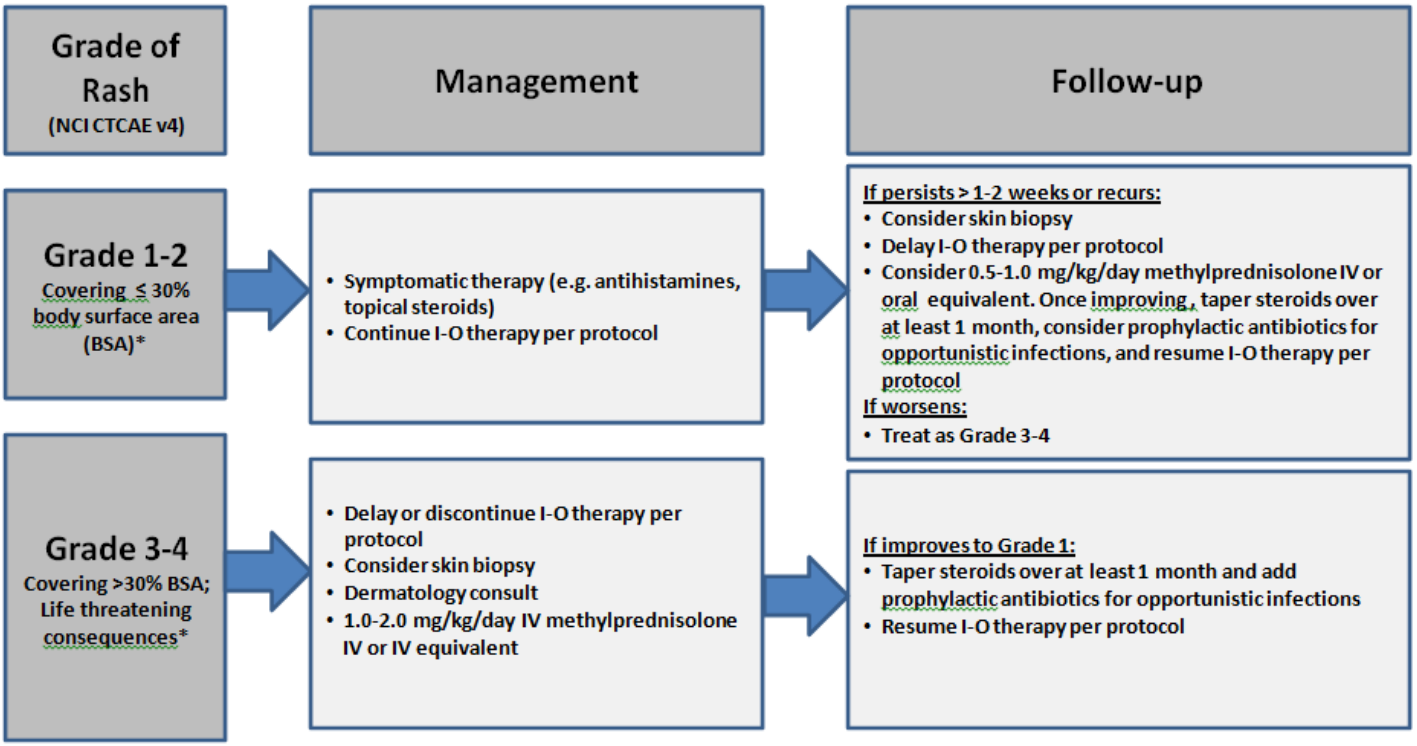
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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

