

Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012;366:2443-54. DOI: 10.1056/NEJMoa1200690.

Table of Contents for Protocols, Amendments, and Statistical Analysis Plan and Appendices

Document Type	Title	Date Issued	Page
Final Protocol	CA209003 Revised Protocol 05: A Phase 1, Open-label, Multicenter, Multidose, Dose-escalation Study of BMS-936558 (MDX- 1106) in Subjects with Selected Advanced or Recurrent Malignancies	08-25-2009	1
Original Protocol	MDX1106-03 Protocol: A Phase 1b, Open-label, Multicenter, Dose-escalation Study of MDX- 1106 in Subjects with Selected Advanced or Recurrent Malignancies	07-23-2008	144
Protocol Amendment	Amendment 05 of Protocol CA209003	01-23-2012	226
Protocol Amendment	Amendment 04 of Protocol CA209003	08-10-2010	231
Protocol Amendment	Amendment 03 of Protocol CA209003	02-08-2010	241
Protocol Amendment	Amendment 02 of Protocol MDX1106-03	08-25-2009	253
Protocol Amendment	Amendment 01 of Protocol MDX1106-03	09-19-2008	281
Statistical Analysis Plan	Statistical Analysis Plan for Clinical Study Report, A Phase 1 Open-label, Multicenter, Multidose, Dose-escalation Study of BMS- 936558 in Subjects with Selected Advanced or Recurrent Malignancies, Protocol CA209-003, Version 1.2	04-10-2012	310
Statistical Analysis Plan Appendix	Statistical Analysis Plan Appendix 1, Listing of PD1 PT for Adverse Events of Special Interest as of February 20, 2012	02-16-2012	343
Statistical Analysis Plan Appendix	Statistical Analysis Plan Appendix 2, Analysis of Safety Data, Reference to CT SOP 109	09-16-2010	392

Page: 1
Protocol Number: CA209003
(MDX1106-03)
Development Phase: Phase 1
IND Number: 100,052
Date: 25-Aug-2009
Revised Date: 23-Jan-2012

Clinical Protocol CA209003 (MDX1106-03)

A Phase 1, Open-label, Multicenter, Multidose, Dose-escalation Study of BMS-936558
(MDX-1106) in Subjects with Selected Advanced or Recurrent Malignancies

Revised Protocol Number: 05
Incorporates Amendment(s) 05, 04, 03, 02, 01, and Administrative Letter 01

Study Director/ Medical Monitor
Ashok Gupta, MBBS, MD, PhD
Medical Director, Discovery Medicine
Office Phone Number: +1-609-252-3464
Office Fax Number: +1-609-252-6816
Email: ashok.gupta@bms.com

24-hr Emergency Phone Number
+1-866-470-2267
International: +1-248-844-7390

Bristol-Myers Squibb Research and Development
Route 206 & Province Line Road
Lawrenceville, NJ 08543

This document is the confidential and proprietary information of Bristol-Myers Squibb Company and its global affiliates (BMS). By reviewing this document, you agree to keep it confidential and to use and disclose it solely for the purpose of assessing whether your organization will participate in and/or the performance of the proposed BMS-sponsored study. Any permitted disclosures will be made only on a confidential "need to know" basis within your organization or to your independent ethics committee(s). Any other use, copying, disclosure or dissemination of this information is strictly prohibited unless expressly authorized in writing by BMS. Any supplemental information (e.g., amendments) that may be added to this document is also confidential and proprietary to BMS and must be

kept in confidence in the same manner as the contents of this document. Any person who receives this document without due authorization from BMS is requested to return it to BMS or promptly destroy it. All other rights reserved.

Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

SYNOPSIS

TITLE

A Phase 1, Open-Label, Multicenter, Multidose, Dose-escalation Study of BMS-936558 (MDX-1106) in Subjects with Selected Advanced or Recurrent Malignancies

PROTOCOL NUMBER

CA209003 (MDX1106-03)

OBJECTIVES

The primary objective is to assess the safety and tolerability of multiple doses of BMS-936558 (MDX-1106) in subjects with selected advanced or recurrent malignancies. The malignancies include: metastatic castration-resistant prostate cancer (mCRPC), renal cell carcinoma (RCC), colorectal adenocarcinoma (CRC), malignant melanoma (MEL), and non-small cell lung cancer (NSCLC).

The secondary objectives are to: 1) assess the host immune response to BMS-936558 (MDX-1106) (immunogenicity); 2) characterize the pharmacokinetic profile of multiple doses of BMS-936558 (MDX-1106); 3) assess the preliminary efficacy of BMS-936558 (MDX-1106) monotherapy; 4) to characterize the dose response relationship in melanoma and in NSCLC; and 5) explore the effects of BMS-936558 (MDX-1106) on humoral and cellular immune responses to tumor antigens and recall responses to a panel of non-tumor antigens.

Exploratory objectives: 1) To explore potential predictive markers associated with BMS-936558 clinical activity based on levels of expression of PD-L1 in tumor specimens prior to treatment. 2) To investigate the immunomodulatory activity of BMS-936558 on selected immune cell populations and soluble factors in blood. 3) to characterize the level of PD-1 receptor occupancy by BMS-936558 in peripheral blood. 4) to assess the overall survival in subjects receiving BMS-936558.

OVERVIEW OF STUDY DESIGN

This is a Phase 1, open-label, multicenter, multidose, dose-escalation study of BMS-936558 (MDX-1106), a fully human monoclonal IgG4 antibody, targeting the Programmed Death-1 (PD-1) membrane receptor on T lymphocytes and other cells of the immune system.

The study will consist of 3 periods: Screening (up to 28 days), Treatment (up to 3 years of active therapy [up to a maximum of 2 years of initial treatment plus additional remaining period if re-initiation of study therapy occurs as outlined in section 3.5]), and Follow-up (up to 46 weeks). Each treatment cycle is comprised of 4 doses of study drug administered on Days 1, 15, 29, and 43 with a response assessment between Days 52 and 56. The response assessment must be completed before the first dose in the next cycle.

Subjects entering the follow-up period with ongoing disease control (ongoing CR, PR, or SD) may be permitted to reinitiate study therapy upon confirmed disease progression after discussion and agreement with the BMS Medical Monitor.

Following completion of the treatment and follow-up periods, all subjects will be followed for survival.

Dose Escalation

Three dose levels are planned: 1, 3, and 10 mg/kg (Note: the 0.1 mg/kg and 0.3 mg/kg dose levels were included as part of Amendment 4 to the protocol and did not impact the dose escalation plan or schedule that has been completed prior to Amendment 4). Subjects will be assigned to a dose level in the order of study entry. Initially, 3 subjects will be enrolled at the 1 mg/kg dose level. If no subject (0 of 3) in a dose cohort experiences a dose-limiting toxicity (DLT) during the first cycle, then the next dose cohort of

3 subjects will be enrolled at the next higher dose level. If 1 of 3 subjects in a dose cohort experiences a DLT during the first cycle, that cohort will be expanded to 6 subjects. Provided that no more than 1 of 6 subjects in the expanded dose cohort experiences a DLT within the first cycle, then the next dose cohort of 3 subjects will be enrolled at the next higher dose level. If ≥ 2 of up to 6 subjects in the 1 mg/kg dose cohort experiences a DLT during the first cycle, that cohort will have exceeded the maximum tolerated dose (MTD), defined as the highest dose studied at which no more than 1 of 6 subjects has experienced a DLT in Cycle 1, and a lower dose level (0.3 mg/kg) will be tested.

If ≥ 2 of up to 6 subjects in the 3 or 10 mg/kg dose cohort experience a DLT during the first cycle, that cohort will have exceeded the MTD, and the following will occur:

- If no subjects (0 of 3) experienced a DLT at the previously tolerated dose level, 3 additional subjects will be dosed at that dose level.
- If ≤ 1 of 6 subjects experienced a DLT at the previously tolerated lower dose level, an intermediate dose level will be tested. The planned intermediate dose levels will be 2 and 7 mg/kg for the 3 and 10 mg/kg cohorts, respectively.

If 2 or more delayed DLTs are noted within a dose escalation cohort, further accrual will be held pending safety analysis of the event, and will be restarted only with Investigator and Sponsor (Bristol-Myers Squibb [BMS])) approval at all sites (with FDA and Institutional Review Board [IRB] notification).

No dose escalations or de-escalations are permitted within each subject's treatment, with the exception of subjects with MEL enrolled in the 0.1 mg/kg or 0.3 mg/kg additional expansion cohorts who meet the criteria for dose escalation as outlined below; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous cycle. A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

Expansion Cohorts

To further characterize safety and efficacy, up to 14 expansion cohorts will be enrolled. Accrual to 7 expansion cohorts has completed; an additional 7 expansion cohorts as described below will be enrolled under Amendment 4. A total of 6 subjects must be enrolled at the MTD (or the highest dose studied where ≤ 1 of 6 subjects experiences a DLT if the MTD is not identified) and evaluated through the end of Cycle 1 before any new subject is dosed in the expansion cohorts. If none of the first 5 subjects have a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following enrollment of the sixth subject.

Up to 7 expansion cohorts will be enrolled (enrollment to these expansion cohorts has completed as noted in [Table 1](#)):

- a. Primary MTD expansion cohorts (5 cohorts): 1 (cohort) in each of the 5 disease indications at a tolerated dose chosen by the Sponsor that may be either the highest dose tested that does not exceed the MTD or a lower dose with evidence of study drug activity.
- b. Non-MTD melanoma expansion cohorts (2 cohorts): an additional 2 cohorts in subjects with MEL will also be enrolled at doses other than the primary expansion dose (such as 1 and 3 mg/kg if the primary expansion occurs at the 10 mg/kg dose level).

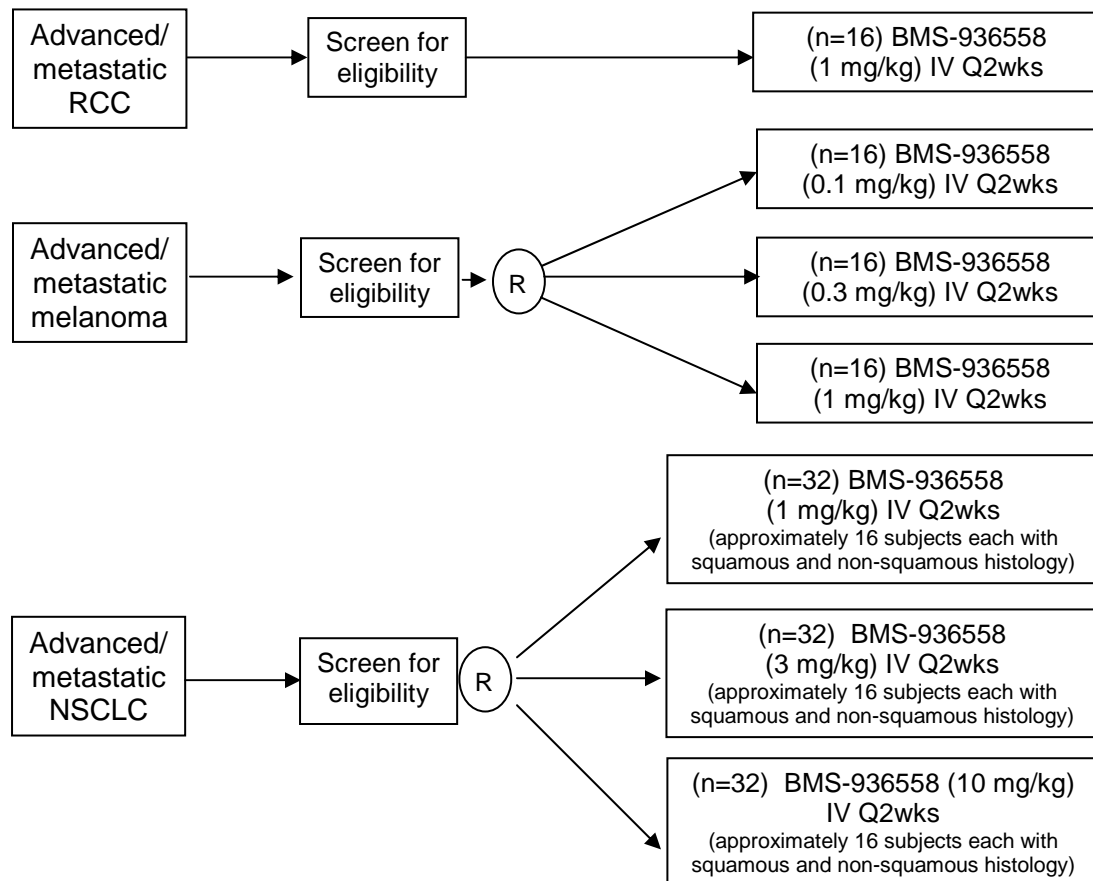
Table 1: Expansion Cohorts Completed Prior to Amendment 4

Tumor Type	Dose Level
Melanoma	1 mg/kg
Melanoma	3 mg/kg
Melanoma	10 mg/kg
Renal Cell Carcinoma	10 mg/kg
Non-small Cell Lung Cancer	10 mg/kg
Colorectal Cancer	10 mg/kg
Prostate Cancer	10 mg/kg

Under Amendment 4 the following 7 additional expansion cohorts will be enrolled (please see [Figure 1](#)):

- c. Additional NSCLC expansion cohorts (3 cohorts): an additional 3 cohorts in subjects with NSCLC will be enrolled; 1 cohort each at the 1 mg/kg, 3 mg/kg, and 10 mg/kg dose levels respectively.
- d. Additional MEL expansion cohorts (3 cohorts): an additional 3 cohorts in subjects with MEL will be enrolled: 1 cohort each at the 0.1 mg/kg, 0.3 mg/kg, and 1 mg/kg dose levels. Subjects enrolled at either the 0.1 mg/kg or 0.3 mg/kg dose levels may be permitted to dose escalate to the 1 mg/kg dose level upon confirmed and worsening PD within the first 2 treatment cycles and in consultation and agreement by the BMS Medical Monitor.
- e. Additional RCC expansion cohort (1 cohort): an additional cohort in subjects with RCC (clear cell histology) will be enrolled at the 1 mg/kg dose level.

Figure 1: Expansion Cohorts Added Under Protocol Amendment 4



In order to avoid allocation bias, subjects enrolled in the MEL and NSCLC expansion cohorts identified above (Figure 1) meeting all eligibility criteria will be randomly assigned to one of the three doses according to a computer-generated randomization schema prepared by a Randomization Coordinator with the Drug Supply Management Department of BMS Research and Development

In each cohort, a subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced (if they were withdrawn for early progression they will be counted in the per protocol estimate of overall efficacy).

Initiation of the Primary MTD Expansion Cohorts

A total of 6 subjects must be enrolled at the MTD (or the highest dose studied where ≤ 1 of 6 subjects experiences a DLT if the MTD is not identified) and evaluated through the end of Cycle 1 before any new subject is dosed in the expansion cohorts. If none of the first 5 subjects have a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following enrollment of the sixth subject.

The primary expansion cohorts will enroll subjects from each of the 5 tumor-specific indications: NSCLC, mCRPC, RCC, CRC, and MEL. Approximately 16 subjects (dose escalation plus expansion) will be enrolled in each of the cohorts at the dose chosen for the expansion.

Initiation of the Additional Non-MTD Melanoma Expansion Cohorts

In order to gain additional safety and tolerability information at other doses, as well as provide an initial estimate of efficacy, 2 additional cohorts of subjects with MEL will be enrolled. Approximately 16 subjects per cohort (including any subjects with MEL who were treated in the dose-escalation cohort corresponding to that dose level) will be treated at a dose other than the primary expansion dose (such as at the 1 and 3 mg/kg dose levels if the primary expansion occurs at 10 mg/kg). Enrollment to the first additional expansion cohort (ie, 1 mg/kg dose level) can begin at the lowest planned dose immediately at the time that the primary expansion opens and will accrue separately beginning from the lowest to the highest dose planned. Accrual to the next higher dose will begin immediately on completion of enrollment to the prior additional cohort.

Initiation of Additional Expansion Cohorts

In order to gain additional safety and tolerability information and preliminary assessment of efficacy in NSCLC, MEL, and RCC a total of 7 additional cohorts will be enrolled as outlined above. Approximately 16 subjects per cohort will be enrolled in the MEL and RCC cohorts. Approximately 32 subjects per cohort will be enrolled in the NSCLC cohorts. Approximately equal numbers of subjects with squamous histology and non-squamous histologies will be enrolled at each dose level. At each dose level, a minimum of 12 subjects will be enrolled in either of the 2 NSCLC histologic types.

Stopping Rules for the Expansion Cohorts

Enrollment may be held in any expansion cohort if the rate of DLTs is $\geq 33\%$ across all 5 indications at the primary expansion dose level, or in a specific indication if the rate of DLTs is $\geq 33\%$ after enrollment of the first 6 subjects in that indication (including subjects from the dose-escalation cohort at the expansion dose). The DLT rate for a dose level will be based on the cumulative number of subjects at that dose level. Enrollment of additional subjects will be held in a dose level where a $\geq 33\%$ DLT rate occurs and at any higher dose level enrolling at that point in time.

Subjects who are tolerating a study drug at a dose level that is being reviewed due to the occurrence of DLTs in another subject will not be automatically precluded from continued dosing during the safety review, and will be allowed to continue dosing for as long as tolerated unless directed otherwise as a result of the safety review. After safety analysis by the Investigators and BMS (with FDA and IRB notification), a decision will be made whether to resume enrollment and continue dosing at the current dose or initiate a new expansion cohort of 16 subjects in 1 or more indications at a lower dose.

For delayed DLTs, enrollment will be held and/or restarted using the same rules as that for DLTs.

Administration of Additional Treatment Cycles

Tumor response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) with modifications. End of cycle tumor response assessments for all subjects will occur within Days 52 to 56 (results of assessments must be reviewed and documented before the first dose of the next cycle).

The maximum duration of study therapy to be administered to an individual subject in this study is 3 years (up to maximum of 2 years of initial treatment plus additional remaining period if re-initiation of study therapy occurs as outlined in section 3.5). Following each treatment cycle, the decision to treat a subject with additional cycles of BMS-936558 (MDX-1106) will be based on tumor assessment (evaluation performed between Days 52 and 56 and before the first dose in the next cycle, and as outlined below).. No subject will be permitted dose escalations or de escalations with the exception of subjects with MEL enrolled in the 0.1 mg/kg or 0.3 mg/kg additional expansion cohorts who meet the criteria for dose

escalation as outlined above; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous cycle.

Subjects who meet the following conditions may be treated with additional cycles:

- Subjects with a Best Overall response (BOR) of complete response (CR), partial response (PR) or stable disease (SD) will continue to receive BMS-936558 (MDX-1106) treatment until the first occurrence of either: 1) achievement of a confirmed CR; 2) clinical deterioration suggesting that no further benefit from treatment is likely; 3) meets criteria for discontinuation of study therapy as outline in sections 8.2 (Dose Limiting Toxicity) and 11.1.7 (Discontinuation of Subjects from Treatment ; 4) other intolerability to therapy; or 5) receipt of the maximum number of cycles
- Subjects with PD that has been confirmed but is not worsening and with otherwise stable or improved clinical status should continue to be treated with study drug until there is further progression or clinical deterioration.

Follow-up Period

The maximum duration of follow-up will be 46 weeks. All subjects should complete Follow-up Visit 1. Completion of subsequent follow-up visits will depend on the status of the subject at the end of the Treatment Period. Except for subjects who discontinue due to worsening PD, all subjects will be followed from the last visit until relapse, initiation of a new therapy, or a total of 1 year follow-up, whichever occurs first. Subjects whose PD is confirmed and who have further progression at a subsequent imaging evaluation will only complete Follow-up Visits 1 and 2; Follow-up Visit 2 (for these subjects only) will only include pharmacokinetic and immunogenicity evaluations and adverse event collection.

Re-initiation of Study Therapy For Subjects in Follow-up Period

Subjects entering the follow-up period with ongoing disease control (ongoing CR, PR, or SD) may be permitted to reinitiate study therapy upon confirmed disease progression after discussion and agreement with the BMS Medical Monitor. Subjects reinitiating study therapy should continue to meet eligibility criteria at the time study drug resumes and should not have experienced a DLT that would require permanent discontinuation of study therapy. Subjects will receive study therapy at the same dose level that they received prior to entering the follow-up period. Subjects that resume study therapy in this setting may receive study therapy for a total of 3 years (including the initial treatment period). Subjects who have completed 1 year of follow-up without evidence of disease progression will not be considered eligible for re-initiation of study therapy. Additional safety and efficacy summaries will be presented for those subjects who reinitiated study therapy.

Survival Follow-up Period

Following completion of the treatment and follow-up periods, all subjects will be followed for survival. At the time of implementation of Amendment 5 of the study protocol, all subjects will be assessed for their survival status and dates of death reported for any subjects that are deceased. After that initial assessment of all study subjects, any surviving subjects will have their survival status assessed every 3 months following completion of the treatment/follow-up phases of the study protocol.

DURATION OF TREATMENT/STUDY PARTICIPATION

The expected maximum duration of study drug treatment for a subject is approximately 3 years.

The expected maximum duration of a subject's participation in this study is up to 4 years.

All subjects will be followed for survival until death after study completion and/or discontinuation of the treatment and follow-up periods.

STUDY POPULATION

Up to 290 subjects will be enrolled (if no subjects require replacement). One hundred thirty (130) subjects have been enrolled thus far. Under Amendment 4 approximately 160 additional subjects will be enrolled. Subjects with pathologically-verified mCRPC, RCC, CRC, MEL, or NSCLC that is clinically advanced or recurrent and progressing after prior treatment with other therapies, and for which no alternative curative option is available, will be eligible to enroll in the study. Only subjects with RCC, MEL, or NSCLC will be enrolled under Amendment 4

DOSAGE AND ADMINISTRATION

BMS-936558 is to be administered as an i.v. infusion, using a volumetric pump with a 0.2 micron in-line filter at the protocol-specified doses. It is not to be administered as an i.v. push or bolus injection. At the end of the infusion, the line should be flushed with a sufficient quantity of normal saline.

At doses of 1, 3, and 10 mg/kg, the total dose needed will be diluted to a total volume of 60 mL in 0.9% sodium chloride. In cases where the total dose volume exceeds 60 mL, no dilution is required. At doses of 1, 3, 10 mg/kg, BMS-936558 should be administered over a 1-hour period; infusions will be controlled by a volumetric pump.

For subjects receiving doses at 0.1 mg/kg and 0.3 mg/kg, BMS-936558 will be diluted to a concentration as close as possible to but not lower than 0.35 mg/mL and infused at a rate of 1 mL/minute.

EFFICACY EVALUATIONS

The primary efficacy parameter is the overall objective response rate (ORR) (number of subjects with confirmed responses of CR or PR, divided by the total number of treated subjects with measurable disease at baseline). Tumor response status will be assessed using RECIST with modifications. Independent review of tumor assessments may be requested at the discretion of BMS.

Additional efficacy parameters may include the following: ORR during the first 3 cycles Best Overall Response (BOR) with response categories CR, PR, SD, PD, disease control rate (number of subjects with CR, PR, or SD divided by the total number of treated subjects with measurable disease at baseline), progression-free survival (PFS) and the time to response and duration of response for those subjects with confirmed responses.

Computed tomography/magnetic resonance imaging (CT/MRI [chest, abdomen, pelvis, and brain]) and bone scans will be performed at Screening and at the end of each cycle. Measurements of change in tumor burden must be reviewed and documented before initiating a new cycle of treatment with BMS-936558 (MDX-1106);

Tumor specific antigen levels for mCRPC (PSA) and CRC (CEA and CA19-9), will be measured to provide additional exploratory assessments of efficacy when appropriate in some tumor types.

Overall Survival will be calculated as an exploratory efficacy endpoint.

Additional exploratory efficacy evaluations may include the application of an immune-related response criteria (irRC) based on modifications to the RECIST (v1.0) which will be referred to as irRECIST and include the following parameters: irBOR with response categories (irCR, irPR, irSD, and irPD), irORR during the entire study, and duration of ir-response for those subjects with ir-responses. The irORR based on the irBOR outcomes in the first 3 cycles may also be derived. An outline of the irRECIST criteria is provided in [Appendix 2](#).

EXPLORATORY IMMUNE FUNCTION EVALUATIONS

Samples will be collected and evaluated for lymphocyte phenotype, serum cytokines, and quantitative immunoglobulins, and additional optional research samples will be collected and stored for future research

which may include (but not limited to) disease-related biomarkers (or antibody responses to selected antigens), exploratory humoral and cellular immune responses to tumor antigens and a panel of recall non-tumor antigens. Available slides and tissue samples from tumor biopsies collected before enrollment in this study may also be examined for tumor markers and inflammatory infiltrates.

Optional research-related tumor or other biopsies (e.g., inflamed tissue) that do not require general anesthesia may be obtained with the subject's explicit consent to assess morphology and the presence or absence of inflammatory infiltrates, and their cellular characterization.

Samples for exploratory immune function evaluation will be collected from subjects with MEL that are enrolled under Amendment 4.

Samples for the sole purpose of exploratory immune function evaluation will not be collected from subjects with NSCLC and RCC that are enrolled under Amendment 4.

SAFETY EVALUATIONS

Assessment of safety will be determined by ongoing review of clinical laboratory tests (blood and urine sampling for clinical laboratory parameters), pregnancy testing, Eastern Cooperative Oncology Group (ECOG) performance status, physical examination including vital sign measurements, electrocardiogram (ECG), and adverse events. Safety will also include evaluations of immune safety (as noted by irAEs, or laboratory tests for autoimmune sera, inflammatory events regardless of causality (IERC) and immunogenicity).

Dose-limiting Toxicity

A DLT is defined as a study drug-related \geq Grade 3 adverse event (using National Cancer Institute [NCI] CTCAE Version 3.0) occurring during the first cycle (56 days) of dosing, excluding: Grade 3 adverse event of tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor), Grade 3 rash, Grade 3 immune-related adverse event (irAE, defined below) that resolves to a Grade 1 or less within 28 days, or a transient (resolving within 6 hours of onset) Grade 3 infusion-related adverse event. A Grade 3 irAE that resolves to a Grade 1 or less within 28 days, while not constituting a DLT for dose escalation/expansion purposes, may preclude further administration of BMS-936558 (MDX-1106) to the subject.

Delayed DLTs are adverse events that meet the criteria of DLTs that occur after Cycle 1. Delayed DLTs will not be used to estimate the MTD for dose escalation.

Immune-Related Adverse Events

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

Given the intended mechanism of action of BMS-936558 (MDX-1106), particular attention will be given to adverse events that may follow enhanced T-cell activation such as dermatitis and colitis, or other irAEs.

Immunogenicity

Blood samples for immunogenicity analysis will be collected at predose on Day 1, predose on Cycle 2 Day 1 and all Follow-up Visits. These samples will be collected from all subjects enrolled or ongoing after implementation of Amendment 4 and will be evaluated for development of Human Anti-Human Antibody (HABA) response.

PHARMACOKINETIC EVALUATIONS

Blood samples for the Pharmacokinetic (PK) evaluation of BMS-936558 (MDX-1106) blood samples will be collected from all the subjects enrolled in additional expansion cohorts under amendment 4.

Serial PK samples will be collected from all subjects enrolled in 0.1, 0.3 and 1 mg/kg MEL cohorts and first 16 patients each from 3 and 10 mg/kg NSCLC cohorts as per [Table 3](#).

Limited PK samples will be collected from subjects enrolled in 1 mg/kg RCC cohort, 1 mg/kg NSCLC and remaining 16 subjects each from 3 and 10 mg/kg NSCLC (Table 3).

Single samples will also be collected to evaluate serum concentrations of BMS-936558 (MDX-1106) at all Follow-up Visits.

Pharmacokinetic parameters such as C_{max}, C_{min}, T_{max}, AUC(TAU) and Accumulation index (AI) will be derived from serum concentration versus time data for subjects with serial PK samples. Data obtained from subjects with serial sampling and limited sampling will be combined with data from other studies for population pharmacokinetic analysis.

STATISTICAL METHODS

A sample size of up to 290 subjects is based on the study design for dose escalation, 5 oncology indications, and the number of possible tumor-specific expansion cohorts for further safety and efficacy evaluation.

Sample Size Considerations

The sample size during dose escalation cannot be precisely determined but depends on the observed toxicity. At expansion cohorts, up to 16 or 32 subjects will be treated at fixed doses in a tumor type, to provide preliminary assessment of tumor response, in addition to safety assessment.

With 16 subjects treated in an expansion cohort, at a fixed dose and tumor type the 90% confidence interval for an objective response rate would be (5.3% to 42%) if 3 (19%) subjects had a response, (9.0% to 48%) if 4 (25%) subjects had a response and (13.2% to 54.8%) if 5 (31%) subjects had a response. Similarly, with 32 subjects in each NSCLC expansion cohort, the 90% confidence interval for an objective response rate would be (3% to 22%) if 3 (9.4%) subjects had a response, (4.4% to 26.4%) if 4 (12.5%) subjects had a response, and (6.4%, 30%) if 5 (16%) subjects had a response.

Statistical Analysis

Safety Analyses: All recorded adverse events will be listed and tabulated by system organ class, preferred term, and dose and coded according to the most current version of MedDRA. The incidence of adverse events will be tabulated and reviewed for potential significance and clinical importance. Vital signs and clinical laboratory test results will be listed and summarized by and dose. Any significant physical examination findings and results of clinical laboratory tests will be listed. ECG listings will be evaluated by the investigator and abnormalities, if present, will be listed. A separate listing and summary of all immune-related adverse events (irAE) and inflammatory events regardless of causality (IERC) will be provided. , Adverse Events will be summarized for all reported data and by study period: a) up to and including 70days post last dose of initial treatment, and b) from first dose of re-initiation of treatment, for subjects who re-initiate study therapy while in follow-up, up to 70 days post-dose of the last re-treatment dose.

Efficacy Analyses: In order to perform preliminary evaluation of anti-tumor activity, BOR outcomes, objective response (ORR), and disease control rate (DCR) will be tabulated by frequency distribution overall, and in the first 3 cycles. For ORR in each expansion cohort, an exact Binomial 95% confidence interval will be determined by Clopper-Pearson method. Median time to response and duration of response will be summarized for those subjects with confirmed responses, using Kaplan-Meier method; PFS will be similarly summarized. Individual tumor measurements, tumor burden and %changes in tumor burden will

be listed. Changes in tumor burden will be presented graphically for each tumor type. Exploratory efficacy analyses will include a frequency of irBOR outcomes and irORR, and a summary of duration of ir-responses. All primary efficacy analyses will be based on the all treated population; the response evaluable population may also be used for sensitivity analyses.

Efficacy results on subjects who re-initiate study therapy in follow-up period will be presented separately in the second treatment period.

In order to characterize the dose response in melanoma cohorts, modeling of tumor response (or AE of interest) as function of dose will be performed, based on parametric, e.g. logistic distribution. For NSCLC cohorts, tumor response measures (e.g. ORR) will also be modeled as a function of dose using some parametric or non-parametric (possibly Bayesian) approach.

Exploratory efficacy analysis to assess the OS will be provided by a Kaplan Meier plot and by estimating the median OS using the Kaplan-Meier approach for each tumor type.

Summary statistics and plots of measures of tumor specific antigen levels for mCRPC (PSA) and CRC (CEA and CA19-9), may be provided for specific tumor types, based on data availability,

Pharmacokinetic Analyses: Summary statistics will be tabulated for the pharmacokinetic parameters of BMS-936558 by dose and study cycle. To describe the dependency on dose, scatter plots of Cmax and AUC(TAU) versus dose will be provided for each cycle/day measured. Dose proportionality will be assessed, by estimating the slope of linear regression of BMS-936558 log(Cmax) on log(dose) and of log(AUC(TAU)) on log(dose) based on a power model. Point estimates and 90% confidence intervals for the dose proportionality parameter (slope of the linear regression) will be calculated for Cmax and AUC(TAU). Summary statistics for trough (Cmin) and end of infusion (Ceinf) concentrations will be tabulated by dose and study cycle. Plots of Cmin and Ceinf vs. cycle will be provided by dose. Pharmacokinetic concentrations from sparse samples will be listed, and may be used in combination with other studies for exposure-response or population pharmacokinetic modeling, which will be part of a separate report.

Immunogenicity Analyses: A listing will be provided of all available immunogenicity data. Additionally, a listing of immunogenicity data from those subjects with at least one positive Human Anti-Human Antibody (HAHA) at any timepoint will be provided by dose regimen. The frequency of subjects with at least one positive HAHA assessment, and frequency of subjects who develop HAHA after a negative baseline assessment will be provided by dose. To examine the potential relationship between immunogenicity and safety, the frequency and type of AEs of special interest may be examined by overall immunogenicity status.

Exploratory Biomarkers (Immune Function and others): Summary statistics for immune function and other exploratory markers, such as but not limited to flow cytometry outcomes, cytokines, quantitative immunoglobulins, receptor occupancy and their changes (or percent changes) from baseline will be tabulated by cycle visit and dose to assess pharmacodynamic effects. In addition, the time course of biomarker outcomes will be investigated graphically, by summary plots (i.e. box plots) or individual subject plots over time. Possible associations between changes in biomarker measures of interest and pharmacokinetic exposure will be explored. Possible associations of various biomarkers measures (baseline value or change from baseline) with clinical outcome (eg, tumor response) may will be explored based on data availability, using response-evaluable subjects, to assess explore predictive markers such as PD-L1 expression in tumors. Methods such as, but not limited to, logistic regression may be used to explore such associations. Measures from markers based on optional samples, e.g. tumor-based markers may be similarly presented, depending on data availability.

Administrative interim analyses on safety and efficacy or on PK, immunogenicity, and selected biomarkers may be provided at several times prior to completion of the study in order to facilitate program decisions and to support study presentations or publications

ABBREVIATIONS

Abbreviation	Term
APC	Antigen-presenting cells
BOR	Best overall response
CA 19-9	Carbohydrate antigen 19-9
CEA	Carcinoembryonic antigen
CR	Complete response
CRC	Colorectal cancer
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCF	Data clarification form
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
ESOI	Events of special interest
GCP	Good clinical practices
GMP	Good manufacturing practices
HIPAA	Health Information Portability and Accountability Act
ICF	Informed consent form
ICH	International Conference on Harmonisation
irAE	Immune-related adverse event
irBOR	Immune-related Best Overall Response
irORR	Immune-related Objective Response Rate
irCR	Immune-related Complete Response
irPD	Immune-related Progressive Disease
irPR	Immune-related Partial Response
irPFS	Immune-related Progression Free Survival

Abbreviation	Term
irRECIST	Immune-related RECIST
irSD	Immune-related Stable Disease
ITIM	Immunoreceptor tyrosine inhibitory motif
ITSM	Immunoreceptor tyrosine-based switch motif
i.v.	Intravenous
IFN	Interferon
IRB/IEC	Institutional review board/independent ethics committee
mAb	Monoclonal antibody
mCRPC	Metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MEL	Metastatic melanoma
MRI	Magnetic resonance imaging
MTD	Maximum-tolerated dose
NCI	National Cancer Institute
NSCLC	Non-small-cell lung cancer
ORR	Objective response rate
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed death-1
PR	Partial response
PSA	Prostate-specific antigen
PVG	Pharmacovigilance
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RT	Radiation therapy
SAE	Serious adverse event
SD	Stable disease

Abbreviation	Term
SLD	Sum of longest diameters
SNP	Single nucleotide polymorphism
SOP	Standard operating procedures
TCR	T-cell receptor
TEAE	Treatment-emergent adverse event
TNF	Tumor necrosis factor
WOCBP	Women of child bearing potential

Table 2: Time and Events Schedule

Period	Screening	Treatment										Follow-up ¹		Survival Follow-up ²
		Cycle 1					Cycles 2-18							
Visit Name	Screening	C1:1	C1:2	C1:3	C1:4	C1:5	Cn:1	Cn:2	Cn:3	Cn:4	Cn:5	Follow-up 1	Follow-up 2-6	
Timepoint Per Cycle (Day)	-28 to -1	1 ³	15 ³	29 ³	43 ³	56 ⁴	1 ⁵	15 ³	29 ³	43 ³	56 ⁴	Last Cn:5 Visit 0 to 7 Days	Previous Follow-up Visit + 56 Days ⁶	Every 3 months
Informed consent/HIPAA ⁷	•													
Inclusion/exclusion criteria	•													
Demographics/medical history ^{8,9}	•													
Diagnosis confirmation and stage	•													
Tumor-specific therapy history	•													
Hepatitis B and C testing ¹⁰	•													
Testosterone testing ¹¹	•													
BMS-936558 (MDX-1106) infusion		•	•	•	•		•	•	•	•				
Serum sample for pharmacokinetics ¹²		Serum for PK will be collected according to schedule in Table 3										•	• ¹³	

Table 2: Time and Events Schedule

Period	Screening	Treatment										Follow-up ¹		Survival Follow-up ²
		Cycle 1					Cycles 2-18							
Visit Name	Screening	C1:1	C1:2	C1:3	C1:4	C1:5	Cn:1	Cn:2	Cn:3	Cn:4	Cn:5	Follow-up 1	Follow-up 2-6	
Timepoint Per Cycle (Day)	-28 to -1	1 ³	15 ³	29 ³	43 ³	56 ⁴	1 ⁵	15 ³	29 ³	43 ³	56 ⁴	Last Cn:5 Visit 0 to 7 Days	Previous Follow-up Visit + 56 Days ⁶	Every 3 months
Serum sample for immunogenicity		•					• ¹⁴					•	•	
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.														
Vital signs ¹⁵	•	•	•	•	•		•	•	•	•		•	•	
Height	•													
Weight	•	•					• ¹⁶							
Complete physical exam ¹⁷	•						•					•		
Limited physical exam ¹⁸		•	•	•	•			•	•	•			•	
Oxygen Saturation ¹⁹		•	•	•	•		•	•	•	•		•	•	
ECOG performance	•	•	•	•	•		•	•	•	•		•	•	
Hematology	•	• ²⁰	• ²⁰	• ²⁰	• ²⁰		• ²⁰	• ²⁰	• ²⁰	• ²⁰		•	•	
Serum chemistry	•	• ²⁰	• ²⁰	• ²⁰	• ²⁰		• ²⁰	• ²⁰	• ²⁰	• ²⁰		•	•	

Table 2: Time and Events Schedule

Period	Screening	Treatment										Follow-up ¹		Survival Follow-up ²
		Cycle 1					Cycles 2-18							
Visit Name	Screening	C1:1	C1:2	C1:3	C1:4	C1:5	Cn:1	Cn:2	Cn:3	Cn:4	Cn:5	Follow-up 1	Follow-up 2-6	
Timepoint Per Cycle (Day)	-28 to -1	1 ³	15 ³	29 ³	43 ³	56 ⁴	1 ⁵	15 ³	29 ³	43 ³	56 ⁴	Last Cn:5 Visit 0 to 7 Days	Previous Follow-up Visit + 56 Days ⁶	Every 3 months
Urinalysis	•	•					•					•	• ¹³	
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.														
Immune safety assays		•					•					•	• ¹³	
Pregnancy test ²¹	•	•	•	•	•		•	•	•	•		•	• ¹³	
Chest radiograph	• ²²													
ECG (12-lead)	• ²²						•					•		
CT/MRI (brain) ^{23,24}	• ²²					• ^{4,25}					• ^{4,25}		• ²⁵	
CT/MRI (chest, abdomen, pelvis)	• ²²					• ⁴					• ⁴		•	
Bone scan ²⁶	•					• ⁴					• ⁴		•	
Tumor-specific blood tests ²⁷	•	•					•					•	•	

Table 2: Time and Events Schedule

Period	Screening	Treatment										Follow-up ¹		Survival Follow-up ²
		Cycle 1					Cycles 2-18							
Visit Name	Screening	C1:1	C1:2	C1:3	C1:4	C1:5	Cn:1	Cn:2	Cn:3	Cn:4	Cn:5	Follow-up 1	Follow-up 2-6	
Timepoint Per Cycle (Day)	-28 to -1	1 ³	15 ³	29 ³	43 ³	56 ⁴	1 ⁵	15 ³	29 ³	43 ³	56 ⁴	Last Cn:5 Visit 0 to 7 Days	Previous Follow-up Visit + 56 Days ⁶	Every 3 months
Response assessment						• ^{4,28}					• ^{4,28}	•	•	
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.														
Tumor or other biopsy ²⁹	•													
Blood sample for SNP analyses		•												
Flow cytometry ³⁰		•					• ¹⁴					•		
PBMC (cryopreserved) ³⁰		•					• ¹⁴					•		
Serum for cytokine panel ³⁰		•					• ¹⁴					•		
Serum for quantitative immunoglobulins ³⁰		•					• ¹⁴					•		
Concomitant medications ³¹	•	•	•	•	•		•	•	•	•		•	• ³²	

Table 2: Time and Events Schedule

Period	Screening	Treatment										Follow-up ¹		Survival Follow-up ²
		Cycle 1					Cycles 2-18							
Visit Name	Screening	C1:1	C1:2	C1:3	C1:4	C1:5	Cn:1	Cn:2	Cn:3	Cn:4	Cn:5	Follow-up 1	Follow-up 2-6	
Timepoint Per Cycle (Day)	-28 to -1	1 ³	15 ³	29 ³	43 ³	56 ⁴	1 ⁵	15 ³	29 ³	43 ³	56 ⁴	Last Cn:5 Visit 0 to 7 Days	Previous Follow-up Visit + 56 Days ⁶	Every 3 months
Adverse events ³¹		•	•	•	•		•	•	•	•		•	• ³²	
Survival Status														•
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.														

Table 2 Footnotes:

- 1 When a subject will discontinue study drug treatment, the date and reason for study drug discontinuation should be documented on the CRF, all remaining visits of that treatment cycle should be completed (without infusions and with only a single pharmacokinetic sample taken at applicable visits), and the subject should enter the Follow-up Period. When a subject will be withdrawn from the study (during the Treatment or Follow-up Period), all evaluations associated with that study visit should be performed and the date and reason for study discontinuation should be documented on the CRF.
- 2 Following completion or discontinuation of the treatment and/or follow-up phases of the study, all subjects will be followed every 3 months to assess their survival status until subject death.
- 3 To be done \pm 2 days of scheduled visit.
- 4 This visit is NOT a clinic visit. The purpose of this visit is for radiologic assessment and subsequent evaluation of results by the Investigator (response assessment). Radiologic procedures and response assessments should occur between Days 52 and 56 and BEFORE administering the first dose of study drug in the next cycle.
- 5 Day 1 of each cycle should occur 56 days following Day 1 of the previous cycle, but no sooner than 14 days after the last dose of the previous cycle.
- 6 To be done \pm 7 days of scheduled visit.
- 7 Informed consent form and Health Information Portability and Accountability Act (HIPAA) authorization are to be provided before initiation of any Screening assessments and may be obtained before Day -28.
- 8 To include collection of prior medication and prior/concurrent medical conditions. For subjects with mCRPC, to include at least 3 PSA measurements over the preceding 6 months.
- 9 Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions CRF.
- 10 Hepatitis B surface antigen and Hepatitis C antibody (with reflex Hepatitis C RNA if antibody test is positive).
- 11 In subjects with mCRPC only. Testosterone level must be \leq 50 ng/dL.
- 12 Pharmacokinetic sampling to be performed according to [Table 3](#).

continued

Table 2 Footnotes: *(continued)*

- 13 Pharmacokinetic samples are to be collected at all Follow-up Visits.
- 14 Cycle 2 only.
- 15 Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure. On the day of each infusion, vital signs will be obtained preinfusion, every 15 minutes during the infusion, at the end of the infusion, and 15, 30, and 60 minutes after completion of the infusion. When slowing or re-starting an infusion due to an infusion reaction/adverse event, vital signs should be monitored every 15 minutes or as directed by the Investigator until the infusion is completed, and 15, 30, and 60 minutes after completion of the infusion and/or until the subject is stabilized. Vital signs should be collected \pm 5 minutes from the scheduled times noted above.
- 16 Dose adjustments are required to be made if there has been a 10% or greater change in weight (increase or decrease) since the previous cycle. (Weights should be determined at the onset of each new treatment cycle as a minimum, but may be done more frequently at sites whose standard dose administration procedures require weight determination before each dose.)
- 17 Complete physical examination includes assessment of the skin, head, eyes, nose, throat, neck, joints, lungs, heart, abdomen (including liver and spleen), lymph nodes, and extremities. A brief neurological examination should also be performed. All abnormal findings noted at the Screening physical examination should be recorded on the Medical History CRF, and any new or worse signs or symptoms are to be recorded on the Adverse Event CRF.
- 18 Limited physical examination includes assessment of the lungs, heart, abdomen, and skin. All abnormal findings noted at the Cycle 1/Day 1 evaluation should be recorded on the Medical History CRF. Abnormal findings of clinical significance that occur after the Cycle 1/Day 1 evaluation (or new adverse events) should be explicitly documented on the Adverse Event CRF.

Continued

Table 2 Footnotes: (*continued*)

- 19 To be done at rest and after mild exertion. On treatment days, to be completed prior to infusion.
- 20 During the study Treatment Period, hematology and serum chemistries will be evaluated by both local and central laboratories at these timepoints. The hematology and clinical chemistry laboratories **must be performed and reviewed before dosing**. (If practicable, central laboratory samples may be drawn up to 48 hours prior to infusions for preinfusion safety review in lieu of local laboratories.) These labs may be performed up to 48 hours prior to the planned dosing. Any new \geq Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the BMS Medical Monitor should be contacted.
- 21 Serum β -HCG pregnancy test at Screening; urine pregnancy test at all other time points for women of childbearing potential. Urine pregnancy tests on days of study drug administration must be performed and negative before study drug administration.
- 22 Baseline imaging and 12-lead ECG done as part of the subject's previous routine care before signing the informed consent form and completed within 28 days before the administration of BMS-936558 (MDX-1106) need not be repeated. Whenever possible, baseline imaging should be done at the same institution/facility and with the same modality which will be used to measure response during the subject's participation in the study.
- 23 Brain scan (MRI preferred) required at Screening if not performed within the previous 2 months (and NOT required for subjects with mCRPC).
- 24 The same technique (CT/MRI) used at baseline should be utilized throughout the study.
- 25 Brain scans during Treatment and Follow-up Periods are required only if there is a prior history of lesions present at Screening, or as clinically indicated. If required, subsequent brain CT scans/MRI should be repeated every other cycle (end of Cycle 2, 4, 6, etc.) and at Follow-Up Visits 2, 4 and 6.
- 26 Bone scans must be done at all visits indicated for subjects with mCRPC. For subjects with MEL, RCC, CRC, and NSLC, bone scans at baseline or subsequent visits will be performed only if clinically indicated. If required, subsequent bone scans should be repeated every other cycle (end of Cycle 2, 4, 6, etc.) and at Follow-Up Visits 2, 4, and 6.
- 27 Blood tests are to be tumor specific (e.g., CEA and CA 19-9 for colorectal cancer; PSA for prostate cancer).

continued

Table 2 Footnotes: *(continued)*

- 28 Tumor response status will be assessed by the Investigators using RECIST with modification. Response assessments must be performed by the Investigators at the end of each cycle to document eligibility for entry into the next treatment cycle. Copies of scans may be requested by BMS for independent review.
- 29 A tumor biopsy is required at baseline if there is no other record of histological diagnosis of tumor. **Tumor tissue (archival or recent acquisition) must be available for correlative studies. Subjects must consent to allow the acquisition of formalin-fixed paraffin-embedded (FFPE) material (block or unstained slides) by study personnel for performance of correlative tissue studies...Consent to request previous tumor biopsy specimens is required.** Optional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed at Screening and at other times during the protocol as clinically indicated. Optional tumor or other biopsy requires specific agreement by the subject in the informed consent.
- 30 Samples will not be collected on subjects enrolled with NSCLC and RCC under Amendment 4
- 31 All subjects who intend to discontinue the study within 70 days after the administration of the last dose of study drug should be followed until resolution and/or stabilization of any study drug-related adverse events and adverse events that lead to the discontinuation, and should be monitored for 70 days following the last dose of BMS-936558 (MDX-1106) for the occurrence of study drug-related adverse events. These subjects should complete Follow-up Visits 1 and 2.
- 32 For all follow-up periods beyond 70 days from the last dose of study drug, only study drug-related serious adverse events or late-occurring immune-related adverse events should be reported.

Table 3: Pharmacokinetic Blood Sampling Schedule

Study Day ^a	Time (Relative To Dosing) Hour	Time (Relative To Dosing) Hour: Min	Serial PK Blood Sample Schedule ^b	Limited PK Sampling Schedule ^c
Cycle 1 Day 1	0 (Predose)	00:00	X	X
Cycle 1 Day 1	1.0 (EOI) ^d	01:00	X	X
Cycle 1 Day 1	4.0	04:00	X	
Cycle 1 Day 1	8.0	08:00	X	
Cycle 1 Day 2	0.0	24:00	X	
Cycle 1 Day 3	0.0	48:00	X	X
Cycle 1 Day 5	0.0	96:00	X	
Cycle 1 Day 8	0.0	168:00	X	X
Cycle 1 Day 15	0 (Predose)	336:00	X	X
Cycle 2 Day 1	0 (Predose)	336:00	X	X
Cycle 3 Day 1	0 (Predose)	336:00	X	X
Cycle 3 Day 1	1.0 (EOI) ^b	01:00	X	X
Cycle 3 Day 1	4.0	04:00	X	
Cycle 3 Day 1	8.0	08:00	X	
Cycle 3 Day 2	0.0	24:00	X	
Cycle 3 Day 3	0.0	48:00	X	X
Cycle 3 Day 5	0.0	96:00	X	
Cycle 3 Day 8	0.0	168:00	X	X
Cycle 3 Day 15	0 (Predose)	336:00	X	X
Follow-up Visits 1-6 ^e			X	X

^a If a subject permanently discontinues study drug treatment, or is not receiving an infusion at a given visit, a single pharmacokinetic sample will be taken at that visit.

^b Serial PK samples will be collected from all subjects enrolled in 0.1, 0.3 and 1 mg/kg MEL cohorts and first 16 patients each from 3 and 10 mg/kg NSCLC cohorts under amendment 4.

^c Limited PK samples will be collected from subjects enrolled in 1 mg/kg RCC cohort, 1 mg/kg NSCLC and remaining 16 subjects each from 3 and 10 mg/kg NSCLC under amendment 4.

^d EOI: End of Infusion. This sample should be taken immediately prior to stopping the infusion. In the event of a delay beyond 1 h, the sample should be taken at the END of the infusion.