Skin Adverse Event Management Algorithm

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

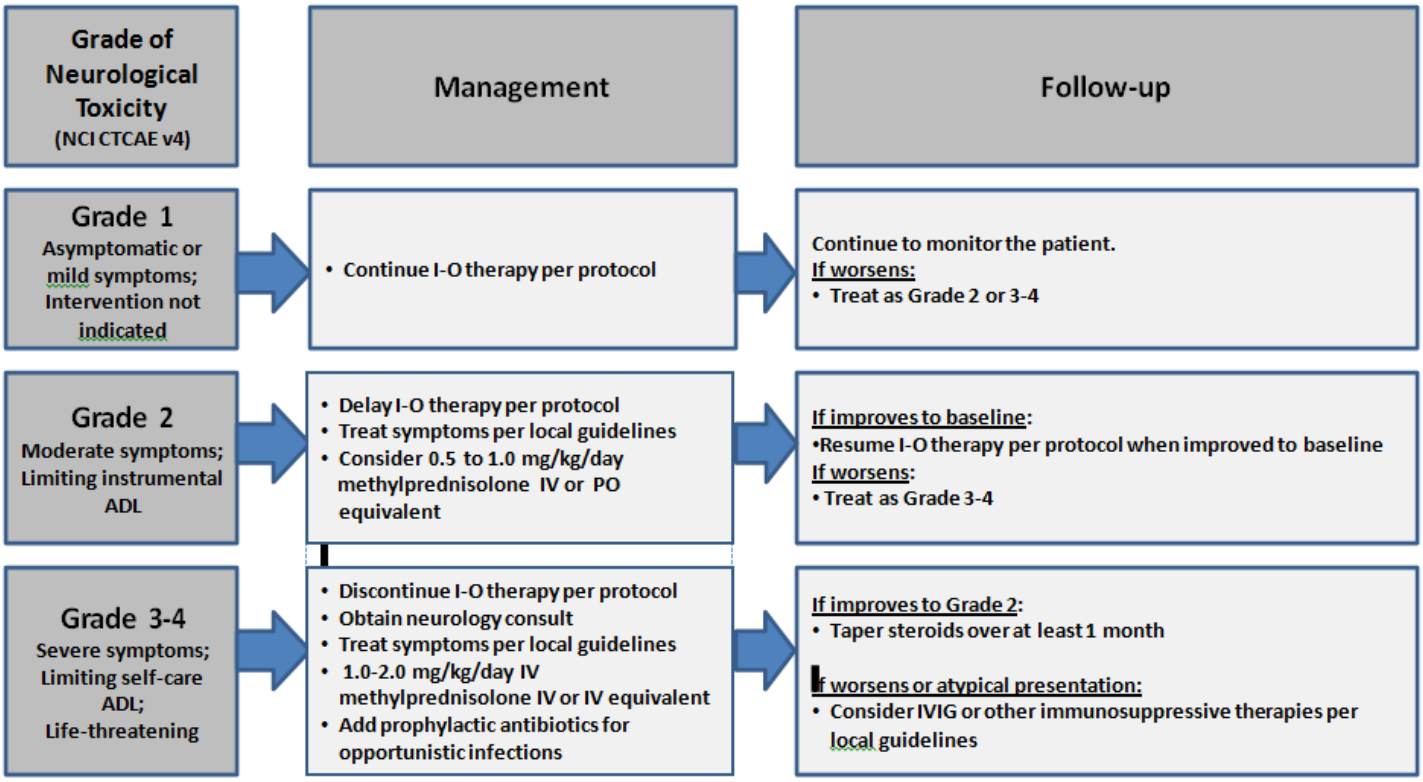


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

*Refer to NCI CTCAE v4 for term-specific grading criteria.

Neurological Adverse Event Management Algorithm

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



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

LIST OF ABBREVIATIONS

Abbreviation	Term
ANC	Absolute Neutrophil Count
APC	Antigen-presenting cell
BID	Twice a Day
BMS	Bristol-Myers Squibb Company
BORR	Best Objective Response Rate
CTLA4	cytotoxic T lymphocyte antigen 4
CT scan	Computed Axial Tomography scan
CBC	Complete Blood Count
CR	Complete Response
DLT	Dose Limiting Toxicity
DMFS	Distant metastasis-free survival
DSMB	Data Safety Monitoring Board
ECOG PS	Eastern Cooperative Oncology Group Performance Status
irAE	Immune-related adverse events
HIPAA	Health Insurance Portability and Accountability Act
IMAE	Immune-mediated adverse events
IRB	Institutional Review Board
irRC	Immune-related response criteria
irCR	Immune-related complete response
irPD	Immune-related progressive dose
FPFV	First patient first visit
LPFV	Last patient first visit
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
OS	Overall survival
PD	Progressive Disease
PFS	Progression Free Survival
PO	By Mouth
PR	Partial Response
QD	Once Daily
SAE	Serious Adverse Event
SPD	Sum of the products diameters
SD	Stable Disease
TNM Staging	Tumor, Node and Metastasis Staging

REFERENCES

1. Lenschow D.J., et al., CD28/B7 system of T cell costimulation. Ann Rev Immunol, 1996. 14:233-258.

2. Schwartz R.H. Costimulation of T lymphoctyes: the role of CD28, CTLA4, and B7/BB1 in interleukin-2 production and immunotherapy. Cell, 1992. 71(7): 1065-1068.

3. Chen L.S., et al., Costimulation of antitumor immunity by the B7 counterreceptor for the T lymphocyte molecules CD28 and CTLA-4. Cell, 1992. 71(7):1093-1102.

4. Townsend S.E., et al., Tumor rejection after direct costimulation of CD8+ T cells by B7-transfected melanoma cells. Science, 1993. 259(5093):368-370.

5. Townsend S.E., et al., Specificity and longevity of antitumor immune responses induced by B7-transfected tumors. Cancer Res, 1994. 54(24):6477-6483.

6. Allison J.P., et al., Manipulation of costimulatory signals to enhance antitumor t cell responses. Curr Opin Immunol, 1995. 7(5):682-686.

7. Linsley P.S., et al., CTLA-4 is a second receptor for the B cell activation antigen B7. J Exp Med, 1991. 174(3):561-569.

8. Thompson C.B., and Allison J.P. The emerging role of CTLA-4 as an immune attenuator. Immunity, 1997. 7(4): p.445-450.

9. Walunas T.L., et al., CTLA-4 can function as a negative regulator of T cell activation. Immunity, 1994. 1(5): p. 405-413.