^e Pharmacokinetic sample will be taken at all Follow-up Visits

TABLE OF CONTENTS

TITLE PAGE	1
SYNOPSIS	3
ABBREVIATIONS	13
TABLE OF CONTENTS	26
1 INTRODUCTION AND RATIONALE	31
1.1 Background.....	31
1.2 Programmed Death-1 and the Antitumor Immune Response	31
1.3 Summary of BMS-936558 (MDX-1106): Preclinical Studies.....	36
1.3.1 Summary.....	36
1.3.2 Preclinical Data with PD-1 Blockade or Deficiency and BMS-936558 (MDX-1106).....	37
1.4 Prior Experience with Similar Investigational Agents .	39
1.4.1 CTLA-4 Blockade	39
1.4.2 Other Immunomodulatory Agents	39
1.5 Clinical Studies	40
1.5.1 Summary of Safety.....	40
1.5.2 Rationale for BMS-936558 (MDX-1106) Dosage Selection.....	42
2 STUDY OBJECTIVES.....	43
2.1 Primary Objective(s)	43
2.2 Secondary Objective(s)	43
2.3 Exploratory Objectives	43
3 OVERVIEW OF STUDY DESIGN.....	44
3.1 Dose Escalation	44
3.2 Expansion Cohorts	45
3.2.1 Initiation of the Primary MTD Expansion Cohorts	48
3.2.2 Initiation of the Additional Non-MTD Melanoma Expansion Cohorts	48
3.2.3 Initiation of the Additional Expansion Cohorts.....	49
3.2.4 Stopping Rules for the Expansion Cohorts	49
3.3 Administration of Additional Treatment Cycles.....	50
3.4 Follow-up Period	52

3.5 Re-Initiation of Study Therapy For Subjects in Follow-up Period.....	53
3.6 Survival Follow-up Period	53
3.7 Post Study Access to Therapy.....	54
4 STUDY POPULATION.....	54
4.1 Inclusion Criteria	55
4.2 Exclusion Criteria	57
5 RANDOMIZATION AND BLINDING	58
6 ASSIGNMENT TO STUDY	59
7 DOSAGE AND ADMINISTRATION	59
7.1 Investigational Product	60
7.2 Non-investigational Product.....	60
7.3 Physical Description of Study Drug	60
7.4 Packaging and Labeling	61
7.5 Ordering Study Drug.....	61
7.6 Storage	61
7.7 Study Drug Preparation and Administration	62
7.8 Drug Accountability.....	64
7.9 Dose Adjustments, Infusion Delays, and Missed Doses	65
7.10 Destruction of Study Drug.....	65
7.11 Return of Study Drug	66
8 TOXICITY AND MANAGEMENT	66
8.1 Dose Escalation	66
8.2 Dose-limiting Toxicity.....	67
8.3 Stopping Rules for Dose-limiting Toxicity During Dose Escalation.....	67
8.4 Stopping Rules for Dose-Limiting Toxicities in the Expansion Cohort.....	68
8.5 Possible Toxicities	68
8.6 Infusion Reactions	70
8.7 Stopping Rules for Clinical Deterioration.....	72
9 COMPLIANCE	73
10 CONCOMITANT THERAPY	73
10.1 Treatment of Isolated Lesions	75
11 STUDY EVALUATIONS.....	75

11.1 Study Procedures by Visit.....	75
11.1.1 Overview	75
11.1.2 Screening Period.....	76
11.1.3 Treatment Period.....	78
11.1.3.1 Cycle 1	78
11.1.3.2 Cycle 2+	81
11.1.4 Follow-up Period	81
11.1.5 Cycle 1 Treatment Completion.....	82
11.1.6 Survival Follow-up	82
11.1.7 Study Participation	82
11.1.8 Discontinuation of Subjects from Treatment	83
11.2 Efficacy Evaluations.....	84
11.2.1 Primary Efficacy Parameter.....	84
11.2.2 Additional Efficacy Parameters	84
11.3 Exploratory Biomarkers of Immune Response	85
11.4 Safety Evaluations	85
11.4.1 Immune Safety Evaluations.....	86
11.4.2 Immunogenicity	86
11.5 Pharmacokinetic Evaluations	86
12 ADVERSE EVENT REPORTING	87
12.1 Definitions	87
12.1.1 Safety Reporting For Adverse Events.....	89
12.2 Serious Adverse Events	90
12.3 Rapid Notification of Serious Adverse Events	91
12.3.1 Reporting Responsibility.....	91
12.3.2 Reporting Procedures	92
12.3.3 Contact Persons and Numbers	94
12.4 Overdose	94
12.5 Pregnancy.....	94
12.5.1 Reporting of Pregnancy.....	95
12.6 Immune-Related Adverse Events	95
12.7 Rapid Notification of Adverse Events of Special Interest (EOSI).....	97
12.8 Other Safety Considerations.....	97
13 STATISTICAL METHODS	98
13.1 Sample Size Determination	98
13.2 Study Populations.....	98
13.2.1 All Enrolled Population	98
13.2.2 All Treated Population	98

13.2.3 Pharmacokinetic Data Set.....	98
13.2.4 Response Evaluable Data Set	99
13.2.5 Exploratory Biomarker of Immune Response Data Set .	99
13.3 Statistical Considerations	99
13.3.1 Demographics and Baseline Characteristics	99
13.3.2 Extent of Exposure	99
13.3.3 Concomitant Medication.....	99
13.3.4 Efficacy	100
13.3.5 Safety	101
13.3.6 Immunogenicity	103
13.3.7 Pharmacokinetic Parameters	104
13.3.8 Exploratory Biomarkers	104
14 ETHICAL ASPECTS	105
14.1 Ethics and Good Clinical Practice	105
14.2 Confidentiality Regarding Study Subjects	106
14.3 Institutional Review Board/Independent Ethics Committee	106
14.4 Informed Consent	107
15 ADMINISTRATIVE REQUIREMENTS.....	109
15.1 Protocol Amendments	109
15.2 Monitoring Procedures.....	110
15.2.1 Investigational Site Training	111
15.3 Recording of Data and Retention of Documents	112
15.3.1 Study Drug Records	113
15.3.2 Case Report Forms	114
15.4 Auditing Procedures	115
15.5 Publication of Results	115
15.6 Disclosure and Confidentiality	116
15.7 Discontinuation of Study	116
15.8 Data Management	116
15.8.1 Data Collection	116
15.8.2 Database Management and Quality Control	117
16 REFERENCES.....	118
APPENDIX 1 RECIST WITH MODIFICATION	123
APPENDIX 2 IMMUNE-RELATED RECIST	128
APPENDIX 3 PROSTATE RESPONSE EVALUATION CRITERIA	133

APPENDIX 4 TUMOR-SPECIFIC	
INCLUSION/EXCLUSION CRITERIA	135
APPENDIX 5 ECOG PERFORMANCE STATUS	140
APPENDIX 6 PRE-EXISTING AUTOIMMUNE DISEASES..	141
APPENDIX 7 LIST OF SYMPTOMS.....	142

1 INTRODUCTION AND RATIONALE

1.1 Background

Preclinical animal models of tumors and chronic infections have shown that blockade of Programmed death-1 (PD-1) by monoclonal antibodies (mAbs) can enhance the immune response and result in tumor rejection or control of infection. Studies of several human tumor types have suggested that the exploitation of the PD-1/PD-L1 pathway may permit immune evasion by tumors. BMS-936558 (MDX-1106) is a fully human, IgG4 (kappa) isotype, mAb that binds PD-1. PD-1 blockade by BMS-936558 (MDX-1106) is therefore proposed to be a promising avenue to pursue for immunotherapy of tumors.

An estimated 1,339,790 new cases of cancer and 564,830 deaths were seen in the United States in 2006.¹ Anti-tumor immunotherapy via PD-1 blockade is not limited in principle to any single tumor type, but may have activity in augmenting therapeutic immune response to a number of histologically distinct tumors. Five tumor types (metastatic castration-resistant prostate cancer [mCRPC], renal cell carcinoma [RCC], colorectal adenocarcinoma [CRC], malignant melanoma [MEL], and non-small cell lung cancer [NSCLC]) were selected for the current study, as they are representative of tumors for which a high medical need for new therapies exist; those for which there is a precedent for clinical responses to other immunotherapies; and those for which there is supportive correlative pathologic data suggesting that the PD-1/PD-L1/2 pathway is important for tumor progression.

1.2 Programmed Death-1 and the Antitumor Immune Response

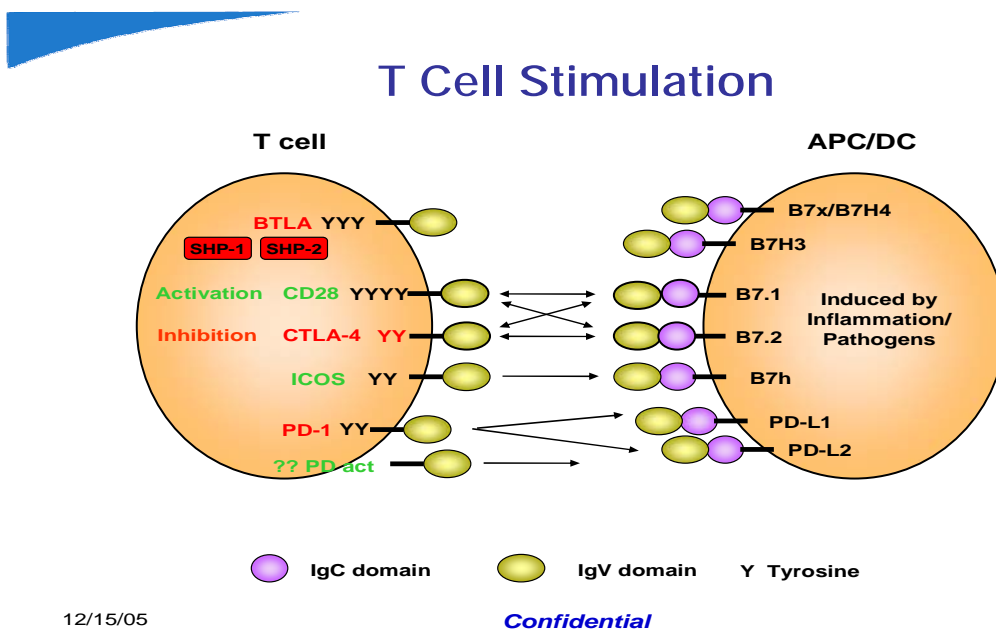
The antigen-specific T-cell immune response initiates after the integration of 2 signals received by the T cell from the antigen-presenting cell (APC).² The first signal is antigen specific, from the T-cell receptor (TCR) interacting with the (peptide) antigen displayed on APC in the context of the Major Histocompatibility Complex Type I or Type II surface molecules, for CD8 and CD4 T cells, respectively. The second signal is not antigen specific, but is a costimulatory signal that arises from the interaction of the T cell CD28 surface molecule with the B7 molecule on the APC (either B7-1, CD80, or B7-2,

CD86), and results in additional intracellular signals and secreted cytokines that drive an effective immune response. The absence of a costimulatory signal results in recognition without activation, or anergy, and may lead to death (by apoptosis) of antigen-specific T cells. Clearance of antigen is followed by the down regulation of the activated T-cell response, mostly by apoptosis. A subpopulation of the T cells matures into long lived memory CD8 and CD4 cells that can then be promptly reactivated upon re-exposure to the antigen by APC. These regulatory mechanisms are likely to have arisen to maintain tolerance of the immune system to normal self antigens, while permitting it to effectively deal with abnormal or foreign antigens.

Immunotherapy of tumors rests on the premise that tumors can be recognized as foreign rather than as self, and effectively attacked. Many tumors express tumor-specific antigens, and ongoing immune surveillance may abort the emergence of many tumors as they arise. Tumor progression may depend upon acquisition of mechanisms to evade an effective immune response.³ Immune evasion may occur by exploiting any of the checkpoints that control the regulatory immune response, including display of antigens and control of costimulatory pathways. Current immunotherapy efforts focus on the effective introduction of cancer antigens via therapeutic vaccination, and the modulation of regulatory checkpoints by costimulation and cytokine manipulation in order to break the apparent tolerance of the immune system to tumor antigens.

CD28, CD80, and CD86 are members of the immunoglobulin superfamily of costimulatory receptors. It is now recognized that this family is quite large, and that 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 TCR (Figure 1).⁴ Collectively, these signals govern the balance between T-cell activation and tolerance to antigens.

Figure 2: T-cell Stimulation



PD-1 (or CD279) is a member of the CD28 family of T-cell costimulatory receptors that include CD28, CTLA-4, ICOS, PD-1, and BTLA. PD-1 is a 55 kD type I transmembrane protein that is part of the immunoglobulin gene superfamily.⁵ 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 (also known as B7-H1 or CD274) and PD-L2 (also known as B7-DC or 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.^{6,7,8} PD-1 delivers a negative signal by the recruitment of SHP-2 to the phosphorylated tyrosine residue in the ITSM in its cytoplasmic region.^{9,10} PD-1 is primarily expressed on activated T cells, B cells, and myeloid cells.⁴

Further evidence for a negative regulatory role of PD-1 comes from studies of PD-1 null mice. PD-1-deficient mice develop various autoimmune phenotypes, including dilated cardiomyopathy, a lupus-like syndrome with arthritis and nephritis, and accelerated diabetes mellitus.^{11,12,13} 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. PD-1 deficiency on the C57BL/6 background results in development of a late-onset progressive arthritis and lupus-like glomerulonephritis,¹¹ while on the BALB/c background, it results in the development of a lethal dilated cardiomyopathy that shows incomplete penetrance, with concomitant evidence of auto-antibodies to troponin-I.^{12,14}

In other murine models, PD-1 blockade has been found to play a role in the development of autoimmune diseases such as encephalomyelitis,¹⁵ graft-versus-host disease,¹⁶ and type I diabetes.¹³

The role of PD-1 and PD-L1 in viral immunity has recently been investigated. PD-1 expression has been found to be a critical mediator of T-cell unresponsiveness in the lymphocytic choriomeningitis virus model system.¹⁷ In addition, PD-1 deficiency enhances anti-viral immunity at effector sites, resulting in rapid clearance of adenovirus in the liver.¹⁸

Several published murine tumor studies using anti-PD-1 and anti-PD-L1 antibodies or PD-1 null mice support the role of this pathway for therapeutic intervention in cancer. Two metastatic models have been shown to be sensitive to PD-1 blockade.¹⁹ Utilizing CT26 (a colon carcinoma that metastasizes to the lung after intravenous [i.v.] injection), tumor growth was inhibited by 50% after treatment with anti-PD-1 antibody. This study also reports that B16 melanoma metastasis to the liver after intrasplenic injection of tumor cells, in which PD-L1 expression was found to be up-regulated in vivo, could be inhibited by anti-PD-1 treatment. Transfection of murine tumors with PD-L1 rendered them less susceptible to the specific T-cell antigen receptor-mediated lysis by cytotoxic T cells in vitro and markedly enhanced tumor growth and invasiveness in vivo.²⁰ Both effects could be reversed by blockade with anti-PD-L1 antibody.^{20,21} Transfection with PD-L1 was able to negate the enhanced immunogenicity conferred by transfection of P815 mastocytoma cells with CD80.²² The 4T1 mammary cell carcinoma is PD-L1 negative in culture but expresses PD-L1 in vivo (or can be induced to express PD-L1 in culture by interferon (IFN)- γ).²³ This tumor is refractory to tumor rejection mediated by an agonistic anti-41BB antibody, an activating receptor that is a member of the tumor

necrosis factor (TNF) family of receptors. While treatment with anti-41BB results in a modest decrease in tumor growth, treatment with anti-41BB in combination with anti-PD-L1 results in dramatic tumor rejection. Murine myeloma cell lines naturally express PD-L1, and their growth in vivo was also inhibited significantly, although transiently, by the administration of anti-PD-L1 antibody. A direct effect of the antibody on the growth of the tumor (by other mechanisms such as antibody-dependent cellular cytotoxicity) was not excluded. Their growth was suppressed completely in syngeneic PD-1-deficient mice.²⁰ In addition, PD-1^{-/-}CD8⁺ TCR transgenic T cells caused tumor rejection in an adoptive transfer model in which wild type and CTLA-4^{-/-} T cells failed to mediate rejection.²⁴ Studies reveal that antitumor activity by PD-1 blockade functions in PD-L1⁺ tumors as well as for tumors that are negative for the expression of PD-L1.^{18,19,20,21,22,23} This suggests that host mechanisms, i.e., expression of PD-L1 in antigen-presenting cells, limits 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.^{21,25,26,27,28,29,30,31} PD-L1 expressed by tumor cells has been shown to enhance apoptosis of activated tumor-specific T cells in vitro.²¹ Moreover, the expression of PD-L1 may protect the tumor cells from the induction of apoptosis by effector T cells.³² In renal cell carcinoma, high surface expression levels of PD-L1 on tumor cells are related to tumor aggressiveness.²⁶ 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. It has been reported that PD-L1 and PD-L2 expression may be a significant prognostic marker in postoperative esophageal cancer subjects.²⁷

1.3 Summary of BMS-936558 (MDX-1106): Preclinical Studies

1.3.1 Summary

BMS-936558 (MDX-1106) has been shown to bind specifically to the PD-1 receptor of the CD28 family. In vitro assays have demonstrated that BMS-936558 (MDX-1106) does not react with the other members of this family. BMS-936558 (MDX-1106) has also demonstrated the ability to block binding of its ligands, PD-L1 and PD-L2, and to enhance T-cell proliferation and IFN- γ release in vitro. A surrogate anti-murine PD-1 antibody was effective in inhibiting tumor growth in several syngeneic tumor models.

In binding studies using fresh, frozen human tissues, BMS-936558 (MDX-1106) demonstrated reactivity with lymphocytes in a variety of tissues. There was also moderate to strong cytoplasmic staining of rare to occasional endocrine cells in the adenohypophysis. This was considered to be low affinity binding as the intensity was moderate to strong at 10 $\mu\text{g/mL}$ and was not present at 1 $\mu\text{g/mL}$. This unexpected reactivity to endocrine cells is not expected to have physiological consequences due to the limited availability of cytoplasmic compartments in vivo. Similar staining patterns were observed in cynomolgus monkey tissues indicating that this is an appropriate animal species to evaluate the potential toxicities of BMS-936558 (MDX-1106). In a cardiovascular, safety pharmacology study in cynomolgus monkeys, there were no significant effects of administration of 10 or 50 mg/kg of BMS-936558 (MDX-1106) on electrocardiographic parameters. BMS-936558 (MDX-1106) was also well tolerated when administered weekly at doses of 1, 10 or 50 mg/kg/dose for 5 weeks and when administered bi-weekly at doses of 10 and 50 mg/kg for 3 months. There were no adverse clinical findings or changes in clinical or anatomic pathology parameters in these studies.

In a study of cynomolgus monkeys which were administered multiple doses of ipilimumab, a fully human mAb to CTLA-4, in combination with BMS-936558 (MDX-1106), 1 monkey at the highest dose level (10 mg/kg ipilimumab/50 mg/kg BMS-936558 (MDX-1106)) died 1 day following the fourth and last doses of ipilimumab and BMS-936558 (MDX-1106), respectively. This early death was attributed to acute gastric dilation, assessed as possibly related to administration of ipilimumab plus BMS-936558 (MDX-1106). Clinical observations in the days before death included

persistent diarrhea, reduced food consumption, weight loss, decreased activity, dehydration, and hypothermia. Pathology findings included marked gas distention of the stomach and moderate gas dilatation of the duodenum, jejunum, ileum, cecum, and colon (correlated with decreased thickness of the gastric and intestinal wall, submucosal and muscularis), mottled, dark red, purple, tan discoloration of the lung (correlated with vascular congestion and a pulmonary granuloma), abnormal appearance of the lung due to atelectasis and hyperinflation (no microscopic correlate), decreased thymus size (correlated with marked, diffuse thymic atrophy), and purple discoloration of the neck and thorax (no microscopic correlate). One microscopic finding of uncertain relationship to ipilimumab plus BMS-936558 (MDX-1106) administration was identified in the kidney: mild multifocal tubular dilation and epithelial degeneration in the renal cortical tubules. Myeloid and eosinophil hypercellularity and erythroid hypocellularity were identified in the bone marrow. Myeloid and eosinophil hypercellularity were believed to be a secondary response to inflammation in the lung and not related to ipilimumab/BMS-936558 (MDX-1106) treatment. The cause of the erythroid hypocellularity was considered uncertain. Additional microscopic findings considered to be related to inappetence or physiological stress and not test article treatment included thymic involution/atrophy, pancreatic acinar cell degranulation, secretory depletion of the adrenal cortex, zona fasciculata and vascular congestion in several organs examined. All other gross observations or microscopic findings were considered incidental. There was no evidence of colitis upon gross or microscopic pathology evaluation of the gastrointestinal tract. The animal did develop diarrhea and this occurred in the cohort receiving the highest doses of the test articles. Therefore, the death may possibly be related to administration of ipilimumab and BMS-936558 (MDX-1106) and may be an immune mediated gastrointestinal toxicity.

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

1.3.2 Preclinical Data with PD-1 Blockade or Deficiency and BMS-936558 (MDX-1106)

PD-1:PD-L1/PD-L2 interactions play a role in the balance between immune activation and tolerance. Several preclinical studies in knockout mice, as well as mice treated with

blocking mAbs have shown the ability to induce or aggravate an autoimmune type disease.^{10,11,12,14,15} The pattern of autoimmunity that develops in PD-1 knockout mice appears to be strain specific and develops with age, rather than appearing at birth. There is no evidence to date for a uniform type of immune-related toxicity. In contrast to CTLA-4-deficient mice, the phenotype of PD-1 null mice is variable and less uniformly dramatic. A variety of autoimmune perturbations have been observed that are strain dependent, not typically lethal, develop weeks or months after birth, and have variable genetic penetrance (ranging from 10% to 100%). Models with high penetrance are those done in backgrounds that are already predisposed to the underlying disease. PD-1 blockade experiments have been able to exacerbate some autoimmune disease in predisposed mouse strains.

Careful monitoring for immune-related adverse events (irAE) is a key part of the general safety monitoring of this protocol, and includes monitoring for specific patterns that have been seen in mice, such as cardiomyopathy, arthritis and diabetes, as well as a general heightened surveillance for immune-mediated pathology. The planned panel of laboratory markers for immune-mediated activation processes will monitor for adverse events that have been observed in these various model systems.

Preclinical evaluation of efficacy against multiple tumors and safety of BMS-936558 (MDX-1106), both in mouse and non-human primate species, have not shown any clear pattern of toxicity elicited by multiple doses of BMS-936558 (MDX-1106) at levels in excess of the doses used in ongoing clinical studies. A pattern of cross reactivity with a pituitary cytoplasmic determinant at high doses has been noted. Given the intracellular location, rare presence, and low affinity of the interaction, the lack of toxicity observed to date in the relevant preclinical model, and the non-complement activating subclass (IgG4) of the mAb, BMS believes the risk of pituitary toxicity to be very low, and it has not yet emerged in clinical studies (see below). Of note, pituitary dysfunction has emerged as an unexpected adverse event in the ipilimumab – anti-CTLA-4 program, another T-cell costimulatory molecule (that was not predicted by the preclinical data), where it has been successfully managed with hormone replacement therapy in the setting of durable clinical responses. Surveillance for altered pituitary function is included in the safety monitoring program.

1.4 Prior Experience with Similar Investigational Agents

1.4.1 CTLA-4 Blockade

As there is only limited data from human studies with BMS-936558 (MDX-1106), examination of the adverse events or other clinical safety issues associated with ipilimumab, an anti-CTLA4 investigational immunomodulatory mAb currently under development by BMS may provide important background information for the clinical use of BMS-936558 (MDX-1106). Preclinical studies with CTLA-4 blockade revealed a severe and uniformly lethal neonatal phenotype in the knockout model associated with massive lymphoproliferation. Blockade with antibodies was shown to exacerbate disease in some autoimmune models in which there was either a genetic predisposition to autoimmunity or in which vaccination with self antigens resulted in enhanced autoimmunity. Clinical studies have shown an incidence of inflammatory adverse events, termed irAEs, which may be triggered by a loss of tolerance to enteric or self antigens. The primary irAEs have been rash, diarrhea, hepatitis, and an inflammatory colitis. Colitis has been a serious adverse event in 10% to 15% of subjects, and has been generally manageable with steroids without apparent abrogation of antitumor responses. Other related serious adverse events have included panhypophysitis and adrenal insufficiency; these have occurred in less than 5% of subjects.

1.4.2 Other Immunomodulatory Agents

BMS has noted the reports of multi-organ failure in healthy volunteers receiving an activating anti-CD28 mAb (TGN 1412) in a Phase 1 study conducted in the United Kingdom. An interim report, published on 05 April 2006, by the Medicines and Healthcare Products Regulatory Agency identified the antibody TGN 1412, as being the cause of the life-threatening adverse event reactions that occurred in 6 healthy volunteers who experienced cytokine release syndrome, a type of severe systemic inflammatory response. BMS has carefully considered whether an antibody to PD-1 could lead to similar issues, given that PD-1 is a CD28 family member.

BMS has concluded that the occurrence of acute T-cell activation syndrome is unlikely for the reasons detailed below:

1. While PD-1 is related to CD28, it functions as an inhibitor of antigen-specific T-cell activation and not as a pan-specific activator.
2. BMS-936558 (MDX-1106) is designed to block the interaction of PD-1 with its ligands, PD-L1 and PD-L2. BMS-936558 (MDX-1106) is expected to augment T-cell activation in the presence of antigen-specific activating signals and PD-1 ligands. Non-specific activation of T cells should not occur as a consequence of PD-1 blockade in the absence of these signals.
3. While blocking PD-1 eliminates a negative regulatory signal, other homeostatic negative regulatory molecules for T-cell activation remain functional (i.e., CTLA-4).
4. The intended mechanism of action and its safety is supported by our preclinical studies. These preclinical models are carried out with antibodies that have high affinity interactions with the PD-1 molecule in the species employed.
5. Most importantly, and providing support for these conclusions, is the fact that, as of April 2008, BMS-936558 (MDX-1106) has been given as a single dose to 39 subjects at doses ranging from 0.3 to 10 mg/kg, including 21 subjects at a dose of 10 mg/kg, without any occurrence of an acute T-cell activation or cytokine storm syndrome.

1.5 Clinical Studies

1.5.1 Summary of Safety

Three Phase 1, dose-escalating clinical studies (at dose levels ranging from 0.01 mg/kg to 10 mg/kg) have been initiated with BMS-936558 (MDX-1106): 2 in oncology (MDX1106-01 and this study, MDX1106-03 [Phase 1]) and 1 in hepatitis C (MDX1106-02). Data entered into the BMS-936558 (MDX-1106) database as of 28 May 2009 show that 78 subjects have received 1 or more doses of BMS-936558 (MDX-1106) (25 at the highest 10 mg/kg dose level). In these studies, there was no pattern in the incidence, severity, or relationship of adverse events to BMS-936558 (MDX-1106) dose level. The

main toxicities noted include fatigue, anemia, increase in blood alkaline phosphatase, decrease in weight, and lymphopenia. No dose-limiting toxicities have been observed, and only 1 subject (1 mg/kg) experienced a serious adverse event considered by the Investigator to be related to BMS-936558 (MDX-1106) (colitis, after receipt of 5 doses over 9 months in Study MDX1106-01). There were no study drug-related deaths.

Preliminary efficacy results for the 2 cancer studies showed sustained objective responses to BMS-936558 (MDX-1106) in 3 subjects, 1 each in the 1 mg/kg (renal carcinoma), 3 mg/kg (colorectal cancer), and 10 mg/kg (renal carcinoma) dose cohorts. The times to response (and durations of response) were 56 days (57+ days), 57 days (530+ days), and 85 (295+ days) for the 1 mg/kg, 3 mg/kg, and 10 mg/kg dose subjects, respectively. A fourth subject with MEL has been stable for 14+ months, and is still receiving intermittent BMS-936558 (MDX-1106) 10 mg/kg. Preliminary efficacy results from the single-dose hepatitis C study showed a response in 1 subject in the 0.1 mg/kg dose cohort (≥ 0.5 -log or greater decrease from the baseline viral load, repeated on ≥ 2 consecutive measures). Due to the limited clinical experience with BMS-936558 (MDX-1106), expected toxicities have not been fully defined. In this current study, BMS-936558 (MDX-1106) may be expected to have a toxicity profile similar to that of ipilimumab.

There have been 2 cases of apparent flare of a syndrome of bilateral polyarticular arthropathy in subjects, both of whom had a prior history of similar type syndromes that was unknown to the Investigators at the time of enrollment into MDX1106-01 (1 subject received BMS-936558 (MDX-1106) 3 mg/kg and 1 received 10 mg/kg). These were not high-grade adverse events, and promptly responded to moderate corticosteroid treatment. These subjects are ineligible for re-treatment, despite 1 subject having had apparent shrinkage in pulmonary lung cancer lesions, and the other having had shrinkage in cutaneous melanoma lesions.

A serious adverse event of diarrhea/colitis has been reported in a subject with ocular melanoma in MDX1106-01. The subject developed colitis more than 5 weeks after receiving his fifth dose of BMS-936558 (MDX-1106) 1 mg/kg over almost 8 months. The colitis has been managed with steroids and infliximab, administered according to treatment guidelines developed for the management of irAEs observed in the ipilimumab development program. The colitis did not occur until approximately 9 months after the subject's first dose of BMS-936558 (MDX-1106). It is noteworthy in MDX1106-01 that

21 subjects have each received at least a single dose of BMS-936558 (MDX-1106) 10 mg/kg, and 6 of these subjects have received at least 1 additional dose of 10 mg/kg without such an adverse event, including 1 subject who has received 10 additional doses over 18 months. The potential for additional instances of colitis to emerge with repeated dosing will be closely monitored in this study.

Updated clinical safety data is available in the Investigator's Brochure for BMS-936558³³

1.5.2 Rationale for BMS-936558 (MDX-1106) Dosage Selection

The dose levels for the initial Phase 1 single-dose protocol (MDX1106-01) were selected based on an evaluation of in vivo activity data and toxicology data. Based on these studies, it was expected that an effective human dose of BMS-936558 (MDX-1106) would be in the range of 3 to 10 mg/kg. In Protocol MDX1106-01, transient shrinkage of lesions has been observed in subjects administered BMS-936558 (MDX 1106) at doses of 3, and 10 mg/kg, and there has been 3 confirmed partial responses (PRs) at dose levels ranging from 3-10 mg/kg. The emergence of a related significant event of colitis after administration of 5 doses of 1 mg/kg of BMS-936558 (MDX-1106) has been noted above. Additional experience in this study, in which 21 subjects have received 10 mg/kg of single doses of BMS-936558 (MDX-1106), as well as 3 subjects who received 3 doses of 10 mg/kg over 16 weeks, suggests that BMS-936558 (MDX-1106) appears to be well tolerated. In light of these data, 1 mg/kg has been chosen as the initial level for multiple dosing in this trial. Protocol CA209-003 (MDX1106-03) will continue to provide safety monitoring for irAEs in general, and heightened surveillance for events of diarrhea or colitis in particular.

Preliminary pharmacokinetic analysis of single-dose administration of BMS-936558 (MDX-1106) indicates that the half-life of BMS-936558 (MDX-1106) is approximately 20-24 days. Thus, dosing of BMS-936558 (MDX-1106) every 2 weeks in this current study is expected to result in a gradual accumulation of drug levels, and is not likely to achieve steady state levels until after 7 to 9 doses (during the second cycle of treatment).

Preliminary pharmacodynamic data demonstrates that BMS-936558 remains bound to PD-1 receptors on circulating t cells with an estimated mean plateau receptor occupancy of 72% for ≥ 57 days following single dose administration of BMS-936558 with doses

ranging from 0.3 - 10 mg/kg. Additionally, a preliminary estimate of the half-life of BMS-936558 is approximately 20-24 days. Based on these preliminary estimates, it is reasonable to expect that the range of biologically active doses includes dose levels at 1 mg/kg or less. Therefore, it is possible that biweekly administration of 0.1 mg/kg and 0.3 mg/kg may result in meaningful biologic and clinical activity. These dose levels will be explored under Amendment 4

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

The primary objective is to assess the safety and tolerability of multiple doses of BMS-936558 (MDX-1106) in subjects with selected advanced or recurrent malignancies. The malignancies include: mCRPC, RCC, CRC, MEL, and NSCLC.

2.2 Secondary Objective(s)

The secondary objectives are to: 1) assess the host immune response to BMS-936558 (MDX-1106) (immunogenicity); 2) characterize the pharmacokinetic profile of multiple doses of BMS-936558 (MDX-1106); 3) assess the preliminary efficacy of BMS-936558 (MDX-1106) monotherapy; 4) to characterize the dose response relationship in melanoma and in NSCLC; and 5) explore the effects of BMS-936558 (MDX-1106) on humoral and cellular immune responses to tumor antigens and recall responses to a panel of non-tumor antigens.

2.3 Exploratory Objectives

- 1) To explore potential predictive markers associated with BMS-936558 clinical activity including, but not limited to, levels of expression of PD-L1 in tumor specimens prior to treatment.
- 2) To investigate the immunomodulatory activity of BMS-936558 on selected immune cell populations and soluble factors in peripheral blood.

- 3) To characterize the level of PD-1 receptor occupancy by BMS-936558 in peripheral blood.
- 4) To assess the overall survival in subjects receiving BMS-936558.

3 OVERVIEW OF STUDY DESIGN

This is a Phase 1, open-label, multicenter, multidose, dose-escalation study of BMS-936558 (MDX-1106), a fully human monoclonal IgG4 antibody, targeting the Programmed Death-1 (PD-1) membrane receptor on T lymphocytes and other cells of the immune system.

The study will consist of 3 periods: Screening (up to 28 days), Treatment (up to 3 years of active therapy [up to maximum of 2 years of initial treatment plus additional remaining period if re-initiation of study therapy occurs as outlined in section 3.5]), and Follow-up (up to 46 weeks). Each treatment cycle is comprised of 4 doses of study drug administered on Days 1, 15, 29, and 43 with a response assessment between Days 52 and 56. The response assessment must be completed before the first dose in the next cycle.

Following completion and/or discontinuation of the treatment and follow-up periods, all subjects will be followed for survival. See Section 3.6 for additional details on collection of survival data.

3.1 Dose Escalation

Three dose levels are planned: 1, 3, and 10 mg/kg (Note: the 0.1 mg/kg and 0.3 mg/kg dose levels were included as part of Amendment 4 to the protocol and did not impact the dose escalation plan or schedule that has been completed prior to amendment.). Subjects will be assigned to a dose level in the order of study entry. Initially, 3 subjects will be enrolled at the 1 mg/kg dose level. If no subject (0 of 3) in a dose cohort experiences a dose-limiting toxicity (DLT) during the first cycle, then the next dose cohort of 3 subjects will be enrolled at the next higher dose level. If 1 of 3 subjects in a dose cohort experiences a DLT during the first cycle, that cohort will be expanded to 6 subjects. Provided that no more than 1 of 6 subjects in the expanded dose cohort experiences a DLT within the first cycle, then the next dose cohort of 3 subjects will be enrolled at the

next higher dose level. If ≥ 2 of up to 6 subjects in the 1 mg/kg dose cohort experiences a DLT during the first cycle, that cohort will have exceeded the maximum tolerated dose (MTD, which is defined as the highest dose studied at which no more than 1 of 6 subjects has experienced a DLT in Cycle 1), and a lower dose level (0.3 mg/kg) will be tested.

If ≥ 2 of up to 6 subjects in the 3 or 10 mg/kg dose cohort experience a DLT during the first cycle, that cohort will have exceeded the MTD, and the following will occur:

- If no subjects (0 of 3) experienced a DLT at the previously tolerated dose level, 3 additional subjects will be dosed at that dose level.
- If ≤ 1 of 6 subjects experienced a DLT at the previously tolerated lower dose level, an intermediate dose level will be tested. The planned intermediate dose levels will be 2 and 7 mg/kg for the 3 and 10 mg/kg cohorts, respectively.

If 2 or more delayed DLTs are noted within a dose escalation cohort, further accrual will be held pending safety analysis of the event, and will be restarted only with Investigator and Sponsor (BMS) approval at all sites (with FDA and Institutional Review Board [IRB] notification).

No dose escalations or de-escalations are permitted within each subject's treatment; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous cycle. A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

3.2 Expansion Cohorts

To further characterize safety and efficacy, up to 14 expansion cohorts will be enrolled. Enrollment to 7 expansion cohorts has completed; an additional 7 expansion cohorts as described below will be enrolled under Amendment 4. A total of 6 subjects must be enrolled at the MTD (or the highest dose studied where ≤ 1 of 6 subjects experiences a DLT if the MTD is not identified) and evaluated through the end of Cycle 1 before any new subject is dosed in the expansion cohorts. If none of the first 5 subjects have a DLT by the end of Cycle 1, enrollment to the MTD expansion cohorts can begin immediately following enrollment of the sixth subject.

Up to 7 expansion cohorts will be enrolled (accrual to these cohorts has completed as specified in Table 4):

- a. 1 in each of the 5 disease indications at a tolerated dose chosen by the Sponsor that may be either at the highest dose tested that does not exceed the MTD or at a lower dose with evidence of study drug activity
- b. an additional 2 cohorts in subjects with MEL will also be enrolled at doses other than the primary expansion dose (such as 1 and 3 mg/kg if the primary expansion occurs at the 10 mg/kg dose level).

Table 4: Expansion Cohorts Completed Prior to Amendment 4

Tumor Type	Dose Level
Melanoma	1 mg/kg
Melanoma	3 mg/kg
Melanoma	10 mg/kg
Renal Cell Carcinoma	10 mg/kg
Non-small Cell Lung Cancer	10 mg/kg
Colorectal Cancer	10 mg/kg
Prostate Cancer	10 mg/kg

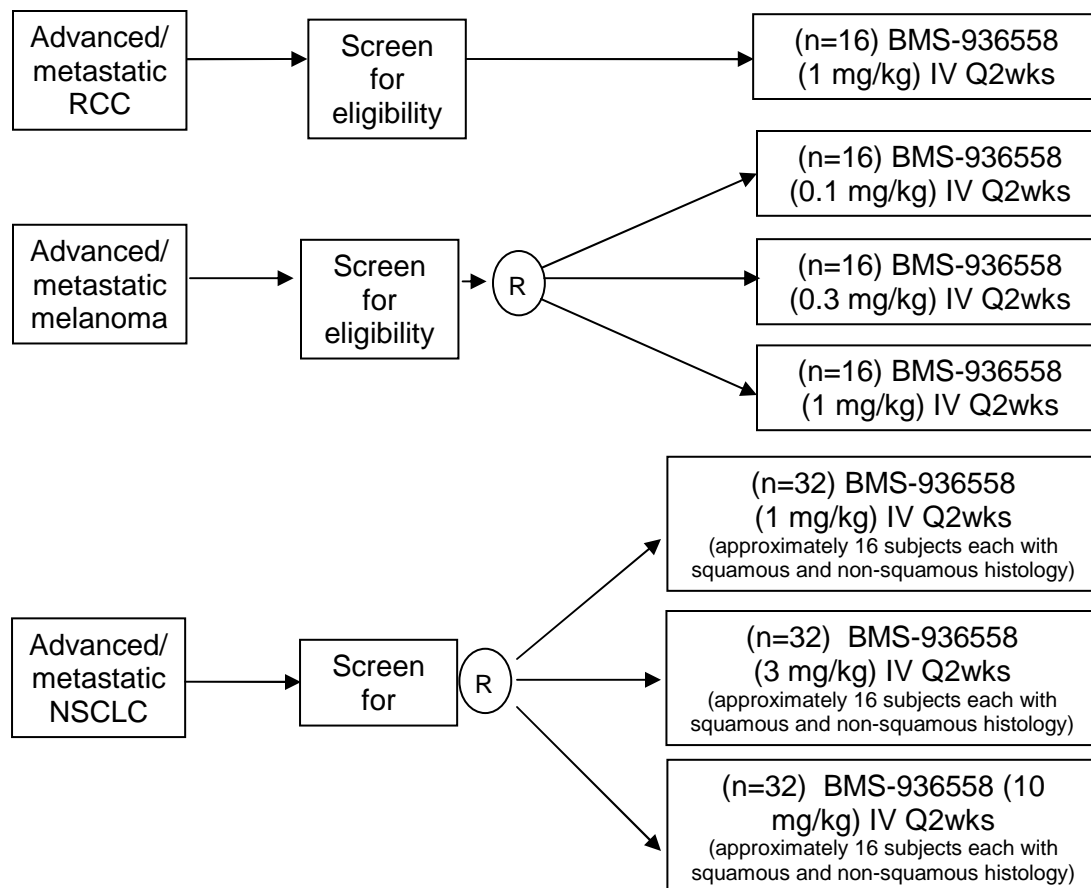
Under this amendment (Amendment 4) the following 7 additional expansion cohorts will be enrolled (please also see [Figure 3](#)):

- c. Additional NSCLC expansion cohorts (3 cohorts): an additional 3 cohorts in subjects with NSCLC will be enrolled; 1 cohort each at the 1 mg/kg, 3 mg/kg, and 10 mg/kg dose levels respectively.
- d. Additional MEL expansion cohorts (3 cohorts): an additional 3 cohorts in subjects with MEL will be enrolled: 1 cohort each at the 0.1 mg/kg, and 0.3 mg/kg dose levels. Subjects enrolled at either the 0.1 mg/kg or 0.3 mg/kg dose levels may be permitted to dose escalate to the 1 mg/kg dose level upon confirmed and worsening

PD within the first 2 treatment cycles and in consultation and agreement by the BMS Medical Monitor.

- e. Additional RCC expansion cohort (1 cohort): an additional cohort in subjects with RCC will be enrolled at the 1 mg/kg dose level.

Figure 3: Expansion Cohorts Added Under Protocol Amendment 4



Subjects with NSCLC enrolled under the additional NSCLC expansion cohorts (c above) will be randomly assigned to one of the 3 dose levels (1, 3, or 10 mg/kg) in order to avoid allocation bias in subject dose assignment.

Subjects with MEL enrolled under the additional MEL expansion cohorts (d above) will be randomly assigned to one of 3 dose levels (0.1, 0.3, or 1 mg/kg) in order to avoid allocation bias in subject dose assignment.

In each cohort, a subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced (if they were withdrawn for early progression they will be counted in the per protocol estimate of overall efficacy).

3.2.1 Initiation of the Primary MTD Expansion Cohorts

A total of 6 subjects must be enrolled at the MTD (or the highest dose studied where ≤ 1 of 6 subjects experiences a DLT if the MTD is not identified) and evaluated through the end of Cycle 1 before any new subject is dosed in the expansion cohorts. If none of the first 5 subjects have a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following enrollment of the sixth subject.

The primary expansion cohorts will enroll subjects from each of the 5 tumor-specific indications: NSCLC, mCRPC, RCC, CRC, and MEL. Approximately 16 subjects (dose escalation plus expansion) will be enrolled in each of the cohorts at the dose chosen for the expansion.

3.2.2 Initiation of the Additional Non-MTD Melanoma Expansion Cohorts

In order to gain additional safety and tolerability information at other doses, as well as provide an initial estimate of efficacy, 2 additional cohorts of subjects with MEL will be enrolled. Approximately 16 subjects per cohort (including any subjects with MEL who were treated in the dose-escalation cohort corresponding to that dose level) will be treated at a dose other than the primary expansion dose (such as at the 1 and 3 mg/kg dose levels if the primary expansion occurs at 10 mg/kg). Enrollment to the first additional expansion cohort (i.e., 1 mg/kg dose level) can begin at the lowest planned dose immediately at the time that the primary expansion opens and will accrue separately beginning from the lowest to the highest dose planned. Accrual to the next higher dose will begin immediately on completion of enrollment to the prior additional cohort.

3.2.3 Initiation of the Additional Expansion Cohorts

In order to gain additional safety and tolerability information and preliminary assessment of efficacy in NSCLC, MEL, and RCC a total of 7 additional cohorts will be enrolled as outlined above. Approximately 16 subjects per cohort will be enrolled in the MEL and RCC cohorts. Approximately 32 subjects per cohort will be enrolled in the NSCLC cohorts. Approximately equal numbers of subjects with squamous histology and non-squamous histologies will be enrolled at each dose level. At each dose level, a minimum of 12 subjects will be enrolled in either of the 2 NSCLC histologic types.

3.2.4 Stopping Rules for the Expansion Cohorts

Enrollment may be held in any expansion cohort if the rate of DLTs is $\geq 33\%$ across all 5 indications at the primary expansion dose level, or in a specific indication if the rate of DLTs is $\geq 33\%$ after enrollment of the first 6 subjects in that indication (including subjects from the dose-escalation cohort at the expansion dose). The DLT rate for a dose level will be based on the cumulative number of subjects at that dose level. Enrollment of additional subjects will be held in a dose level where a $\geq 33\%$ DLT rate occurs and at any higher dose level enrolling at that point in time.

Subjects who are tolerating study drug at a dose level that is being reviewed due to the occurrence of DLTs in another subject will not be automatically precluded from continued dosing during the safety review, and will be allowed to continue dosing for as long as tolerated unless directed otherwise as a result of the safety review. After safety analysis by the Investigators and BMS (with FDA and IRB notification), a decision will be made whether to resume enrollment and continue dosing at the current dose or initiate a new expansion cohort of 16 subjects in 1 or more indications at a lower dose.

For delayed DLTs, enrollment will be held and/or restarted using the same rules as that for DLTs.

3.3 Administration of Additional Treatment Cycles

Tumor response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) with modifications. End of cycle tumor response assessments for all subjects will occur within Days 52 to 56 (results of assessments must be reviewed and documented before the first dose of the next cycle).

The maximum duration of study therapy to be administered to an individual subject in this study is 3 years (up to maximum of 2 years of initial treatment plus additional remaining period if re-initiation of study therapy occurs as outlined in section 3.5).

Following each treatment cycle, the decision to treat a subject with additional cycles of BMS-936558 (MDX-1106) will be based on tumor response evaluation. The response assessment must be completed before the first dose in the next cycle. Unless the subject develops a \geq Grade 3 (CTCAE) adverse event or other adverse event related to BMS-936558 (MDX-1106) that precludes further treatment, subjects will be treated until confirmed complete response (CR) or progressive disease (PD) that is both confirmed and then further progresses as described below..

- **Unconfirmed CR:** Subject will receive an additional cycle of treatment until confirmation of the CR at the next scheduled imaging time point.
- **Confirmed CR:** Subjects will stop treatment and enter the Follow-up Period.
- **Confirmed CR in mCRPC:** Subjects will stop treatment and enter the Follow-up Period if at the end of a treatment cycle they have a confirmed complete prostate-specific antigen (PSA) response (PSA $<$ 0.5 ng/mL for 2 consecutive measurements separated by at least 3 weeks) AND either a confirmed radiologic CR (subjects with measurable disease) OR a radiological response of SD or better (subjects with only non-measurable bony disease).
- **PR or stable disease (SD):** Subjects will continue to receive BMS-936558 (MDX-1106) therapy until confirmed CR, PD (under the conditions defined below), toxicity (as defined below), or the maximum number of cycles allowed have been administered. Subjects will then enter the Follow-up Period.
- **PD:** Accumulating evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological (or PSA – for mCRPC) progression, or the appearance of new lesions or some enlarging lesions while certain target lesions are regressing (“mixed response”). It is thus reasonable, in the absence of clinical deterioration, to continue to treat these subjects until radiologic

progression is **both** confirmed **and** found to have worsened at a subsequent imaging evaluation. Evidence of PD will be based on a comparison with baseline (or nadir) scans, in which there is either an increase of 20% or more in the sum of the longest diameters (SLD) of target lesions taking as reference the smallest sum of the longest diameters (nadir) recorded since Screening, and/or unequivocal progression of non-target lesions, with or without the development of 1 or more new lesions (at least 2 new bone lesions for mCRPC). PD should be confirmed by repeat scans at the next scheduled imaging evaluation 8 weeks later (but no sooner than 4 weeks).

Subjects with PD should be managed in the study as follows:

- PD at the end of Cycle 1: In the absence of clinical deterioration, subjects may continue treatment. In the presence of clinical deterioration, the decision whether to stop treatment should be discussed with the BMS Medical Monitor as described in Section 8.7.
- PD at the end of Cycle 2 or later: Subjects with stable or improved clinical status will continue to be treated with study drug until their next scheduled imaging evaluation.
 - If, at each subsequent imaging evaluation (Cycle 3 or later), **there is no further increase** in the SLD, no unequivocal increase in non-target lesions, and no additional new lesions develop (non-worsening PD), and the subject's clinical status remains stable or has improved, treatment should be continued.
 - If at any subsequent imaging evaluation (Cycle 3 or later), **there is further increase** in the SLD, unequivocal increase in non-target lesions, or development of additional new lesions (worsening PD), the subject should stop treatment and return for Follow-up Visit 1.

For mCRPC, isolated PSA progression in the absence of radiologic or clinical deterioration will **not** be used to determine PD. Stopping treatment for clinical deterioration should be guided by clinical observations outlined in Section 8.7 and Investigator judgment.

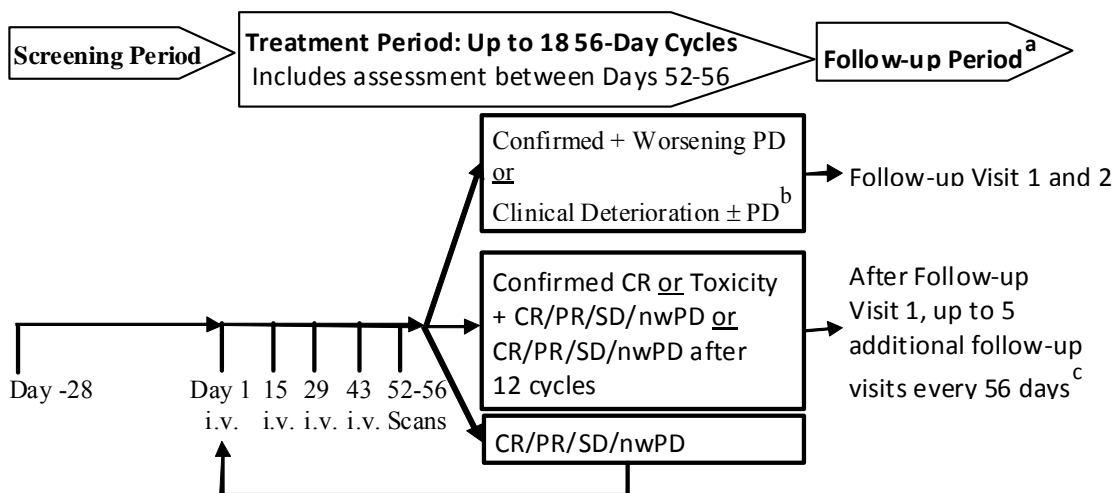
- **Development of a \geq Grade 3 (CTCAE) intolerability or adverse event related to BMS-936558 (MDX-1106) that precludes further treatment with the study drug, but subject does not have worsening progression:** Subjects will complete the remaining visits of their current treatment cycle (without infusions) if possible. Subjects will then enter the Follow-Up Period until worsening progression or completion of all (6) Follow-up Visits.

3.4 Follow-up Period

The maximum duration of follow-up will be 46 weeks. All subjects should complete Follow-up Visit 1 (0 to 7 days after the last visit of the last treatment cycle). Completion of subsequent follow-up visits (Follow-up Visits 2 to 6) will depend on the status of the subject at the end of the Treatment Period. Except for subjects who discontinue due to worsening PD, all subjects will be followed from the last visit until relapse, initiation of a new therapy, or a total of 1 year follow-up, whichever occurs first. Subjects whose PD is confirmed and who have further progression at a subsequent imaging evaluation will only complete Follow-up Visits 1 and 2; Follow-up Visit 2 (for these subjects only) will only include pharmacokinetic and immunogenicity evaluations and adverse event collection.

The flow of subjects through the study is diagrammed in Figure 2 below.

Figure 2: Individual Subject Flow (Up to 2 Years Treatment, Up to 1 Year Follow-up)



CR = complete response; PR = partial response; SD = stable disease;
nwPD = non-worsening progressive disease

^a For all subjects, all adverse events occurring within 70 days of administration of the last dose of study drug will be collected for subjects continuing in the study. For subjects who will discontinue from the study within 70 days after the administration of the last dose of study drug: 1) study drug-related adverse event information will be collected and should be followed to resolution/stabilization, 2) a telephone contact for a safety update would be acceptable if the subject cannot manage an office visit, otherwise the subject should complete Follow-up Visit 2; and 3) only clinically significant or serious adverse

- events that become known and are considered related to study drug will be reported more than 70 days after administration of the last dose of study drug.
- ^b PD that has been confirmed and then worsens or there is clinical deterioration at a subsequent visit. Follow-up Visits 1 and 2 should be done unless precluded by disease progression or clinical deterioration.
- ^c Follow-up should continue until relapse, initiation of a new therapy, or a total of 46 weeks (Follow-up Visits 1 and 2 only for worsening PD), whichever occurs first.

Additional, separate, safety and efficacy summaries will be presented for those subjects who reinitiated study therapy.

3.5 Re-Initiation of Study Therapy For Subjects in Follow-up Period

Subjects entering the follow-up period with ongoing disease control (ongoing CR, PR, or SD) may be permitted to reinitiate study therapy upon confirmed disease progression after discussion and agreement with the BMS Medical Monitor. Subjects reinitiating study therapy should continue to meet eligibility criteria at the time study drug resumes and should not have experienced a DLT that would require permanent discontinuation of study therapy. Subjects will receive study therapy at the same dose level that they received prior to entering the follow-up period. Subjects that resume study therapy in this setting may receive study therapy for a total of 3 years (including the initial treatment period). Re-initiation of study therapy will only be permitted once for any given subject.

Subjects who have completed 1 year of follow-up without evidence of disease progression will not be considered eligible for re-initiation of study therapy.

Additional, separate, safety and efficacy summaries will be presented for those subjects who reinitiated study therapy.