10. Kearney E.R., et al., Antigen-dependent clonal expansion of a trace population of antigen-specific CD4+ T cells in vivo is dependent on CD28 costimulation and inhibited by CTLA-4. J Immunol, 1995. 155(3): 1032-1036.

11. Krummel M.F. and Allison J.P. CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation. J Exp Med 1995; 182(2): 459-465.

12. Krummel M.F., et al., Superantigen responses and co-stimulation: CD28 and CTLA-4 have opposing effects on T cell expansion in vitro and in vivo. Int Immunol, 1996. 8(4): 519-523.

13. Tivol E.A., et al., Loss of CTLA-4 leads to massive lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4. Immunity, 1995. 3(5): 541-547.

14. Waterhouse P. et al., Lymphoproliferative disorders with early lethality in mice deficient in CTLA-4. Science, 1995. 270(5238): 985-988.

15. Chambers C.A., et al., Lymphoproliferation in CTLA-4-deficient mice is mediated by costimulation-dependent activation of CD4+ T cells. Immunity, 1997, 7(6): 885-895.

16. Randomized, double-blind, placebo-controlled, Phase 2 study comparing the safety of ipilimumab administered with or without prophylactic oral budesoride (Entocort™ EC) in patients with unresectable stage III or IV malignant melanoma (Protocol CA184007). Bristol-Myers Squibb Research and Development; 2010. Document Control No. 930043852.

17. A multicenter, single arm Phase 2 study of MDX-010 (BMS-734016) monotherapy in patients with previously treated unresectable stage III or IV melanoma (Protocol CA184008). Bristol-Myers Squibb Research and Development; 2010. Document Control No. 930043858.

18. A randomized, double-blind, multicenter, Phase 2, fixed study of multiple dose of ipilimumab (MDX-010) monotherapy in patients with previously treated unresectable stage III or IV melanoma (Protocol CA184022). Bristol-Myers Squibb Research and Development; 2010. Document Control No. 9.0043860.

19. A randomized, double-blind multicenter study comparing MDX010-10 monotherapy, MDX-010 in combination with a melanoma peptide vaccine and melanoma vaccine monotherapy in HLA-A*201-postive patients with previously treated unresectable stage III or IV melanoma (Protocol MDX0102). Bristol-Myers Squibb Research and Development; 2010. Document Control No. 930043837.

20. An exploratory study to determine potential predictive markers of response and/or toxicity in patients with unresectable stage III or IV malignant melanoma randomized and treated with ipilimumab (MDX-010/BMS-734016) at two dose levels (Protocol CA184004). Bristol-Myers Squibb Research and Development; 2010. Document Control No. 930043855.

21. A randomized study comparing MDX-010 alone or in combination with DTIC in the treatment of patients with chemotherapy naive metastatic melanoma (Protocol

MDX01008). Bristol-Myers Squibb Research and Development; 3008. Document Control No. 930023182.

22. Interim report of a multicenter Phase 2 study to evaluate response to ipilimumab (BMS-734016) monotherapy in subjects with melanoma brain metastases (Protocol CA184042). Bristol-Myers Squibb Research and Development.
23. Collection of long-term outcome data for subjects who have previously participated in selected ipilimumab (MDX-010) studies in metastatic melanoma (Protocol MDX01028). Bristol-Myers Squibb Research and Development; 2009. Document Control No. 9300038451.
24. Ipilimumab Summary of Clinical Safety. Bristol-Myers Squibb Research and Development. 2010; Document Control No. 930043848.
25. Sato T., et al., The biology and management of uveal melanoma. Curr Oncol Rep, 2008. 10:431-8.
26. Singh A.D., et al., Metastatic uveal melanoma. Ophthalmol Clin North Am, 2005. 18:143-150.
27. Onken M.D., et al., A accurate, clinically feasible multi-gene expression assay for predicting metastasis in uveal melanoma. J Mol Diagn, 2010. 12:461-8.
28. Onken M.D., et al., Association between gene expression profile, proliferation and metastasis in uveal melanoma. Curr Eye Res, 2010. 35:857-63.
29. Shields C.L., et al., Metastasis of uveal melanoma millimeter-by-millimeter in 8033 consecutive eyes. Arch Ophthalmol, 2009. 127:989-98.
30. Shields C.L., et al., Prognosis of uveal melanoma in 500 cases using genetic testing of fine-needle aspiration biopsy specimens. Ophthalmology, 2011. 118 (2):396-401.
31. Eskelin S., et al., Tumor doubling times in metastatic malignant melanoma of the uvea: tumor progression before and after treatment. Ophthalmology, 2000. 107:1443-9.
32. Lane A.M., et al., Adjuvant interferon therapy for patients with uveal melanoma at high risk of metastasis. Ophthalmology, 2009. 116(11):2206-12.
33. Augsburger J.J., et al., Effectiveness of treatments for metastatic uveal melanoma. Am J Ophthalmol 2009. 148:119-27.