3.6 Survival Follow-up Period

Following completion of the treatment and follow-up periods, all subjects will be followed for survival after completion of treatment phases and through the follow up period of the protocol. At the time of implementation of Amendment 5 of the study protocol, all subjects will be assessed for their survival status and dates of death reported

for any subjects that are deceased. After that initial assessment of all study subjects, any surviving subjects will have their survival status assessed approximately every 3 months by either a telephone or in-person contact until study completion or termination by the Sponsor. No other data (e.g. subsequent therapies, performance status etc.) beyond survival will be collected during these calls/visits.

3.7 Post Study Access to Therapy

At the end of the protocol-specified periods of active study therapy, the sponsor will not continue to supply study drug to subjects/investigators unless the sponsor chooses to extend the study. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

4 STUDY POPULATION

Up to 290 subjects will be enrolled (if no subjects require replacement). One hundred thirty (130) subjects have been enrolled thus far. Under Amendment 4 approximately 160 additional subjects will be enrolled. Subjects with pathologically-verified mCRPC, RCC, CRC, MEL, or NSCLC that is clinically advanced or recurrent and progressing after prior treatment with other therapies, and for which no alternative curative option is available, will be eligible to enroll in the study. Only subjects with RCC, MEL, or NSCLC will be enrolled under Amendment 4.

As soon as the subject is considered for this study and before conducting any study procedures, the subject will have the nature of the study explained to them and will be asked to sign an informed consent form (ICF) and provide Health Insurance Portability and Accountability Act (HIPAA) authorization. The ICF and HIPAA authorization must be obtained before conducting any procedures that do not form a part of the subject's normal care. After signing the ICF and HIPAA Authorization, subjects will be evaluated for study eligibility during the Screening Period (no more than 28 days before study drug administration) according to the following inclusion/exclusion criteria.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

If there is a question about the inclusion or exclusion criteria listed below, the investigator should consult with the sponsor's Medical Monitor, or designee, before enrolling the subject into the study.

For entry into the study, the following criteria MUST be met.

4.1 Inclusion Criteria

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

1. Adults at least 18 years of age;
2. Subjects must have mCRPC, RCC, CRC, MEL, or NSCLC, confirmed by available pathology records or current biopsy, that is advanced (non-resectable), or recurrent and progressing since last antitumor therapy, and for which no alternative, curative standard therapy exists. Indication-specific criteria are detailed in [Appendix 3](#);
3. Tumor tissue (archival or recent acquisition) must be available for correlative studies. Subjects must consent to allow the acquisition of formalin-fixed paraffin-embedded (FFPE) material (block or unstained slides) by study personnel for performance of correlative tissue studies. This inclusion criteria will only apply to subjects enrolled under Amendment 4;
4. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 ([Appendix 4](#));
5. Life expectancy \geq 12 weeks;
6. Must have at least 1 measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) with modification (see [Appendix 1](#)) progressing or new since last antitumor therapy. The measurable lesion(s) must be outside the field of radiation therapy (RT) if there was prior treatment with RT. Subjects with mCRPC and with only non-measurable bone lesions must have either progression with 2 or more new lesions or have PSA progression within the 6-week period before study drug administration;

7. At least 1 and up to 5 prior systemic therapies for advanced/recurrent and progressing disease (unlimited hormonal therapies allowed); Subjects with a diagnosis of mCRPC who have received hormonal therapy, but have not received any other form of systemic therapy (e.g., chemotherapy, immunotherapy) will be considered eligible;
8. Prior chemotherapy or immunotherapy (tumor vaccine, cytokine, or growth factor given to control the cancer) must have been completed at least 4 weeks before study drug administration, and all adverse events have either returned to baseline or stabilized;
9. Prior treated brain or meningeal metastases must be without MRI evidence of progression for at least 8 weeks and off immunosuppressive doses of systemic steroids (> 10 mg/day prednisone or equivalent) for at least 2 weeks before study drug administration;
10. Prior systemic radiation therapy must have been completed at least 4 weeks before study drug administration. Prior focal radiotherapy completed at least 2 weeks before study drug administration. No radiopharmaceuticals (strontium, samarium) within 8 weeks before study drug administration;
11. Immunosuppressive doses of systemic medications, such as steroids or absorbed topical steroids (doses > 10 mg/day prednisone or equivalent) must be discontinued at least 2 weeks before study drug administration;
12. Prior surgery that required general anesthesia must be completed at least 2 weeks before study drug administration. Surgery requiring regional/epidural anesthesia must be completed at least 72 hours before study drug administration and subjects should be recovered. Cutaneous biopsies with only local anesthesia should be completed at least 1 hour prior to study drug administration;
13. Screening laboratory values must meet the following criteria:

WBC	$\geq 2000/\mu\text{L}$
Neutrophils	$\geq 1500/\mu\text{L}$
Platelets	$\geq 100 \times 10^3/\mu\text{L}$
Hemoglobin	≥ 9.0 g/dL

- | | |
|------------|-------------------------------------------------------------------------------------------------------|
| Creatinine | ≤ 2 mg/dL |
| AST | ≤ 2.5 X ULN without, and ≤ 5 x ULN with hepatic metastasis |
| ALT | ≤ 2.5 X ULN without, and ≤ 5 x ULN with hepatic metastasis |
| Bilirubin | ≤ 2 X ULN (except subjects with Gilbert's syndrome, who must have total bilirubin < 3.0 mg/dL) |
14. Women must meet 1 of the following criteria: postmenopausal for at least 24 consecutive months; surgically incapable of bearing children (i.e., have had a hysterectomy or bilateral oophorectomy); or utilizing a reliable form of contraception (either medication [oral, implant, or injection] or a barrier method). In general, the decision for appropriate methods to prevent pregnancy should be determined by discussions between the investigator and the study subject. Women of child bearing potential (WOCBP) must agree to use a reliable form of contraceptive during the study Treatment Period and for at least 70 days following the last dose of study drug. Women must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to the start of investigational product; and
15. Men must agree to the use of contraception during the study Treatment Period and for at least 180 days after the last dose of study drug.

4.2 Exclusion Criteria

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

1. History of severe hypersensitivity reactions to other mAbs;
2. Prior malignancy active within the previous 2 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix or breast;
3. Subjects with any active autoimmune disease ([Appendix 5](#)) or a documented history of autoimmune disease, or history of syndrome that required systemic steroids or immunosuppressive medications, except for subjects with vitiligo or resolved

- childhood asthma/atopy. Subjects with asthma who require intermittent use of bronchodilators (such as albuterol) will not be excluded from this study;
4. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PDL-2, or anti-CTLA-4 antibody (or any other antibody targeting T cell co-stimulation pathways);
 5. Known history of Human Immunodeficiency Virus;
 6. Active infection requiring therapy, positive tests for Hepatitis B surface antigen or Hepatitis C ribonucleic acid (RNA);
 7. Underlying medical conditions that, in the Investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of toxicity determination or adverse events;
 8. Concurrent medical condition requiring the use of immunosuppressive medications, or immunosuppressive doses of systemic or absorbable topical corticosteroids;
 9. Use of other investigational drugs (drugs not marketed for any indication) within 28 days or at least 5 half-lives (whichever is longer) before study drug administration;
 10. Use of any vaccines against infectious diseases (e.g., influenza, varicella, etc.) within 4 weeks (28 days) of initiation of study therapy;
 11. Pregnant or nursing;
 12. Prisoners or subjects who are involuntarily incarcerated; or
 13. Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

5 RANDOMIZATION AND BLINDING

Blinding is not applicable as this is an open-label study.

The dose escalation part of the study and the primary MTD expansion cohorts and additional non-MTD melanoma expansion cohorts were not randomized.

Under Amendment 4, subjects with NSCLC enrolled under the additional NSCLC expansion cohorts (see sections 3.2 and 3.2.3) will be randomly assigned to one of the 3 dose levels (1, 3, or 10 mg/kg) in order to avoid allocation bias in subject dose assignment. Randomization in these cohorts will be stratified by histology cell type (squamous vs. non-squamous).

Similarly, subjects with MEL enrolled under the additional MEL expansion cohorts (see #2 under section 3.2.3) will be randomly assigned to one of 3 dose levels (0.1, 0.3, or 1 mg/kg) in order to avoid allocation bias in subject dose assignment.

Subjects enrolled in the expansion cohorts identified above meeting all eligibility criteria will be randomly assigned to one of the three doses according to a computer-generated randomization schema prepared by a Randomization Coordinator with the Drug Supply Management Department of BMS Research and Development. Randomization numbers will be assigned in the order of enrollment within the Melanoma added expansion cohorts and within the NSCLC added expansion cohorts. Subjects in these cohorts who need to be replaced will be randomized to receive the same dose as the original subject.

6 ASSIGNMENT TO STUDY

The investigative site will contact BMS for treatment assignment once a subject is determined to be eligible for enrollment. Subjects who meet all eligibility requirements will be assigned to a treatment group as determined by BMS. Once assigned, numbers for any screening failures, non-treated, non-evaluable, or discontinued subjects will not be re-used.

7 DOSAGE AND ADMINISTRATION

All protocol-specified investigational and non-investigational products are considered study drug.

7.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as follows:

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

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

In this protocol, investigational product(s) is: BMS-936558 (MDX-1106).

7.2 Non-investigational Product

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 non-investigational products.

In this protocol, non-investigational product(s) is/are: Not applicable for this study.

7.3 Physical Description of Study Drug

BMS-936558 (MDX-1106) is supplied in a single-use 10 mL vial. Each vial contains a concentrated solution with the equivalent of 100 mg of BMS-936558 (MDX-1106) (10 mg/mL).

7.4 Packaging and Labeling

The study drug will be packaged and labeled according to current good manufacturing practices (GMP). Details of the packaging and labeling of clinical supplies may be found in the Pharmacy Manual.

7.5 Ordering Study Drug

Clinical supplies may be requested by completing a Request Form and faxing it or e-mail it to the Drug Supply Coordinator at BMS.

7.6 Storage

BMS-936558 (MDX-1106) vials must be stored at a temperature of 2°C to 8°C and should be 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 BMS-936558 (MDX-1106) include laboratory coats and gloves. After BMS-936558 (MDX-1106) has been prepared for administration, the total storage time (combination of refrigeration and room temperature) is not to exceed 24 hours.

Stability data for BMS-936558 (MDX-1106) following dilution and transfer to the i.v. bag supports either: 24 20 hours at 2°C to 8°C in the refrigerator, or 6 4 hours at room temperature/under room light and 18 16 hours at 2°C to 8°C in the refrigerator. 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 BMS 936558 (MDX-1106) and polyolefin bags have been observed.

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the sponsor. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately.

7.7 Study Drug Preparation and Administration

BMS-936558 is to be administered as an i.v. infusion, using a volumetric pump with a 0.2 micron in-line filter at the protocol-specified doses. It is not to be administered as an i.v. push or bolus injection. At the end of the infusion, the line should be flushed with a sufficient quantity of normal saline.

At doses of 1, 3, and 10 mg/kg, the total dose needed will be diluted to a total volume of 60 mL in 0.9% sodium chloride. In cases where the total dose volume exceeds 60 mL, no dilution is required. At doses of 1, 3, 10 mg/kg, BMS-936558 should be administered over a 1-hour period; infusions will be controlled by a volumetric pump.

For subjects receiving doses at 0.1 mg/kg and 0.3 mg/kg, BMS-936558 will be diluted to a concentration that is as close as possible to but **not lower than** 0.35 mg/mL and infused at a rate of 1 mL/minute. Rounding during dose preparation should be performed only when absolutely necessary and should only be done in a manner that will allow the minimum concentration of 0.35 mg/mL to be maintained.

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 BMS-936558 and polyolefin bags have been observed..

1. Allow the appropriate number of vials of BMS-936558 (MDX-1106) to stand at room temperature for approximately 5 minutes before preparation.
2. Ensure that the BMS-936558 (MDX-1106) solution is clear, colorless and essentially free from particulate matter on visual inspection.
3. Aseptically withdraw the required volume of BMS-936558 (MDX-1106) solution into a syringe, and dispense into an i.v. bag. (If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall and so on.)
4. For subjects receiving doses of 1, 3, and 10 mg/kg, please use the following example to guide study drug preparation:

The total dose to be administered will be diluted to a total volume of 60 mL in sterile normal saline (0.9% sodium chloride). In cases where the total volume is more than 60 mL, no additional dilution is necessary.

Prepare the BMS-936558 (MDX-1106) solution for infusion per the example provided below:

Total dose should be calculated as follows:

Subject body weight in kg x 3 mg (for the 3 mg/kg cohort) = total dose, mg

For example, a subject with a body weight of 70 kg would be administered 210 mg of BMS-936558 (MDX-1106) (70 kg x 3.0 mg/kg = 210 mg). Twenty-one (21) mL of BMS-936558 (MDX-1106) and 39 mL of normal saline would be mixed in the i.v. bag and the solution would be infused over 60 minutes.

5. For subjects receiving doses at 0.1 or 0.3 mg/kg, please see the following example for guidance on how to calculate the required volume for infusion

For 0.3 mg/kg dose and assume subject body weight of 70 kg (other body weights can be calculated similarly):

Total drug to be administered:	0.3 mg/kg x 70 kg = 21 mg
Total prepared dose volume:	21 mg / 0.35 mg/ml = 60 ml
Drug needed for dose preparation:	21 mg / 10 mg/ml = 2.1 ml
0.9% sodium chloride needed for dilution:	60 ml – 2.1 ml = 57.9 ml

For 0.1 mg/kg dose and assume subject body weight of 70 kg (other body weights can be calculated similarly):

Total drug to be administered:	0.1 mg/kg x 70 kg = 7 mg
Total prepared dose volume:	7 mg / 0.35 mg/ml = 20 ml
Drug needed for dose preparation:	7 mg / 10 mg/ml = 0.7 ml
0.9% sodium chloride needed for dilution:	20 ml – 0.7 ml = 19.3 ml

6. Mix by GENTLY inverting several times. DO NOT shake.
7. Visually inspect the final solution. If the infusion is not clear or the contents appear to contain precipitate, the solution should be discarded (according to the instructions in Section 7.6) and documented on the Drug Accountability Log.
8. Record the time BMS-936558 (MDX-1106) was prepared on the i.v. bag label.
9. Attach the i.v. bag containing the BMS-936558 (MDX-1106) solution to the infusion set, 0.2 µm in line filter, and infusion pump.
10. For subjects at the 1, 3, and 10 mg/kg dose levels, the infusion rate of the infusion pump should be adjusted to allow for a total infusion time of 60 minutes. For subjects at the 0.1 mg/kg and 0.3 mg/kg, the infusion rate of the infusion pump should be adjusted to allow for an infusion rate of 1 mL/minute.
11. At the end of the infusion period, flush the line with a sufficient quantity of normal saline.

Do not enter into each vial more than once.

Do not prepare BMS-936558 (MDX-1106) for infusion in glass syringes.

Do not administer study drug as an i.v. push or bolus injection.

7.8 Drug Accountability

BMS is the manufacturer and provider of the study drug supply. All study drug(s) will be supplied to the Investigator by BMS or its designee. Study drug supplies must be kept in an appropriate, secure locked area and stored in accordance with the conditions specified on the labels.

The Investigator or designated study person must maintain an accurate record of dispensing the study drug in a Drug Accountability Log, a copy of which must be given to BMS at the end of the study. The Drug Accountability Log will record the study drugs received, dosages prepared, time prepared, doses dispensed, and doses and/or vials

destroyed. The Drug Accountability Log will be reviewed by the field monitor during site visits and at the completion of the study.

7.9 Dose Adjustments, Infusion Delays, and Missed Doses

There will be no dose adjustments allowed for BMS-936558 (MDX-1106) except for weight changes (10% or greater [increase or decrease]) at the beginning of each cycle and for MEL subjects enrolled in 0.1 and 0.3 mg/kg dose cohorts who meet criteria for intra-subject dose escalation as outlined in section 3.2. In the case that an infusion cannot be administered at a scheduled visit, it has to be administered as soon as possible. If the delay is between 1 and 7 days, the procedures at the original scheduled visit should be performed. If the delay is more than 7 days, the procedures at the next visit should be performed, and subsequent visits will follow every 2 weeks (the infusion at the original scheduled visit will be considered a missed dose). Subjects with infusion delays > 35 days (i.e., 2 missed doses + 7 days) should normally discontinue treatment and enter the Follow-up Period with the exception of delays related to prophylactic vaccinations as outlined in section 10 or after specific consultation and agreement between the investigator and BMS Medical Monitor in settings where benefit/risk may justify continued study therapy (e.g., subject deriving clinical benefit who requires prolonged steroid taper for management of non-DLT irAEs)

7.10 Destruction of Study Drug

If study drugs (those supplied by the sponsor or sourced by the investigator) are to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor.

7.11 Return of Study Drug

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

8 TOXICITY AND MANAGEMENT

8.1 Dose Escalation

Three dose levels are planned: 1, 3, and 10 mg/kg (Note: the 0.1 mg/kg and 0.3 mg/kg dose levels were included as part of Amendment 4 to the protocol and did not impact the dose escalation plan or schedule that has been completed prior to Amendment 4). Subjects will be assigned to a dose level in the order of study entry. Initially, 3 subjects will be enrolled at the 1 mg/kg dose level. If no subject (0 of 3) in a dose cohort experiences a DLT (see definition under Section 8.2) during the first cycle, then the next dose cohort of 3 subjects will be enrolled at the next higher dose level. If 1 of 3 subjects in a dose cohort experiences a DLT during the first cycle, that cohort will be expanded to 6 subjects. Provided that no more than 1 of 6 subjects in the expanded dose cohort experiences a DLT within the first cycle, then the next dose cohort of 3 subjects will be enrolled at the next higher dose level. If ≥ 2 of up to 6 subjects in the 1 mg/kg dose cohort experiences a DLT during the first cycle, that cohort will have exceeded the MTD, defined as the highest dose studied at which no more than 1 of 6 subjects has experienced a DLT in Cycle 1, and a lower dose level (0.3 mg/kg) will be tested. If ≥ 2 of up to 6 subjects in the 3 or 10 mg/kg dose cohorts experience a DLT during the first cycle, that cohort will have exceeded the MTD, and the following will occur:

- If no subjects (0 of 3) experienced a DLT at the previously tolerated dose level, 3 additional subjects will be dosed at that dose level.
- If ≤ 1 of 6 subjects experienced a DLT at the previously tolerated lower dose level, an intermediate dose level will be tested. The planned intermediate dose levels will be 2 and 7 mg/kg for the 3 and 10 mg/kg cohorts, respectively.

No dose escalations or de-escalations are permitted within each subject's treatment.

8.2 Dose-limiting Toxicity

A DLT is defined as a \geq Grade 3 study drug-related adverse event (using NCI CTCAE Version 3.0) occurring during the first cycle (56 days) of dosing, excluding:

- Grade 3 adverse event of tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor),
- Grade 3 rash,
- Grade 3 irAE that resolves to a Grade 1 or less within 28 days, or
- A transient (resolving within 6 hours of onset) Grade 3 infusion-related adverse event.

A Grade 3 irAE that resolves to a Grade 1 or less within 28 days, while not constituting a DLT for dose escalation/expansion purposes, may preclude further administration of BMS-936558 (MDX-1106) to the subject unless agreed upon with the BMS Medical Monitor.

A DLT will be considered related to study drug unless there is a clear, well-documented, alternative explanation for the toxicity. Delayed DLTs are adverse events that meet the criteria of DLTs that occur after Cycle 1. Delayed DLTs will not be used to estimate the MTD for dose escalation.

All adverse events that meet DLT or delayed DLT criteria, as well as any Grade 3 or 4 infusion reactions whether or not the event is a DLT, must be reported to BMS, within 24 hours using the rapid notification procedures described in Section 12.3.

8.3 Stopping Rules for Dose-limiting Toxicity During Dose Escalation

Two or more DLTs in a dose escalation cohort will exceed the MTD.

Delayed DLTs will be evaluated on a case-by-case basis. If 2 or more delayed DLTs are noted within a dose escalation cohort, further accrual will be held pending safety analysis of the adverse events, and will be restarted only with Investigator and BMS, approval at all sites (with FDA and IRB notification).

If there is a previous DLT in a cohort followed by a Grade 3 irAE, further enrollment and treatment of subjects in the cohort should be held for up to 28 days while awaiting the outcome of the Grade 3 irAE. If the Grade 3 irAE does not resolve to Grade 1 or less within 28 days, it will be considered a DLT.

Initial analyses of pharmacokinetic samples from protocol MDX1106-01 indicate that the half life of BMS-936558 (MDX-1106) is approximately 20 to 24 days. Dose-related toxicity is therefore most likely to occur during treatment or within 24 days following treatment.

8.4 Stopping Rules for Dose-Limiting Toxicities in the Expansion Cohort

Enrollment may be held if either the rate of DLTs is $\geq 33\%$ across all indications (including subjects from the dose-escalation cohort at the expansion dose) **or** if the rate of DLTs is $\geq 33\%$ for a specific indication after enrollment of the first 6 subjects in that indication (including subjects from the dose-escalation cohort at the expansion dose). The DLT rate will be based on the total number of subjects in a cohort (dose-escalation plus expansion). New enrollment should be held in the dose level where a $\geq 33\%$ DLT rate occurs and at any higher dose level that might also be enrolling at that point in time (lower dose level expansion may continue). Subjects who are tolerating a study drug dose level that is being reviewed due to DLTs that occurred in other subjects will not be automatically precluded from continued dosing during this safety review, and will be allowed to continue dosing for as long as it is tolerated unless the safety review mandates dose reduction. After safety analysis by the Investigators and BMS (with FDA and IRB notification), a decision will be made whether to resume enrollment and continue dosing at the current dose, or initiate a new expansion cohort of 16 subjects in each of 1 or more of the indications at a lower BMS-936558 (MDX-1106) dose (chosen according to the de-escalation rules above). For delayed DLTs, enrollment will be held and/or restarted using the same rules as that for DLTs.

8.5 Possible Toxicities

There is not enough clinical experience with BMS-936558 (MDX-1106) to define expected toxicities. Possible toxicities could affect the immune system, hematologic,

cardiovascular, hepatic, musculoskeletal, and other systems, and may include the following:

- **Allergic reaction/hypersensitivity:** Fever, chills, shakes, itching, rash, hyper- or hypotension, difficulty breathing. It is likely that most infusion-related adverse events will occur within the first 24 hours after beginning the infusion, and may be treated by slowing or interruption of the infusion, or with supportive treatment as indicated.
- **Widespread immune activation/cytokine storm:** Cytokine storm adverse events may initially look like allergic reaction/hypersensitivity, but are distinguished by more sustained and profound hemodynamic disturbances related to the widespread release of cytokines such as IL-1 and TNF. Symptoms may include fever, myalgia, change in mental status, hypotension, pulmonary infiltrates, metabolic acidosis and acute renal failure. Cytokine storm has been observed with an agonistic anti-CD28 antibody (TGN1412), but is not expected with BMS-936558 (MDX-1106), and has not been seen in either preclinical testing or in human subjects with cancer treated to date.
- **Tumor lysis syndrome:** Rapid lysis of tumors may result in asymptomatic laboratory abnormalities to clinical changes secondary to electrolyte disturbances, including cardiac arrhythmias, neuromuscular irritability, tetany, seizures, and mental status changes (hypocalcemia), acute renal failure (hyperuricemia and hyperphosphatemia), and metabolic acidosis (acute renal failure and lactic acidosis).
- **Immune-related adverse events:** It is possible that syndromes may develop that are most consistent with an underlying enhanced immune response as the driving factor. Such events may consist of persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, or cardiomyopathy. Experience with other immunomodulatory mAbs indicates that irAEs are typically low grade and self limited, more often occur after multiple doses, and most frequently involve the gastrointestinal tract (diarrhea/colitis), skin (rashes), liver (hepatitis), and endocrine systems (a variety of endocrinopathies).
 - **Gastrointestinal system:** Colitis, characterized by new onset of diarrhea, which may be accompanied by abdominal pain and or GI bleeding. Events of Grade 3 or Grade 4 diarrhea as well as Grade 2 diarrhea with blood in stool should be evaluated for colitis. **Any \geq Grade 2 diarrhea/colitis must be reported to BMS, within 24 hours using the rapid notification procedures described in Section 12.3.**
- **Immune suppression:** Subjects should be monitored for signs of new infection or return of a previous infection, with rash, fever, chills, other localizing symptoms, or sepsis that could require antibiotics either as prevention or treatment.
- **Musculoskeletal system:** Muscle or joint aches or swelling, weakness

- **Blood:** A decrease in blood components (platelets, white or red cells) that could lead to infection, bleeding, or anemia.
- **Skin:** The most likely adverse events are rash and pruritus, which generally resolve when drug therapy is discontinued.

8.6 Infusion Reactions

Since BMS-936558 (MDX-1106) contains only human protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. Since this antibody specifically binds to PD-1, this makes it less likely that such a reaction would occur.

As of May 28, 2010, one subject experienced a Grade 3 hypersensitivity reaction necessitating discontinuation of the infusion and investigational product.

Reactions may manifest with symptoms such as fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions will be evaluated as to whether or not the event is a DLT and should be reported within 24 hours using the rapid notification procedures described in Section 12.3.

Prophylactic premedication may be given anytime after the first dose of Cycle 1.

Infusion reactions should be graded according to NCI CTCAE (Version 3.0) guidelines. Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

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

- Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional BMS-936558 (MDX-1106) administrations.

For Grade 2 symptoms: (Moderate reaction, requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g., antihistamines, non-steroidal

anti-inflammatory drugs, narcotics, corticosteroids, i.v. fluids]; prophylactic medications indicated for ≤ 24 hours)

- Stop the BMS-936558 (MDX-1106) infusion, begin an i.v. infusion of normal saline, and treat the subject with diphenhydramine 50 mg i.v. (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid therapy may 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 BMS-936558 (MDX-1106) will be administered at that visit. Administer diphenhydramine 50 mg i.v., and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the case report form (CRF). 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 BMS-936558 (MDX-1106) administrations. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

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

- Immediately discontinue infusion of BMS-936558 (MDX-1106). Begin an i.v. 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 i.v. administration, and/or diphenhydramine 50 mg i.v. with methylprednisolone 100 mg i.v. (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. BMS-936558 (MDX-1106) will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms.

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

8.7 Stopping Rules for Clinical Deterioration

Accumulating evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological (or PSA – for mCRPC) progression, or appearance of new lesions or some enlarging lesions while certain target lesions are regressing (“mixed response”). It is thus reasonable to allow for these possibilities and continue to treat the subject until progression is confirmed and found to be advancing and continuing at the next imaging assessment. These considerations should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment.

Such deterioration will be assessed to have occurred after a clinical event that, in the Investigator’s opinion, is attributable to disease progression, is unlikely to reverse with continued study treatment and therefore indicates that the subject is not benefiting from study treatment **and** can not be managed by the addition of supportive care (such as bisphosphonates and/or bone directed radiotherapy, thoracentesis or paracentesis of accumulating effusions). The decision to continue or stop treatment should be discussed with the BMS Medical Monitor and will be documented in the study records.

Examples of events that may, in the Investigator’s opinion, indicate a lack of clinical benefit include, but are not limited to, the following:

- Performance status decrease of at least 2 points from baseline
- Skeletal related events defined by the following:
 - pathologic bone fracture in the region of cancer involvement
 - cancer related surgery to bone
 - spinal cord or nerve root compression
- Bladder outlet or urethral obstruction
- Development of new central nervous system (CNS) metastases
 - Subjects that develop new CNS metastases in the setting of improving baseline disease may have focal radiation, resection, or other local curative procedures performed after consultation with the Medical Monitor.
 - ◆ If continued study therapy is deemed to offer the subject potential benefit, subjects may be allowed to restart study therapy after recovery from

symptoms related to the procedure performed (i.e., local edema) and steroid dosing at < 10 mg prednisone/day or equivalent.

- ◆ Subjects that have locally curative procedures while on study drug and subsequently develop new CNS metastases at a subsequent imaging assessment should discontinue study therapy and enter the follow-up period.
- Or any setting where the initiation of new anti-neoplastic therapy has been deemed beneficial to the subject even in the absence of any such documented clinical events.

9 COMPLIANCE

The Investigator or their designated study personnel will maintain a log of all study drugs received, dispensed, destroyed, and returned. Drug supplies will be inventoried and accounted for throughout the study.

The Investigator and the study personnel will ensure that each subject receives the calculated dose of the study drug based on body weight.

10 CONCOMITANT THERAPY

All medications taken within 28 days before the administration of study drug and all concomitant therapy administered during the study will be recorded on the relevant CRF, along with the reason for and details of therapy use.

1. Prophylactic premedication may be given if indicated by previous experience with BMS-936558 (MDX-1106) in an individual subject as described in Section 8.6.
2. Inhaled or intranasal corticosteroids (with minimal systemic absorption) may be continued if the subject is on a stable dose. Non-absorbed intra-articular steroid injections will be permitted. Systemic corticosteroids required for the control of infusion reactions or irAEs must be tapered and be at non-immunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) for at least 2 weeks before the next study drug administration. The use of steroids as prophylactic treatment for subjects with contrast allergies to diagnostic imaging contrast dyes will be permitted.

3. Use of new herbal remedies, other marketed anti-cancer chemo/immunotherapy drugs, or investigational drugs (drugs not marketed for any indication) is not permitted.
4. New chemotherapy or immunotherapy is not permitted.
5. Palliative/therapeutic therapies (e.g., focal radiotherapy for pain, thoracocentesis or paracentesis for comfort) may be administered after consultation with the Medical Monitor.
6. The use of live vaccines while on study is prohibited. The use of any killed or attenuated vaccines for the prevention of influenza is permitted at any time without a study drug washout interval. The use of other killed or attenuated vaccines for the prevention of infectious diseases may be permitted on a case-by-case basis and must be discussed with the medical monitor prior to its use. A washout interval prior to and post vaccination may be required in these instances. Any vaccinations administered while on study must be documented in the subject's medical records and recorded in the Case Report Form.

All subjects should be maintained on the same concomitant medications throughout the study period, as medically feasible. Any new concomitant medications prescribed for the subject or changes to dosing/schedule of concomitant medications should be recorded on the appropriate CRF page. The addition of a new concomitant medication for which there is a concern that it may not be permitted should be first reviewed with the BMS Medical Monitor.

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

10.1 Treatment of Isolated Lesions

Treatment of isolated/symptomatic lesions by local surgery or radiation therapy is permitted for palliative or potentially curative management at any time beyond Cycle 2. All interventions should be discussed in advance with the BMS Medical Monitor.

11 STUDY EVALUATIONS

11.1 Study Procedures by Visit

11.1.1 Overview

The study is divided into periods with associated evaluations and procedures that must be performed at specific time points. The Time and Events Schedule ([Table 2](#)) summarizes the frequency and timing of efficacy, safety, and other study measurements. The Pharmacokinetic Blood Sampling Schedule ([Table 3](#)) delineates the frequency and timing of serum sampling for pharmacokinetic assessment.

As soon as the subject is considered for this study and before performing any study procedures, the subject will have the nature of the study explained to him/her, and will be asked to give written informed consent and HIPAA authorization. Informed consent/HIPAA authorization must be obtained before any procedures that do not form a part of the subject's normal care. Baseline imaging and ECG performed as part of the subject's previous routine care before signing the informed consent form and completed within 28 days before the administration of BMS-936558 (MDX-1106) need not be repeated.

All subjects (withdrawn or completed) will have final evaluations and procedures performed.

11.1.2 Screening Period

Subjects will be evaluated for entry criteria during the Screening Period within 28 days before administration of study drug. The following procedures and evaluations will be completed for each subject before Day 1 and before inclusion in the study:

- Informed consent/HIPAA may be obtained greater than 28 days before receiving study drug, before any Screening procedures.
- Inclusion/exclusion criteria
- Demographics and medical history (to include collection of prior medications administered to the subject during the Screening Period, prior and concurrent medical conditions, and baseline signs and symptoms). For subjects with mCRPC, medical history will include at least 3 PSA measurements over the preceding 6 months.
- Baseline signs and symptoms: Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions CRF.
- Diagnosis confirmation and stage
- Tumor-specific therapy history
- Hepatitis B and C testing, including Hepatitis B surface antigen and Hepatitis C antibody (with reflex Hepatitis C RNA if antibody test is positive)
- Testosterone testing in subjects with mCRPC only. Testosterone level must be ≤ 50 ng/dL.
- Vital sign measurements including temperature, pulse, and blood pressure
- Height;
- Weight;
- Complete physical examination (including examination of skin, head, eyes, nose, throat, neck, joints, lungs, heart, abdomen [including liver and spleen], lymph nodes, and extremities). A brief neurological examination should also be performed.
- ECOG performance status
- Clinical laboratory tests ([central laboratory]):
 - Hematology: Complete blood count (CBC) with differential (including absolute lymphocyte count) and direct platelet count.
 - Chemistry: Albumin
SGOT (AST)
SGPT (ALT)
Alkaline phosphatase

- Bilirubin (direct and total)
- Calcium
- Creatinine
- Glucose
- Lactate dehydrogenase (LDH)
- Total protein
- Urea nitrogen (BUN)
- Uric acid
- Electrolytes (including sodium, phosphorous, potassium, chloride, and bicarbonate)
- Urinalysis:
 - Gross examination including specific gravity, protein, glucose, and blood.
 - Microscopic examination including WBC/HPF, RBC/HPF, and any additional findings
- Serum β -HCG pregnancy test (for all women of childbearing potential; serum pregnancy test must be negative to continue)
- Chest radiograph
- 12-lead Electrocardiogram (ECG)
- A brain CT/MRI scan is required at Screening if not performed within the previous 2 months (and NOT required for subjects with mCRPC).
- Tumor imaging (CT/MRI chest/abdomen/pelvis). The same imaging modality technique should be used throughout the protocol.
- Bone scans for subjects with mCRPC and as clinically indicated in subjects in other indications.
- Tumor-specific antigens (PSA [for mCRPC only] including at least 3 PSA measurements over the preceding 6 months; CEA and CA19-9 [for CRC only]).
- Tumor biopsy required if there is no other record of histological diagnosis of tumor.
- Optional research-related tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed at Screening and at other times during the protocol as clinically indicated. Optional tumor or other biopsy for research purposes requires specific agreement by the subject in the informed consent. From those subjects who enroll under Amendment 4 and who consent for optional research-related tumor or other biopsies, a peripheral blood samples will be collected prior to initiation of study therapy and at the time of biopsy. These samples will be analyzed for flow cytometry parameters, cytokine panel, and quantitative immunoglobulins as outlined in section 11.1.3.
- Concomitant medications

11.1.3 Treatment Period

The Treatment Period of the study is divided into cycles with associated evaluations and procedures that must be performed at specific time points (see [Table 2](#)). Subjects who meet selection criteria may start BMS-936558 (MDX-1106) treatment within 0 to 28 days of Screening. Subjects will receive 4 doses of BMS-936558 (MDX-1106) every 14 days during each cycle. Following Cycle 1, the decision whether to treat a subject with additional cycles of BMS-936558 (MDX-1106) will be determined as summarized in Section 3.3. Results of assessments must be reviewed before administering the first dose of the next cycle. No subject will be permitted dose escalations. The maximum duration of study therapy to be administered to an individual subject in this study is 3 years (up to maximum of 2 years of initial treatment plus additional remaining period if re-initiation of study therapy occurs as outlined in section 3.5).

Every effort should be made to schedule visits within the protocol-specified windows. For infusion delays (i.e., by 1 to 13 days) or missed doses, see Section 7.7 for administration details.

A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

11.1.3.1 Cycle 1

Cycle 1 will begin with the first i.v. infusion of BMS-936558 (MDX-1106) (Day 1) and will continue through to completion of evaluations by Day 56. The subject will be given a 60-minute i.v. infusion every 14 days for a total of 4 infusions (Days 1, 15, 29, and 43) with a response assessment between Days 52 and 56.

During Cycle 1, the following evaluations will be performed as indicated in Table 2, and the results will be recorded on the CRF:

- BMS-936558 (MDX-1106) infusions (after all other evaluations for the visit according to the Time and Events Table have been completed except for the post-infusion pharmacokinetic samples)
- Serum sample for pharmacokinetics as outlined in [Table 3](#). (Post-infusion samples should be drawn from a site other than the infusion site [i.e., contralateral arm] on infusion days.)

- Serum sample for immunogenicity (collected before infusion)
- Vital sign measurements to include temperature, pulse, and blood pressure will be obtained as defined in the Time and Events Schedule (Table 2).
- Weight
- Limited physical examination (including measurement of vital signs as well as pulmonary, heart, abdomen, and skin assessments)
- ECOG performance status
- Clinical laboratory tests ([local and central laboratories]; Hematology and clinical chemistry laboratories **must be performed and reviewed before dosing.**)

Any new \geq Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the BMS Medical Monitor should be contacted. Samples should be drawn from a site other than the infusion site [i.e., contralateral arm]) on the days of infusion:

- Hematology with differential (as outlined in Section 11.1.2)
- Clinical chemistry (as outlined in Section 11.1.2)
- Urinalysis

- Immune Safety Assays: Rheumatoid Factor (RF), Thyroid Stimulating Hormone (TSH), Free T4 Level, adrenocorticotrophic hormone (ACTH), C-reactive protein (CRP), Antinuclear Antibody (ANA) titer and pattern.

The following tests, may also be performed on selected stored samples at a later date: anti-DNA antibody, anti-phospholipid antibody, anti-SSA antibody (Ro), anti-islet cell antibody; anti-SSB antibody (La), anti-neutrophil cytoplasm antibody, antithyroglobulin antibody, C3 and C4, anti-LKM antibody, and CH50.

Abnormal endocrine results should be followed up with prolactin and a.m. cortisol tests, and may require an endocrine consult and additional testing.

- Flow cytometry: Fresh whole blood will be sent to the central laboratory. Phenotypic markers to be tested include: CD3, CD4, CD8, CD19, CD14, CD16+56, CD4+CD25, CD4+CD25+CD45RO, CD8+CD25, CD4+HLA-DR, CD8+HLA-DR, CD4+45RO, and CD8+45RO. These samples will not be collected for subjects with RCC and NSCLC enrolled under Amendment 4.
- Serum for subsequent cytokine panel assays: may include: IL-1, 4, 5, 6, 10, 13 and IFN gamma, TNF alpha, and TGF beta. These samples will not be collected for subjects with RCC and NSCLC enrolled under Amendment 4.

- Serum for quantitative immunoglobulins: Samples will be analyzed for IgM, IgG1, IgG2, IgG3, IgG4, IgA. These samples will not be collected for subjects with RCC and NSCLC enrolled under Amendment 4.
- Urine pregnancy test to be performed locally (for all women of childbearing potential; urine pregnancy test must be negative before study drug administration to continue)
- CT/MRI Brain (Not required for mCRPC, or for subjects with other indications with a normal screening CT/MRI Brain, unless clinically indicated by the development of new symptoms that suggest new CNS involvement.)
- Tumor imaging (CT/MRI chest/abdomen/pelvis)
- Bone scan (for all subjects with mCRPC, or if clinically indicated or positive at baseline for other indications)
- Tumor-specific antigens (PSA [only for subjects with mCRPC]; CEA and CA19-9 [only for subjects with CRC])
- Response assessment and documentation
- Blood sample for SNP analyses (These samples will be collected only for subjects enrolled under Amendment 4)
- The following optional test will be performed for research purposes:
 - Cryopreserved peripheral blood mononuclear cells (PBMCs) and plasma: Samples may be subsequently analyzed for immunoreactivity to a panel of peptide recall antigens (Cytomegalovirus, Epstein Barr Virus, and Influenza virus [CEF]). Tumor-specific antigen reactivity or other biomarker testing will be governed by type of tumor and availability of test antigens. These samples will not be collected for subjects with RCC and NSCLC enrolled under Amendment 4.
- For subjects enrolled under Amendment 4, any remaining tumor and blood samples that are available after completion of designated analyses may be used in the future for identification of potential predictive and/or pharmacodynamic markers. Potential assays can include, but are not necessarily limited to, evaluation of peripheral blood samples for soluble-Lymphocyte-activation gene 3 (sLAG-3) and NGKG2D/KLRK1 (killer cell lectin-like receptor subfamily K, member 1) or its ligands. All available tumor biopsy specimens collected during the conduct of this study may be evaluated for expression of PD-1 pathway related markers, such as PDL-1. Together, these assessments will provide exploratory insights into the immunomodulatory activity of BMS-936558.
- Concomitant medications
- Adverse event assessment including specific elicitation of symptoms (see [Appendix 6](#)) that may be indicative of irAEs.

11.1.3.2 Cycle 2+

Following Cycle 1, subjects may receive up to 17 additional cycles of therapy. Day 1 of each cycle is 56 days following Day 1 of the previous cycle. During each of these cycles, subjects will be given a 60-minute i.v. infusion every 14 days for a total of 4 infusions on Days 1, 15, 29, and 43 of each cycle with a response assessment between Days 52 and 56. Following each cycle, the decision whether to treat a subject with additional cycles of BMS-936558 (MDX-1106) will be determined as summarized in Section 3.3. The maximum duration of study therapy to be administered to an individual subject in this study is 3 years (up to maximum of 2 years of initial treatment plus additional remaining period if re-initiation of study therapy occurs as outlined in section 3.5).

The evaluations performed in Cycle 1 will be repeated during Cycle 2 and subsequent cycles as indicated in [Table 2](#), and the results will be recorded on the CRF. The following additional evaluations will also be performed as indicated in Table 2.

- Complete physical examination (as outlined in Section 11.1.2)
- ECG

11.1.4 Follow-up Period

Up to 6 follow-up visits will be conducted after completion of the Treatment Period or as indicated in Section 3.4. The maximum duration of follow-up will be 46 weeks. All subjects should complete Follow-up Visit 1 (0 to 7 days after the last visit of the last treatment cycle). Follow-up Visit 2 (56 days after Follow-up Visit 1) should also be completed if subject stops treatment less than 70 days from discontinuing to obtain follow-up safety information. Completion of subsequent follow-up visits (Follow-up Visits 3 to 6) will depend on the status of the subject at the end of treatment. Except for subjects who discontinue due to worsening PD, all subjects will be followed from the last visit for approximately 1 year until relapse, initiation of a new therapy, or a total of 1 year follow-up, whichever occurs first. Subjects whose PD is confirmed and who have further progression at a subsequent imaging evaluation will only complete Follow-up Visit 1 and 2. The evaluations performed during the Follow-up Visits as indicated in Table 2, with the results will be recorded on the CRF

11.1.5 Cycle 1 Treatment Completion

Whether or not each subject completed study drug treatment through the first cycle will be documented on the CRF, including how many doses in Cycle 1 were received. Subjects will be considered to have completed Cycle 1 treatment if they:

- Completed 4 doses of BMS-936558 (MDX-1106) in Cycle 1, and
- Completed all evaluations at the end of Cycle 1.

11.1.6 Survival Follow-up

Following completion of the treatment and follow-up periods, all subjects will be followed for survival after completion of treatment phases and through the follow up period of the protocol. Subjects will have their survival status assessed approximately every 3 months by either a telephone or in-person contact until study completion or termination by the Sponsor. No other data (e.g. subsequent therapies, performance status etc.) beyond survival will be collected during these calls/visits.

11.1.7 Study Participation

Each subject will have their study participation documented, including the number of cycles completed, the duration of the Follow-up Period, and if discontinuing from the study, the reason for discontinuation. At the end of each cycle, the subject continuation status for each subject will be documented on the CRF.

If for any reason, either study treatment or observations were discontinued, the reason will be recorded. The primary reasons for discontinuation will be documented:

- Adverse event(s)
- Protocol violation
- Disease progression
- Subject withdrew consent
- Subject is lost to follow-up
- Death
- Other

Subjects who discontinue from the study should be followed until resolution and/or stabilization of any adverse event. All subjects who discontinue from the study should complete Follow-up Visits 1 and 2 to be monitored for 70 days following the last dose of BMS-936558 (MDX-1106) for the occurrence of study drug-related adverse events or other clinically significant adverse event. Subjects who are unable to complete the follow-up visits should be contacted at least once within 70 days following the last dose of BMS-936558 (MDX-1106). Telephone contact is acceptable and should be within ± 10 days of the 70-day time point.

11.1.8 Discontinuation of Subjects from Treatment

Subjects **MUST** discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Inability to comply with protocol.
- Discretion of the investigator.
- Disease progression or clinical deterioration as defined in Section 3.3
- Dosing delays greater than the maximum allowed dosing delays as defined in Section 7.9

All subjects who discontinue should comply with protocol specified follow-up procedures as outlined in Section 11.1.6. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

11.2 Efficacy Evaluations

11.2.1 Primary Efficacy Parameter

The primary efficacy parameter is the objective response rate (ORR) (number of subjects with confirmed responses of CR or PR, divided by the total number of treated subjects with measurable disease at baseline) for each indication. Tumor response status will be assessed using RECIST with modification (as detailed in [Appendix 1](#))

11.2.2 Additional Efficacy Parameters

Additional efficacy parameters may include the ORR during the 3 cycles, and Best Overall Response (BOR) for each indication and across all indications with response categories (CR, PR, SD, PD), disease control rate (number of subjects with CR, PR, or SD divided by the total number of treated subjects with measurable disease at baseline), progression free survival (PFS) and the time to response and duration of response for those subjects with a confirmed response, based on RECIST with modification ([Appendix 1](#)).

Exploratory efficacy evaluations will include an immune-related response criteria (irRC) ([Appendix 2](#)) based on modifications to the RECIST (v1.0) (denoted as irRECIST) with the following parameters: irBOR with response categories (irCR, irPR, irSD, and irPD), immune-related Response Rate (irORR) during the entire study, and duration of ir-responses for those subjects with ir-responses. The irORR based on the irBOR outcomes in the first 3 cycles may also be derived.

Overall Survival (OS) will also be calculated as an exploratory efficacy endpoint.

Tumor specific antigen levels for mCRPC (PSA) and CRC (CEA and CA19-9), ([Appendix 3](#)) will be measured to provide additional exploratory assessments of efficacy when appropriate in some tumor types.

11.3 Exploratory Biomarkers of Immune Response

Additional sample collections efficacy may be performed to measure the impact of BMS-936558 (MDX-1106) upon the potency of the immune response and evaluate biomarkers that may ultimately be associated with beneficial clinical responses.

- Samples (including serum and PBMCs) for evaluation of cytokines, lymphocyte phenotype (by flow cytometry), quantitative immunoglobulins, disease-related biomarkers (or antibody responses to selected antigens), cellular immune responses to tumor antigens, and a panel of recall non-tumor antigens may be assessed.
- Expression levels of PD-L1 protein will be assessed by immunohistochemistry techniques in tumor sections collected prior to treatment to explore potential associations with BMS-936558 clinical activity.
- Cryopreserved peripheral blood mononuclear cells will be used to determine PD-1 receptor occupancy using a flow cytometry-based method.
- Available slides and tissue samples from tumor biopsies collected before enrollment in this study may also be examined for tumor markers and inflammatory infiltrates.
- Readily accessible tissue from the optional research-related biopsies may be collected at the time of apparent inflammatory infiltrate or clinical event of note at the tumor or other site. Tissue samples from these tumor biopsies, as well as from any other clinically indicated and consented biopsies conducted during the study will be collected, to assess morphology and the presence or absence of inflammatory infiltrates, and their cellular characterization.
- Additional sample collections and analyses may be performed at selected study sites with a site-specific amendment. All samples collected for these exploratory analyses will be stored, and may be used for subsequent research relevant to tumor immune response.

11.4 Safety Evaluations

The following evaluations will be performed during the study to measure the safety and tolerability of BMS-936558 (MDX-1106): clinical laboratory tests (blood and urine sampling for clinical laboratory parameters), pregnancy testing, ECOG performance

status, physical examinations including vital sign measurements, ECG, and the incidence and severity of treatment-emergent adverse events. Safety assessment will also include evaluations of immune safety and immunogenicity.

11.4.1 Immune Safety Evaluations

Immune safety assays refer to clinical laboratory tests that measure the emergence of auto-immune or other unintended reactivities that the subject may develop as a consequence of BMS-936558 (MDX-1106)-mediated stimulation of the immune system. The presence of these new reactivities may or may not be associated with clinical consequences, and are being monitored as part of the safety surveillance in this protocol.

11.4.2 Immunogenicity

Immunogenicity refers to the development of an immune response to the BMS-936558 (MDX-1106) drug itself, and is characterized by antibodies that the subject may develop that react with BMS-936558 (MDX-1106). These may result in more rapid clearance of BMS-936558 (MDX-1106) from the bloodstream, or predispose the subject to an infusion reaction if the subject is to be retreated with BMS-936558 (MDX-1106) at a later date. Blood samples for immunogenicity analysis will be collected from all subjects at predose on Day 1, predose on Cycle 2 Day 1 and all Follow-up Visits. Samples will be evaluated for development of Human Anti-Human Antibody (HAHA) in subjects.

11.5 Pharmacokinetic Evaluations

Blood samples will be collected for pharmacokinetic evaluation of BMS-936558 (MDX-1106) according to schedule listed in [Table 3](#) of the Time and Events Schedule. Blood samples should be drawn from a site other than the infusion site (i.e., contralateral arm) on days of infusion. If the infusion was interrupted, the reason for interruption will also be documented on the CRF. Blood samples will be processed to collect serum and stored at -70oC. Serum samples will be analyzed for BMS-936558 by a validated ELISA method. Further details of pharmacokinetic sample collection and processing will be provided to the site in the procedure manual.

Pharmacokinetic parameters (C_{max}, C_{min}, T_{max}, AUC(TAU)) will be derived from serum concentration versus time data from subjects with intensive PK sampling. Accumulation Index (AI) will be calculated. Data obtained from subjects with serial sampling and limited sampling will be combined with data from other studies for population pharmacokinetic model and will be reported separately.

12 ADVERSE EVENT REPORTING

Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions CRF.

12.1 Definitions

An adverse event is any undesirable sign, symptom, clinically significant laboratory abnormality, or medical condition occurring after starting study treatment, even if the event is not considered to be study drug-related. Each adverse event is to be reported on an Adverse Event CRF page. Adverse events are graded using the Cancer Therapy Evaluation Program (CTEP) CTCAE, Version 3.0.³⁴ If CTCAE grading does not exist for an adverse event, the severity of mild (1), moderate (2), severe (3), life-threatening (4), and death related to an adverse event (5) will be used. Information about all adverse events, whether volunteered by the subject, discovered by Investigator questioning, or detected through physical examination, laboratory testing, or other means, will be collected and recorded on the Adverse Event CRF page and followed as appropriate. Adverse event monitoring should be continued until adverse event resolution/stabilization (whichever is later).

Medical conditions/diseases present before the infusion of study drug are only considered adverse events if they worsen after receiving any study drug. Clinical events occurring before the administration of study drug but after signing the ICF and providing HIPAA authorization are to be recorded on the Medical History/Current Medical Conditions CRF page. All laboratory values are to be reviewed by the Investigator and abnormal values will be graded according to CTCAE Version 3 and reported in the study report.

A laboratory abnormality is considered an adverse event if it results in

- discontinuation from study drug,
- necessitates therapeutic medical intervention,
- if the Investigator assesses the abnormality as an adverse event, or
- any laboratory test that is clinically significant or meets the definition of an SAE

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value). These adverse events will be recorded on the Adverse Events CRF page and will include all signs, symptoms, or diagnosis associated with them.

As far as possible, each adverse event will also be described by:

1. Description
2. Duration (start and end dates)
3. CTCAE Grade 1 through 5 or severity if CTCAE is not available
4. Relationship to the study drug - related or not related
5. Action(s) taken with study drug
6. Whether event was serious
7. Whether event is ongoing

Relationship to Study Drug

The relationship of each adverse event to study drug will be defined as “not related” or “related”. The Investigator is responsible for determining the study drug relationship for each adverse event that occurs during the study. Assessments are to be recorded on the appropriate CRF page.

Not related

The temporal relationship of the clinical event to study drug administration **makes a causal relationship unlikely**, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

Related

The temporal relationship of the clinical event to study drug administration **makes a causal relationship possible**, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

Action(s) Taken

The actions taken with study drug in response to an adverse event are described on a numerical scale that covers the various possibilities. One or more of these are to be selected:

- | | |
|---|---------------------------------------------------------------|
| 0 | No action taken |
| 2 | Study drug permanently discontinued due to this adverse event |
| 6 | Study drug temporarily interrupted |
| 7 | Study drug dosage adjusted |

12.1.1 Safety Reporting For Adverse Events

All adverse events or other clinically significant adverse events occurring up to 70 days after administration of the last dose of study drug will be collected for subjects continuing in the study.

For subjects who discontinue from the study within 70 days after the administration of the last dose of study drug:

- Study drug-related adverse event information will be collected and should be followed to resolution/stabilization.
- Adverse events that lead to the discontinuation should be followed to resolution/stabilization.
- A telephone contact for the safety update would be acceptable if the subject cannot manage an office visit.

Only study drug-related serious or other clinically significant (e.g., late emerging irAEs that are not serious) adverse events will be collected for all subjects > 70 days after the administration of the last dose of study drug

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

The collection of nonserious AE information should begin at initiation of study drug and should conclude 70 days after last dose of study drug. Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 12.3). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

12.2 Serious Adverse Events

A serious adverse event is defined in general as an untoward (unfavorable) adverse event which:

1. is fatal or life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
2. requires or prolongs hospitalization;
3. is significantly or permanently disabling or incapacitating;
4. constitutes a congenital anomaly or a birth defect; or
5. may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above (Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization).

Suspected transmission of an infectious agent (eg, any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.

Although pregnancy, overdose and cancer are not always serious by regulatory definition, these events must be handled as SAEs for data transmission purposes (See Section 12.5.1 or reporting pregnancies).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

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

Hospitalizations occurring under the following circumstances are not considered serious adverse events: admission to a hospice for respite care; hospitalizations planned before entry into the clinical study; hospitalization for elective treatment of a condition unrelated to the studied indication or its treatment; hospitalization on an emergency, outpatient basis that does not result in admission (unless fulfilling the criteria above); hospitalization as part of the normal treatment or monitoring of the studied indication; or hospitalization to facilitate the work up of a Grade 1 adverse event, including overnight hospitalization following study drug administration for non-medical reasons.

12.3 Rapid Notification of Serious Adverse Events

12.3.1 Reporting Responsibility

Any serious adverse event occurring in a subject after he/she has provided informed consent and HIPAA authorization, and while receiving study treatment; or during the

70 days following study drug administration; or within 30 days of the last visit for screen failures must be reported. The timeframe for reporting after discontinuation of study drug may be extended if there is a strong suspicion that the study drug has not yet been eliminated or the pharmacodynamic effects of the study drug persist beyond 70 days. All serious adverse events must also be reported for the timeframe in which the study drug interferes with the standard medical treatment given to a subject.

The investigator should collect any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

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

Each serious adverse event must be reported by the Investigator to the BMS Pharmacovigilance (PVG) Desk (SAE Reporting FAX Number), or designee, within 24 hours of learning of its occurrence, even if it is not felt be related to study drug. Serious adverse events occurring after 70 days from the last dose of BMS-936558 (MDX-1106) must be reported if deemed related to study drug. The report must include the adverse event term, subject identifier, attribution, description, concomitant medication used to treat the adverse event, and any other relevant information. Follow-up information about a previously reported serious adverse event must also be reported to BMS within 24 hours of receiving the information. BMS, or its designee, may contact the Investigator to obtain further information about a reported serious adverse event. If warranted, an Investigator Alert may be issued to inform all Investigators involved in any study with the same study drug that a serious adverse event has been reported.

12.3.2 Reporting Procedures

The Investigator must complete the Serious Adverse Event Report Form in English, assess the causal relationship to study drug, and send the completed form to the **SAE Reporting FAX Number** within 24 hours, to BMS or its designee. The study monitor

will review the Serious Adverse Event Report Form and the supporting source documents during monitoring visits.

Follow-up information should be sent to the same PVG Desk that received the original Serious Adverse Event Form, within 24 hours of the time the information is known. Either a new Serious Adverse Event Report Form is faxed (indicating that the information is a follow-up), or the original form may be re-faxed (with the new information highlighted and a new date provided). The follow-up report should describe whether the serious adverse event has resolved or is continuing, if and how it was treated, and whether the subject continued or permanently discontinued study participation. The form(s) and FAX confirmation sheet(s) must be retained in the investigational site study file.

The Investigator is responsible for informing the Institutional Review Board/Independent Ethics Committee (IRB/IEC) of the serious adverse event and providing them with all relevant initial and follow-up information about the event. BMS or designee will communicate serious adverse events to the study sites as required by regulatory authorities.

SAEs must be recorded on the BMS SAE Report Form; pregnancies on a BMS Pregnancy Surveillance Form. These original BMS Forms are to remain on site. SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours via confirmed facsimile (fax) transmission, or scanned and reported via electronic mail to:

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: See Contact Information list.

SAE Telephone Contact (required for pregnancy reporting): See Contact Information list.

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

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

All SAEs should be followed to resolution or stabilization.

12.3.3 Contact Persons and Numbers

The BMS Central Emergency Contact telephone and SAE telefax numbers are listed on the cover page of the protocol.

12.4 Overdose

An overdose is defined as the accidental or intentional ingestion/infusion of any excessive dose of a product. For reporting purposes, BMS considers an overdose, regardless of adverse outcome, as a serious adverse event (see Section 12.3, Serious Adverse Events).

12.5 Pregnancy

Pregnancy testing must be performed in all women of childbearing potential throughout the study as specified in the Time and Event Schedule table, and the results of all pregnancy tests (positive or negative) are to be recorded on the CRF. All women of childbearing potential must have a negative pregnancy test before each infusion. If the pregnancy test is positive, the subject must not receive BMS-936558 (MDX-1106) and must not continue in the study. The subject will be followed to determine the outcome of the pregnancy.

In addition, all women of childbearing potential 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 the study Treatment Period part of the study or during the 70-day period following their last dose of study drug.

Male subjects should contact the Investigator immediately if they suspect they may have fathered a child during the study Treatment Period part of the study or during the 180-day

period following their last dose of study drug. When possible, partner's pregnancies should be followed (to term) to determine the outcome.

12.5.1 Reporting of Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject or a female partner of a male study participant 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 for the female study participant in an appropriate manner (eg, dose tapering if necessary for subject safety). Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS within 24 hours and in accordance with SAE reporting procedures described in Section 12.5.1.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form. Infants should be followed for a minimum of 8 weeks.

12.6 Immune-Related Adverse Events

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

Given the intended mechanism of action of BMS-936558 (MDX-1106), namely disinhibition of cellular immune responses, it is possible that syndromes may develop that are most consistent with an underlying enhanced immune response as the driving factor. Such events may consist of persistent rash, diarrhea and colitis, autoimmune

hepatitis, arthritis, glomerulonephritis, or cardiomyopathy. The spectrum of irAEs is currently hypothetical, as very few human subjects have been treated to date, and are based upon preclinical studies in mice deficient in PD-1, as well as experience with other monoclonal antibodies that act by disinhibiting the immune response. Such irAEs may resolve with time, or may require institution of counteracting immunosuppressive therapies.

BMS has observed irAEs in another development program with an immunostimulatory antibody, ipilimumab (anti-CTLA-4). Ipilimumab-induced irAEs are typically low grade and self limited, more often occur after multiple doses, and most frequently involve the gastrointestinal tract (diarrhea/colitis), skin (rashes), liver (hepatitis), and endocrine systems (a variety of endocrinopathies). In addition, the known animal and human toxicity profiles of anti-CTLA-4 antibodies such as ipilimumab include colitis as an expected adverse event. Based on these considerations, BMS-936558 (MDX-1106) may also cause immune-mediated colitis.

Colitis is characterized by new onset of diarrhea, which may be accompanied by abdominal pain and or gastrointestinal bleeding. Events of Grade 3 or Grade 4 diarrhea as well as Grade 2 diarrhea with blood in stool should be evaluated for colitis. All adverse events of colitis \geq Grade 2 are deemed to be Events of Special Interest (ESIs), and should be reported using the reporting procedures described in Section 12.7, even if the adverse event itself is not deemed as serious.

Management Algorithms for High Grade irAEs

Management algorithms for high grade irAEs have been established for ipilimumab, where timely application of defined immunosuppressive regimens appear to be effective in limiting the morbidity and mortality from such events without compromising therapeutic efficacy. A general management algorithm with recommended guidelines for the treatment and monitoring of suspected irAEs, as well as algorithms for specific irAEs (i.e., diarrhea/colitis, endocrinopathy, and hepatotoxicity) are provided in the Investigator Brochure. **All incidents of diarrhea should be managed according to the diarrhea/colitis algorithm.** Additional clinical experience will be required to define the spectrum of irAE-like events that may emerge in the BMS-936558 (MDX-1106)

program, and these algorithms are useful guides towards establishing an effective management approach as experience accumulates.

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

12.7 Rapid Notification of Adverse Events of Special Interest (EOSI)

In addition to serious adverse events, the following adverse events will be reported to the BMS clinical team within 24 hours even if the nature of the adverse event is not deemed serious:

- adverse events that potentially meet DLT criteria
- adverse events that potentially meet the delayed DLT criteria
- Grade 3 or 4 infusion reactions whether or not the event is a DLT
- \geq Grade 2 diarrhea/colitis
- \geq Grade 3 irAE other than diarrhea/colitis
- Any potential Hy's Law case ($> 3 \times$ ULN of either ALT/AST with concurrent $>2 \times$ ULN of Total Bilirubin and lack of alternate etiology)

12.8 Other Safety Considerations

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

13 STATISTICAL METHODS

13.1 Sample Size Determination

The sample size during dose escalation cannot be precisely determined but depends on the observed toxicity. At expansion cohorts, up to 16 or 32 subjects will be treated at fixed doses in a tumor type, to provide additional safety information and preliminary assessment of tumor response, within a disease indication.

With 16 subjects treated in an expansion cohort, at a fixed dose and tumor type the 90% confidence interval for an objective response rate would be (5.3% to 42%) if 3 (19%) subjects had a response, (9.0% to 48%) if 4 (25%) subjects had a response and (13.2% to 54.8%) if 5 (31%) subjects had a response. Similarly, with 32 subjects in each NSCLC expansion cohort, the 90% confidence interval for an objective response rate would be (3% to 22%) if 3 (9.4%) subjects had a response, (4.4% to 26.4%) if 4 (12.5%) subjects had a response, and (6.4%, 30%) if 5 (16%) subjects had a response..

13.2 Study Populations

13.2.1 All Enrolled Population

All subjects who sign informed consent form will be included. Subject disposition will be tabulated using this data set.

13.2.2 All Treated Population

All subjects who receive at least 1 dose or any partial dose of BMS-936558 (MDX-1106). This population will be used for safety analyses, and primary efficacy analyses.

13.2.3 Pharmacokinetic Data Set

All available concentration-time data from subjects who receive BMS-936558 will be reported. All available derived PK parameter values will be included in the PK data set and reported, but only subjects with adequate PK profiles will be included in the summary statistics and statistical analysis.

13.2.4 Response Evaluable Data Set

Response evaluable subjects will be defined as all subjects who receive at least one dose of BMS-936558, have a baseline tumor assessment with measurable disease, and one of the following: 1) at least one on-treatment tumor evaluation, 2) clinical progression, or 3) death prior to the first on-treatment tumor evaluation.

13.2.5 Exploratory Biomarker of Immune Response Data Set

All subjects who receive at least one dose of BMS-936558 and have at least one measurement for a specific marker will be included in the data set for that marker. All treated subjects with at least one baseline measurement will be included in predictive analyses; Treated subjects with baseline measurement and at least one on treatment measurement will be included in pharmacodynamic assessments.

13.3 Statistical Considerations

13.3.1 Demographics and Baseline Characteristics

Subject demographics and baseline characteristics including age, sex, race, ethnicity, weight, baseline disease diagnosis, and medical conditions will be summarized by dose level using descriptive statistics.

13.3.2 Extent of Exposure

The dose of BMS-936558 (MDX-1106) taken by subjects will be summarized by dose level. A by-subject listing of treatment exposure will be generated.

13.3.3 Concomitant Medication

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODD). Concomitant medications will be summarized. Tabulation will be made with respect to the proportion of subjects taking at least 1 concomitant medication for each preferred term during the study. A listing of concomitant medications by subject will be provided.

13.3.4 Efficacy

The primary efficacy parameter is the objective response rate: ORR (number of subjects with confirmed responses of CR or PR, divided by the total number of treated subjects with measurable disease at baseline). Tumor response status will be defined according to RECIST with modification ([Appendix 1](#)). To perform an evaluation of anti-tumor activity, BOR outcomes, objective response rate (ORR), and disease control rate (DCR: number of subjects with CR, PR, or SD divided by the total number of treated subjects with measurable disease at baseline) will be tabulated by frequency distribution overall, and in the first 3 cycles. For ORR in each expansion cohort, an exact Binomial 95% confidence intervals will be determined, by Clopper-Pearson method and presented by tumor type and dose. Median time to response and duration of response will be summarized for those subjects with confirmed responses, using Kaplan-Meier methods; PFS will be similarly summarized. Listings of individual tumor measurements, tumor burden and %changes in tumor burden will be provided. Changes in tumor burden will be presented graphically for each disease type, e.g. by waterfall or other plots.

Exploratory analysis to assess the effect of BMS-936558 on OS will be based on Kaplan-Meier plots and estimating median OS using the Kaplan-Meier approach for each tumor type.

Exploratory efficacy analyses determined by an immune related criterion: irRECIST ([Appendix 2](#)) will include a frequency of irBOR outcomes and irORR, and a summary of duration of ir-responses. All primary efficacy analyses will be based on the all treated population; the response evaluable population may also be used for sensitivity analyses.

The primary efficacy analyses will include all subjects from the first treatment period and follow-up period until disease progression. Efficacy results on subjects who re-initiate study therapy during the follow-up period will be presented separately for the second treatment period.

In order to characterize the dose response in melanoma cohorts, modeling of tumor response (or AE of interest) as a function of dose will be performed, based on parametric, e.g. logistic distribution model. For NSCLC cohorts, tumor response measures (e.g.

ORR) will also be modeled as a function of dose using some parametric or no-parametric (possibly Bayesian) approach.

Summary statistics and plots of measures of tumor specific antigen levels: PSA (for subjects with mCRPC; [Appendix 3](#)), or CEA and CA 19-9 for subjects with CRC, may be provided for these tumor types, based on data availability.

Administrative interim analyses on efficacy may be conducted at various times prior to study completion in order to facilitate program decisions and to support scientific publications or presentations. Interim efficacy summaries may be presented separately for the initial study cohorts (pre-Amendment 4) due to the potentially different follow-up time of subjects enrolled in those cohorts versus those enrolled under the additional expansion cohorts (post-Amendment 4).

13.3.5 Safety

The following safety parameters will be evaluated:

Adverse Events

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. 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.)

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 70 days of discontinuation of dosing or within 30 days of the last visit for screen failures. The investigator should collect any SAE occurring after these time periods that

is believed to be related to study drug or protocol-specified procedure. An SAE report should be completed for any event where doubt exists regarding its status of seriousness. If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

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

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) to categorize a system organ class and a preferred term for each adverse event. The number of subjects who experienced at least 1 adverse event, study drug related adverse event, severe (Grade 3 or above) adverse event, serious adverse event, irAE, immune-related serious adverse event, and the number of subjects withdrawn due to adverse events will be summarized. For each system organ class and preferred term, summaries will be made with respect to the number and proportion of subjects having at least 1 occurrence of an adverse event during the study, using the worst grade reported within a subject. The incidence of adverse events will be presented overall, by system organ class and preferred term, intensity (based on NCI CTCAE Version 3.0), irAEs, and additional grouping by severity and relationship to study drug. Individual listings of adverse events will be provided.

DLTs and study drug-related Grade ≥ 2 adverse events will be listed individually.

Immune Safety Evaluations

A separate listing and summary of all immune-related adverse events (irAE) and inflammatory events regardless of causality (IERC) will be provided by dose and overall.

Administrative interim analyses on safety may be conducted at various times prior to study completion in order to facilitate program decisions and to support scientific publications or presentations. Such safety summaries may include separate presentations for the initial study cohorts (pre-Amendment 4) due to the potentially different follow-up time of subjects enrolled in those cohorts versus those enrolled under the additional

expansion cohorts (post-Amendment 4). Selected safety tabulations may also be provided by tumor.

Physical Examination

Abnormal findings in physical examinations will be recorded as adverse events or baseline medical history and will be included in the respective summaries.

Vital Signs

Vital signs measurements will be summarized by dose level using descriptive statistics.

ECGs

12-lead ECG results will be summarized by dose level.

Clinical Laboratory Tests

Clinical laboratory test values outside the normal range will be flagged in the data listing.

Laboratory data will be summarized by dose level using descriptive statistics. The results of the immune safety tests will be summarized appropriately.

NCI CTCAE Version 3.0 Grade will be assigned to some of the laboratory parameters, which are included in “CTCAE Version 3.0”. Laboratory values will be listed. The laboratory values which are outside normal range will be flagged as H (above high normal limit), L (below lower normal limit), or A (abnormal) in the data listings. The NCI CTCAE Version 3.0 Grade will also be flagged in the data listings.

ECOG Performance Status

ECOG performance status will be summarized by dose level using descriptive statistics.

13.3.6 Immunogenicity

A listing will be provided of all available immunogenicity data. Additionally,

A listing of immunogenicity data from those subjects with at least one positive Human Anti-Human Antibody (HAHA) at any timepoint will be provided by dose regimen. The frequency of subjects with at least one positive HAHA assessment, frequency of subjects who develop HAHA after a negative baseline assessment will be provided by dose. To examine the potential relationship between immunogenicity and safety, the frequency and type of AEs of special interest may be examined by overall immunogenicity status.

Administrative interim analyses on immunogenicity may be provided at various times during the study in order to support program decisions or publications

13.3.7 Pharmacokinetic Parameters

Summary statistics will be tabulated for the pharmacokinetic parameters of BMS-936558 by dose and study cycle/day. To describe the dependency on dose, scatter plots of C_{max} and AUC(TAU) versus dose will be provided for each cycle/day measured. Dose proportionality will be assessed, by estimating the slope of linear regression of BMS-936558 log(C_{max}) on log(dose) and of log(AUC(TAU)) on log(dose) based on a power model. Point estimates and 90% confidence intervals for the dose proportionality parameter (slope of the linear regression) will be calculated for C_{max} and AUC(TAU). Summary statistics for trough (C_{min}) and end of infusion (C_{ei}) concentrations will be tabulated by dose and study cycle. Plots of C_{min} and C_{ei} vs. cycle will be provided by dose. Pharmacokinetic concentrations from limited samples will be listed, and may be used in combination with other studies for exposure-response or population pharmacokinetic modeling, which will be part of a separate report.

Administrative interim analyses of pharmacokinetic may be provided at various times during the study in order to support program decisions or publications

13.3.8 Exploratory Biomarkers

The pharmacodynamic effects based on the immunomodulatory activity of BMS-936558 (MDX-1106) on selected immune cell populations (flow cytometry) and soluble factors in blood and those based on the level of PD-1 receptor occupancy by BMS-936558 in peripheral blood, exploratory immune function markers including flow cytometry markers, humoral and cellular immune responses to tumor antigens (when available) and

a panel of recall non-tumor antigens will be assessed by summary statistics for outcomes from these markers and their changes (or percent changes) from baseline tabulated by cycle visit and dose. In addition, the time course of biomarker measures will be investigated graphically, by summary plots (i.e. box plots) or individual subject plots over time. Possible associations between changes in biomarker measures of interest and pharmacokinetic exposure will be explored.

Potential associations of various biomarker measures (baseline value or change from baseline) with clinical outcome (e.g., tumor response or disease control) will be explored e.g. for expression levels of PD-L1 protein measured by immunohistochemistry techniques in tumor sections at baseline may be explored based on data availability, using response-evaluable subjects, to explore assess potential predictive effects of these markers. Methods such as, but not limited to, logistic regression may be used to further assess such associations.

Measures from markers based on optional samples, e.g. tumor-based markers may be similarly presented, depending on data availability.

Administrative interim analyses of biomarker data may be provided at various times during the study (e.g. for the initial and the additional study cohorts) in order to support program decisions or publications.

14 ETHICAL ASPECTS

14.1 Ethics and Good Clinical Practice

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

The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable

opinion before initiation of the study. Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical license, debarment).

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

14.2 Confidentiality Regarding Study Subjects

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

Personal medical information may be reviewed and/or copied for research, quality assurance, and/or data analysis. This review may be conducted by the study monitor, properly authorized persons on behalf of BMS, an independent auditor, IRBs/IECs or regulatory authorities. Personal medical information will always be treated as confidential.

14.3 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed ICF, and other information provided to subjects must be reviewed by an IRB/IEC. A signed and dated statement that the protocol, and ICF, subject recruitment materials/process (eg, advertisements), and any other written information to be provided to subjects have been approved by the IRB/IEC must be given to BMS before study initiation. The name and occupation of the chairperson and the members of the IRB/IEC (preferred) or the IRB's Health and Human Safety Assurance number must be supplied to BMS or its designee. Any amendments to the protocol which need formal approval, as required by local law or procedure, will be

approved by this committee. The IRB/IEC will also be notified of all other administrative amendments (i.e., administrative changes).

The investigator or sponsor should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects and any updates.

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

14.4 Informed Consent

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

The Investigator, or designee, will explain to each subject (or legally authorized representative) the nature of the research study, its purpose, the procedures involved, the expected duration of subject participation, alternative treatment, potential risks and benefits involved, and any discomfort which may occur during the subject's participation in the study. Each subject will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it and should be given a copy of the signed document. No subject can enter the study and no study-related procedures can be done before his/her informed consent has been obtained.

The ICF must be submitted by the Investigator with the protocol for IRB/IEC approval. BMS supplies a proposed ICF template that complies with regulatory requirements, includes all elements required by ICH, GCP and applicable regulatory requirements, and

is considered appropriate for the study. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki. Any changes to the proposed ICF suggested by the Investigator must be agreed to by BMS or its designee before submission to the IRB/IEC, and a copy of the approved version must be provided to the BMS study monitor after IRB/IEC approval.

Investigators must:

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

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

Subjects unable to give their written consent (eg, stroke patients, or subjects with severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with the subjects' understanding, and should they become capable, personally sign and date the consent form as soon as possible. The explicit wish of a

subject unable to give his or her written consent, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

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

15 ADMINISTRATIVE REQUIREMENTS

15.1 Protocol Amendments

Any change or modification to this protocol requires a written protocol amendment that must be approved by BMS before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the IRB/IEC of all centers and, in some countries, by the regulatory authority. A copy of the written approval of the IRB/IEC must be given to the BMS study monitor, or their designee. Examples of amendments requiring such approval are:

1. Increase in drug dosage or duration of exposure of subjects, or any significant increase in the number of subjects under study;
2. Significant change in the study design (e.g., addition or deletion of a control group);
3. Increase in the number of procedures to which subjects are exposed; or
4. Addition or deletion of a test procedure intended to improve safety monitoring.

These requirements for approval should in no way prevent any immediate action from being taken by the Investigator or by BMS in the interests of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt by the Investigator to be necessary and is implemented by him/her for safety reasons, BMS should be notified and the IRB/IEC for the center should be informed within 1 working day. Any significant deviation must be documented in the CRF.

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

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

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

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

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

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC approval; however, the IRB/IEC for each center must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB/IEC approval that can be treated as administrative amendments include, but are not limited to:

1. Changes in the staff used to monitor studies (e.g., BMS staff versus a contract research organization); and
2. Minor changes (within regulatory guidelines) in the packaging or labeling of study drug.

15.2 Monitoring Procedures

Before study initiation, at a site initiation visit or at an Investigator's meeting, a BMS representative will review the protocol, CRFs, and other study documents with the

Investigators and their staff. During the study, the BMS study monitor, or designee, will visit the site regularly to check the completeness of subject records, accuracy of entries on the CRFs, adherence to the protocol and to GCP, progress of enrollment, and also to ensure that study drug is being stored, dispensed, and accounted for according to specifications.

The Investigator must give the study monitor access to relevant hospital or clinical records to confirm their consistency with the CRF entries. No information in these records about the identity of the subjects will leave the study center. BMS monitoring standards require full verification for the presence of informed consent, HIPAA authorization, adherence to the inclusion/exclusion criteria, documentation of serious adverse events, and recording of efficacy and safety variables. Additional checks of the consistency of source data with the CRFs are performed according to the study-specific monitoring plan.

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

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

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

15.2.1 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

15.3 Recording of Data and Retention of Documents

All information required by the protocol should be provided; any omissions or corrections should be explained. All CRFs should be completed and available for collection within a timely manner, preferably no more than 10 days after the subject's visit (except for the last visit of the last subject, which should be completed in a timely manner, preferably within 5 working days), so that the study monitor may check the entries for completeness, accuracy and legibility, ensure the CRF is signed by the Investigator and transmit the data to BMS or its designee.

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

If Electronic Data Capture (EDC) system is deployed, the eCRF will be completed by the authorized study site personnel. Electronic queries will be used to communicate eligible discrepant data with the study sites.

The Investigator must maintain source documents for each subject in the study. All information on CRFs will be traceable to these source documents, which are generally maintained in the subject's file. The source documents will contain all demographic and medical information, including laboratory data, ECGs, etc., and also a copy of the signed informed consent/HIPAA authorization, which should indicate the study number and title of the study.

Essential documents, as listed below, will be retained by the Investigator for the maximum period required to comply with national and international regulations, or institutional procedures, or for the period specified by the sponsor, whichever is longer. BMS will notify the Investigator(s)/institution(s) when study-related records are no longer required to be retained. The Investigator agrees to adhere to the document retention procedures by signing the protocol. The investigator must contact BMS prior to destroying any records associated with the study.

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

Essential documents include:

1. Signed protocol and all amendments;
2. IRB/IEC approvals for the study protocol and all amendments;
3. All source documents and laboratory records;
4. CRF copies;
5. Subjects' ICF/HIPAA authorization; and
6. Any other pertinent study documents.

15.3.1 Study Drug Records

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

- amount received and placed in storage area
- amount currently in storage area
- label ID number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- non-study disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to the sponsor
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product (IP) dispensing/accountability, as per the Delegation of Authority Form.

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

15.3.2 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

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

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

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

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

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

15.4 Auditing Procedures

In addition to the routine monitoring procedures, BMS, or its designees, may conduct audits of clinical research activities in accordance with internal SOPs to evaluate compliance with the principles of GCP. BMS, its designee, or a regulatory authority may wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority, the Investigator will inform BMS immediately that this request has been made.

15.5 Publication of Results

Any formal presentation or publication of data collected from this study will be considered as a joint publication by the Investigator(s) and the appropriate personnel of BMS. Authorship will be determined by mutual agreement. For multicenter studies, it is mandatory that the first publication be based on data from all centers, analyzed as stipulated in the protocol by BMS statisticians, and not by the Investigators themselves. Investigators participating in multicenter studies agree not to present data gathered from one center or a small group of centers before the full, initial publication, unless formally agreed to by all other Investigators and BMS.

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

BMS must receive copies of any intended communication in advance of submission (at least 30 working days for a journal submission and 15 days for an abstract or oral presentation). BMS will review the communications for accuracy (thus avoiding potential discrepancies with submissions to health authorities), verify that confidential information

is not being inadvertently disclosed, and provide any relevant supplementary information. Authorship of communications arising from pooled data may include members from each of the contributing centers, as well as BMS personnel.

15.6 Disclosure and Confidentiality

By signing the protocol, the Investigator agrees to keep all information generated in connection with the study or provided by BMS or its designee in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC. Study documents provided by BMS (protocols, Investigators' Brochures, CRFs, and other material) will be stored appropriately to ensure their confidentiality. Such confidential information may not be disclosed to others without direct written authorization from BMS, except to the extent necessary to obtain informed consent/HIPAA authorization from subjects who wish to participate in the study.

15.7 Discontinuation of Study

BMS reserves the right to discontinue any study for any reason at any time.

15.8 Data Management

15.8.1 Data Collection

Investigators must enter the information required by the protocol onto the BMS CRFs that are printed on "no carbon required" paper. BMS study monitors or designees will review the CRFs for completeness and accuracy, and instruct site personnel to make any required corrections or additions. The CRFs will be forwarded to BMS, or its designee, with one copy retained at the study site.

If Electronic Data Capture (EDC) system is deployed, eCRF will be completed by the authorized study site personnel. An electronic version of the final eCRF book for each subject will be forwarded to the study sites for record keeping at the study site closure.

15.8.2 Database Management and Quality Control

Data items from the CRFs will be entered into the study database using double data entry with verifications.

Subsequently, the information entered into the database will be systematically checked by Data Management staff following BMS, or its designee, data management procedures. Obvious errors will be corrected by BMS personnel, or its designee. Other errors, omissions, or requests for clarification will be queried; queries will be returned to the study site for resolution using a Data Clarification Form (DCF). A copy of the signed DCF will be kept with the CRFs. After receipt in Data Management, the resolutions will be entered into the database. Quality control audits of all key safety and efficacy data in the database will be conducted as agreed upon by relevant team members.

If EDC is deployed, data will be entered into the EDC system by the authorized study site personnel. Electronic queries will be used to communicate eligible discrepant data with the study sites.

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by joint written agreement of the BMS study team.

16 REFERENCES

- ¹ Cancer Facts and Figures (2006). American Cancer Society. Atlanta GA. 2006.
- ² Bernard A, Lamy L, Alberti I. The Two-signal model of T-cell activation after 30 years. *Transplant* 2002;73:S31-35.
- ³ Pardoll D. Does the immune system see tumors as foreign or self? *Annu Rev Immunol* 2003;21:807-39.
- ⁴ Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. *Annu Rev Immunol* 2004;23:515-48.
- ⁵ Nishimura H, Honjo T. PD-1: an inhibitory immunoreceptor involved in peripheral tolerance. *Trends Immunol* 2001;22(5):265-8.
- ⁶ Freeman GJ, Long AJ, Iwai Y, Bourque K, Chernova T, Nishimura H, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. *J Exp Med* 2000;192(7):1027-34.
- ⁷ Latchman Y, Wood CR, Chernova T, Chaudhary D, Borde M, Chernova I, et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. *Nat Immunol* 2001;2(3):261-8.
- ⁸ Carter LL, Fouser LA, Jussif J, Fitz L, Deng B, Wood CR, et al. PD-1:D-L inhibitory pathway affects both CD4+ and CD8+ T cells and is overcome by IL-2. *Eur J Immunol* 2002;32(3):634-43.
- ⁹ Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. *J Immunol* 2004;173(2):945-54.

(continued)

REFERENCES (*continued*)

- ¹⁰ Sheppard KA, Fitz LJ, Lee JM, Benander C, George JA, Wooters J. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. *FEBS Letters* 2004 Sep 10;574(1-3):37-41.
- ¹¹ Nishimura H, Nose M, Hiai H, Minato N, Honjo T. Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. *Immunity* 1999;11(2):141-51.
- ¹² Nishimura H, Okazaki T, Tanaka Y, Nakatani K, Hara M, Matsumori A, et al. Autoimmune dilated cardiomyopathy in PD-1 receptor-deficient mice. *Science* 2001;291(5502):319-22.
- ¹³ Wang J, Yoshida T, Nakaki F, Hiai H, Okazaki T, Honjo T. Establishment of NOD-Pdcd1^{-/-} mice as an efficient animal model of type I diabetes. *Proc Natl Acad Sci USA* 2005;102(33):11823-8.
- ¹⁴ Okazaki T, Tanaka Y, Nishio R, Mitsuiye T, Mizoguchi A, Wang, J, et al. Autoantibodies against cardiac troponin I are responsible for dilated cardiomyopathy in PD-1-deficient mice. *Nat Med* 2003;9(12):1477-83.
- ¹⁵ Salama AD, Chitnis T, Imitola J, Ansari MJ, Akiba H, Tushima F, et al. Critical role of the programmed death-1 (PD-1) pathway in regulation of experimental autoimmune encephalomyelitis. *J Exp Med* 2003;198(1):71-8.
- ¹⁶ Blazar BR, Carreno BM, Panoskaltsis-Mortari A, Carter L, Iwai Y, Yagita H, et al. Blockade of programmed death-1 engagement accelerates graft-versus-host disease lethality by an IFN- γ -dependent mechanism. *J Immunol* 2003;171(3):1272-7.
- ¹⁷ Barber DL, Wherry EJ, Masopust D, Zhu B, Allison JP, Sharpe AH, et al. Restoring function in exhausted CD8 T cells during chronic viral infection. *Nature* 2006;439:682-7.

(*continued*)

REFERENCES (*continued*)

- ¹⁸ Iwai Y, Terawaki S, Ikegawa M, Okazaki T, Honjo T. PD-1 inhibits antiviral immunity at the effector phase in the liver. *J Exp Med* 2003;198(1):39-50.
- ¹⁹ Iwai Y, Terawaki S, Honjo T. PD-1 blockade inhibits hematogenous spread of poorly immunogenic tumor cells by enhanced recruitment of effector T cells. *Int Immunol* 2004;17(2):133-44.
- ²⁰ Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo H, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade, *Proc Natl Acad Sci USA* 2002;99(19):12293-7.
- ²¹ Strome SE, Dong H, Tamura H, Voss SG, Flies DB, Tamada K, et al. B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma. *Cancer Res* 2003;63:6501-5.
- ²² Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. *Nat Med* 2002;8(8):793-800.
- ²³ Hirano F, Kaneko K, Tamura H, Dong H, Wang S, Ichikawa M, et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. *Cancer Res* 2005;65(3):1089-96.
- ²⁴ Blank C, Brown I, Peterson AC, Spiotto M, Iwai Y, Honjo T, et al. PD-L1/B7H-1 inhibits the effector phase of tumor rejection by T cell receptor (TCR) transgenic CD8+ T cells. *Cancer Res* 2004;64:1140-45.
- ²⁵ Konishi J, Yamazaki K, Azuma M, Kinoshita I, Dosaka-Akita H, Nishimura M. B7-H1 Expression on non-small cell lung cancer cells and its relationship with tumor-infiltrating lymphocytes and their PD-1 expression. *Clin Cancer Res* 2004;10(15):5094-100.

(*continued*)

REFERENCES (*continued*)

- ²⁶ Thompson RH, Gillett MD, Cheville JC, Lobse CM, Dong H, Webster WS, et al. Costimulatory B7-H1 in renal cell carcinoma subjects: indicator of tumor aggressiveness and potential therapeutic target. Proc Natl Acad Sci USA 2004;101(49):17174-9.
- ²⁷ Ohigashi Y, Sho M, Yamada Y, Tsurui Y, Hamada K, Ikeda N, et al. Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand-2 expression in human esophageal cancer. Clin Cancer Res 2005;11(8):2947-53.
- ²⁸ Tsushima F, Tanaka K, Otsuki N, Youngnak P, Iwai H, Omura K, et al. Predominant expression of B7-H1 and its immunoregulatory roles in oral squamous cell carcinoma. Oral Oncol 2005 (article in press).
- ²⁹ Thompson RH, Webster WS, Cheville JC, Lohse CM, Dong H, Leibovich BC, et al. B7-H1 glycoprotein blockade: a novel strategy to enhance immunotherapy in subjects with renal cell carcinoma. Urology 2005;66(5A):10-14.
- ³⁰ Thompson RH, Gillett MD, Cheville JC, Lohse CM, Dong H, Webster WS, et al. Costimulatory Molecule B7-H1 in primary and metastatic clear cell renal cell carcinoma. Cancer 2005 Nov 15;104(10):2084-91.
- ³¹ Dong H, Chen L. B7-H1 pathway and its role in the evasion of tumor immunity. J Mol Med 2003;81(5):281-7.
- ³² Azuma T, Yao S, Zhu G, Flies A, Flies S, Chen L. B7-H1 is a ubiquitous antiapoptotic receptor on cancer cells. Blood 2008;111(7) 3635-3643.

(*continued*)

REFERENCES (*continued*)

- ³³ Anti-PD-1 Human Monoclonal Antibody Investigator Brochure (Version No. 06). Bristol-Myers Squibb Pharmaceutical Research Institute; 2010. Document Control No. 930038243.
- ³⁴ Cancer Therapy Evaluation Program (CTEP) Common Terminology Criteria for Adverse Event (CTCAE), Version 3.0, Division of Cancer Treatment and Diagnosis (DCTD), NCI, National Institute of Health (NIH), Department of Health and Human Services (DHHS), 16 April 2003 (located on the internet at <<http://ctep.cancer.gov>>).

APPENDIX 1 RECIST WITH MODIFICATION

Solid Tumor Response

Measurable disease/target lesions and non-measurable disease/non-target lesions are to be evaluated according to the new standardized RECIST established by the NCI. Each category (measurable and non-measurable lesions) will be assessed and reported independently. (Adapted from Therasse, Arbuck et al. 2000).

Method

CT scans (or MRI) will be performed to evaluate tumor response. All measurements should be taken and recorded in metric notation (mm) using a ruler or calipers.

CT and MRI are the best currently available and reproducible methods to measure target lesions and qualitatively assess non-target lesions selected for response assessment. Conventional CT (non-spiral or non-helical) and conventional MRI (MRI performed without fast scanning techniques) should produce images contiguously reconstructed at 10 mm or less. Spiral (helical or multidetector) CT should produce images contiguously reconstructed between 5 and 8 mm.

Lesions identified on a chest x-ray should be imaged by a CT or MRI scan.

The same method of assessment and the same technique should be used to characterize each site of disease at baseline and during follow-up evaluations.

Documentation of Target and Non-target Lesions

All measurable or target lesions, up to a maximum of 5 lesions per organ and 10 lesions total, representative of all sites of disease, will be identified and measured at baseline and followed as target lesions throughout the study. Target lesions should be selected on the basis of their size (longest diameter) and suitability for accurate reproducibility and measurement on follow-up imaging. The SLD for all target lesions will be calculated and reported as the baseline SLD. The baseline SLD will be used as a reference by which to characterize the objective tumor response at each subsequent tumor assessment point (timepoint). The smallest sum of the longest diameters recorded since baseline will be

used as reference when evaluating for progression. **All other lesions (or sites of disease) should be identified as non-target lesions** and should be recorded at baseline. Measurement of these lesions is not required, but the presence, absence, or worsening of each should be noted throughout follow-up.

Response Confirmation

To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive repeat assessments that should be performed no less than 28 days after the criteria for response are first met. **For this study, the next scheduled tumor assessment can meet this requirement.**

Overall Timepoint Responses (RECIST) for all Possible Combinations of Tumor Responses in Target and Nontarget Lesions With or Without the Appearance of New Lesions

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR/NA	No	CR
CR	SD	No	PR
CR	UE/ND	No	UE
PR	Non-PD/NA	No	PR
PR	UE/ND	No	UE
SD	Non-PD/NA	No	SD
SD	UE/ND	No	UE
PD	Any	Yes or no*	PD
Any	PD	Yes or no*	PD
Any	Any	Yes*	PD
UE	Non-PD/NA	No	UE
ND	Non-PD/NA	No	UE
NA	SD	No	SD
NA	CR	No	CR

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease

UE = unable to evaluate (any target or non-target lesion present at baseline which was not assessed or unable to be evaluated leading to an inability to determine the status of that particular tumor for that timepoint)

NA = not applicable (no target or nontarget lesions identified at baseline)

ND = not done (scans not performed at this timepoint)

* See study specific definition of progressive disease below with regard to assessment of new lesions.

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time are to be classified as having “symptomatic deterioration.” (See Section 8.7)

Definitions

Measurable lesions	Target lesions that can be measured accurately in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques, or as ≥ 10 mm with spiral (helical) computed tomography (CT) scan or two (2) times the reconstruction interval (RI) when using spiral (helical) or multidetector CT, but not less than 10 mm.
Nonmeasurable lesions	Non-target lesions not classified as measurable lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan) and truly nonmeasurable lesions. These include bone lesions on BS, effusions, and leptomeningeal disease. Any measurable lesions that were not classified as target lesions will be classified as non-target lesions.
Target lesions	<p>All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, are to be identified as target lesions and recorded and measured. Target lesions are to be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).</p> <ul style="list-style-type: none"> • Longest diameter for target lesions - The sum of the longest diameter for all target lesions (SLD). • Complete response - Disappearance of all target lesions. • Partial response - At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the Screening sum longest diameter. • Stable disease - Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease. • Progressive disease - At least a 20% increase in the sum of the longest diameters of target lesions (with addition of diameters of any newly emergent measurable lesions), taking as reference the smallest sum of the longest diameters (nadir) recorded since screening. • UE/ND/NA

continued

Definitions (continued)

Nontarget lesions	<p>All lesions other than target lesions (or sites of disease) are to be identified as nontarget lesions and are to be recorded. Measurements of these lesions are not required, but the presence or absence of each is to be noted.</p> <ul style="list-style-type: none">• Complete response - Disappearance of all nontarget lesions.• Incomplete response/stable disease - Persistence of one or more nontarget lesion(s).• Progressive disease - Unequivocal progression of a nontarget lesion or appearance of 1 or more new lesions.• UE/ND/NA
Best overall response	<p>The best overall response is the confirmed overall response. To be assigned a best overall response of partial response or complete response, change in tumor measurements must be confirmed by repeat assessment no less than 4 weeks after the criteria for response of CR or PR are first met.</p>
Methods of measurements	<p>The same imaging modality, method of assessment, and technique must be used throughout the study to characterize each identified and reported lesion. All measurements are to be made with a ruler or calipers; measurements are to be recorded in metric notation.</p>
Clinical examination	<p>Clinically detected lesions are only to be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For skin lesions, documentation by color photography—including a ruler to estimate the size of the lesion—is recommended.</p>
Chest X-ray	<p>Lesions on the chest X-ray are to be acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. Chest X ray is to be performed in full inspiration in the poster-anterior projection. The film to tube distance is to remain constant between examinations. If subjects with advanced disease are not well enough to fulfill these criteria, such situations are to be reported together with the measurements. Lesions bordering the thoracic wall, and lesions bordering or involving the mediastinum, are not suitable for measurements by chest x-ray.</p>

continued

Definitions (continued)

Computed Tomography and Magnetic Resonance Imaging	<p>CT is the imaging modality of choice. Conventional CT and magnetic resonance imaging (MRI) are to be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT is to be performed by use of a 5 mm contiguous reconstruction algorithm. CT scans of the thorax, abdomen, and pelvis are to be contiguous throughout the anatomic region of interest. The minimum size of the lesion is to be no less than double the slice thickness. The longest diameter of each target lesion is to be selected in the axial plane only. For spiral CT scanners, the minimum size of any given lesion at Screening may be 10 mm, provided the images are reconstructed contiguously at 5 mm intervals. For conventional CT scanners, the minimum-sized lesion is to be 20 mm by use of a contiguous slice thickness of 10 mm.</p> <p>In subjects in whom the abdomen and pelvis have been imaged, oral contrast agents are to be given to accentuate the bowel against other soft-tissue masses. Intravenous contrast agents are also to be given, unless contraindicated for medical reasons such as allergy. An adequate volume of a suitable contrast agent is to be given so that the metastases are demonstrated to best effect. All images from each examination are to be included and not “selected” images of the apparent lesion.</p> <p>All window settings are to be included, particularly in the thorax, where the lung and soft-tissue windows are to be considered. Lesions are to be measured on the same window setting on each examination.</p> <p>When MRI is used, lesions are to be measured in the same anatomic plane by use of the same imaging sequences on subsequent examinations. Wherever possible, the same scanner is to be used.</p>
Bone scan	Bone scans are to be used for the assessment of non-target lesions only.
Ultrasound	Ultrasound is not to be used to measure tumor lesions that are clinically not easily accessible.

APPENDIX 2 IMMUNE-RELATED RECIST

Immune-related RECIST (irRECIST) is derived from modified RECIST conventions.

Definitions of Measurable/non-Measurable Lesions

All measurable and non-measurable lesions should be assessed at Screening and at the defined tumor assessment time points (see [Table 1](#)). Additional assessments may be performed, as clinically indicated for suspicion of progression. The Investigator will base response to treatment using the irRECIST.

Measurable Lesions

Target lesions that can be measured accurately in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques, or as ≥ 10 mm with spiral (helical) computed tomography (CT) scan or two (2) times the reconstruction interval (RI) when using spiral (helical) or multidetector CT, but not less than 10 mm.

Non-Measurable Lesions

Non-target lesions not classified as measurable lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan) and truly nonmeasurable lesions. These include bone lesions on BS, effusions, and leptomeningeal disease. Any measurable lesions that were not classified as target lesions will be classified as non-target lesions.

Definitions of Index/non-Index Lesions

Index Lesions

Measurable lesions, up to a maximum of 5 lesions per organ and ten lesions in total, must be identified as index lesions to be measured at Screening. The index lesions should be representative of all involved organs. In addition, index lesions must be selected based on their size (eg, lesions with the longest diameters), their suitability for accurate repeat assessment by imaging techniques, and how representative they are of the subject's tumor burden. At Screening, a Sum of the Longest Diameters (SLD) for all index lesions will be

calculated and considered the baseline SLD. The baseline sum will be used as the reference point to determine the objective tumor response of the index lesions at tumor assessment.

Non Index Lesions

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 evaluated at the same assessment time points as the index lesions. In subsequent assessments, changes in non-index lesions will contribute only in the assessment of complete response.

Calculation of Sum of Longest Diameters (SLD)

Sum of Longest Diameters is an estimate of tumor burden. The greatest perpendicular diameters are used to estimate the size of each tumor lesion. The SLD is calculated as the sum of the longest diameters for index tumor lesions. Several variations of the SLD are identified for the purpose of classification of tumor responses.

SLD at Baseline: The sum of the longest diameters for all index lesions identified at baseline prior to treatment on Day 1.

SLD at tumor assessment: For every on-study tumor assessment collected per protocol or as clinically indicated, the SLD at tumor assessment will be calculated using tumor imaging scans. All index lesions and all new measurable lesions that have emerged after baseline will contribute to the SLD at tumor assessment (irSLD).

SLD at NADIR: For tumors that are assessed more than 1 time after baseline, the lowest value of the SLD (SLD Baseline or SLD at tumor assessment) is used to classify subsequent tumor assessments for each subject. The SLD at tumor assessment using the irRECIST for progressive disease incorporates the contribution of new measurable lesions. Each net percentage change in tumor burden per assessment using irRECIST accounts for the size and growth kinetics of both old and new lesions as they appear. In this study the ir-response as defined by the Investigator will serve as the basis of exploratory efficacy analyses and guide clinical care.

Definition of Index Lesion Response

Immune-related Complete Response (irCR), which is defined as complete disappearance of all index lesions. Lymph nodes that shrink to < 10 mm short axis are considered normal.

Immune-related Partial Response (irPR), which is defined as a decrease, relative to baseline, of 30% or greater in the sum of the longest perpendicular diameters of all index and all new measurable lesions (ie, Percentage Change in Tumor Burden), in the absence of irCR.

Note: the appearance of new measurable lesions is factored into the overall tumor burden, but does not automatically qualify as progressive disease until the SLD increases by $\geq 20\%$ when compared to SLD at nadir

Immune-related Stable Disease (irSD), which is defined as not meeting the criteria for irCR or irPR, in the absence of immune-related progressive disease (irPD)

Immune-related Progressive Disease (irPD), which is defined as at least a 20% increase in Tumor Burden (ie, taking sum of the products of all index lesions and any new measurable lesions) when compared to SLD at nadir.

Definition of Non-Index Lesion Response

Immune-related Complete Response (irCR), which is defined as complete disappearance of all non-index lesions. Lymph nodes that shrink to < 10 mm short axis are considered normal.

Immune-related Partial Response (irPR), non-index lesion(s) are not considered in the definition of PR, this term does not apply.

Immune-related Stable Disease (irSD), non-index lesion(s) are not considered in the definition of SD, this term does not apply.

Immune-related Progressive Disease (irPD), increases in number or size of non-index lesion(s) does not constitute progressive disease unless/until Tumor Burden increases by

20% (ie, the SLD at nadir of index lesions and any new measurable lesions increases by the required amount).

Impact of New Lesions on irRECIST

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

Definition of Overall Response Using irRECIST Will Be Based on the Following Criteria:

- **Immune-related Complete Response (irCR):** Complete disappearance of all tumor lesions (index and non-index), together with no new measurable or unmeasurable lesions, for at least 4 weeks from the date of documentation of irCR. All lymph nodes short axes must be < 10 mm.
- **Immune-related Partial Response (irPR):** The sum of the longest perpendicular diameters of all index lesions is measured and captured as the SPD baseline. At each subsequent tumor assessment, the sum of the longest perpendicular diameters of all index lesions and of new measurable lesions are added together to provide the Immune Response Sum of the Longest Diameters (irSLD). A decrease, relative to baseline of the irSLD of 30% or greater is considered an irPR, in the absence of irCR. Must be confirmed no less than 4 weeks from the first 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 (eg, increase in SLD or irSLD accompanied with significant individual lesion regression, “mixed response”, or in presence of stable or improving performance status/clinical condition) to confirm PD at the following tumor assessment. Any of the following will constitute progressive disease:
 - At least 20% increase in the SLD of all index lesions over nadir SLD calculated for these lesions.
 - At least a 20% increase in the SLD of all index lesions and new measurable lesions (irSLD) over the nadir SLD calculated for the index lesions.

irRC Definitions					
Index Lesion Definition	Non Index Lesion Definition	New Measureable Lesions	New Unmeasureable Lesions	% Change in irSLD Tumor Burdon (including measurable new lesions when present)	Overall irRC Response
Complete Response	Complete Response	No	No	-100%	irCR
Partial Response	Any	Any	Any	≤ -30%	irPR
				> -30% to < +20%	irSD
				≥ +20%	irPD
Stable Disease	Any	Any	Any	> -30% to < +20%	irSD
				≥ +20%	irPD
Progressive Disease	Any	Any	Any	≥ +20%	irPD

Best Overall Response and Date of Progression Using irRECIST (irBOR)

The Investigator will be asked to provide all responses on study and date(s) of progression, if applicable, and the best overall response will be calculated by the sponsor or designee based on the time point responses and tumor measurements provided by the Investigators.

APPENDIX 3 PROSTATE RESPONSE EVALUATION CRITERIA

PSA Assessment

PSA Assessment will be evaluated according to the recommendations of the Prostate cancer Clinical Trials Working Group¹ with modification.

- **PSA Complete Response** is defined as a PSA concentration <0.5 ng/mL for 2 consecutive measurements separated by at least 3 weeks
- **PSA Response** will be defined as a PSA concentration $< 50\%$ of the PSA reference value occurring at any time after treatment is initiated. The PSA reference value will be the PSA concentration measured immediately prior to treatment.²
- PSA decrease of $\geq 30\%$ from baseline by Week 16 will also be assessed.
- **PSA Progression** is defined as follows:
 - In subjects where no decline in PSA from baseline is documented, PSA progression is a $\geq 25\%$ increase from the baseline value along with an increase in absolute value of 2 ng/mL or more after 16 weeks of treatment. It should be confirmed by a second value obtained 3 or more weeks later.
 - In subjects whose PSA nadir is $<100\%$ of the baseline value, PSA progression is $\geq 25\%$ increase from the nadir and an absolute increase of 2 ng/mL or more from the nadir, confirmed by a second value obtained 3 or more weeks later.

Radiographic Assessment

- Bone lesions
 - Progression is defined as the appearance of 2 or more new lesions.
 - Progression should be confirmed by a repeat measurement at least 6 weeks later demonstrating additional new lesions.
- Soft tissue lesions
 - Soft tissue lesions should be assessed according to the modified RECIST ([Appendix 1](#)).

¹ Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, et al. Design and End Points of Clinical Trials for Patients With Progressive Prostate Cancer and Castrate Levels of Testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008; 26:1148-1159.

² Bubley GJ, Carducci M, Dahut W, Dawson N, Daliani D, Eisenberger M, et al. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the prostate-specific antigen working group. J Clin Oncol 1999;17:3461-7.

Subjects should be kept on study until confirmed radiographic or symptomatic response, which is a better reflection of a change in clinical status than PSA measurements, is documented, and an effort should be made not to discontinue therapy solely on the basis of a rise in PSA in the absence of other indicators of disease progression.

APPENDIX 4 TUMOR-SPECIFIC INCLUSION/EXCLUSION CRITERIA

PROSTATE CANCER

Inclusion criteria:

1. Histologic diagnosis of adenocarcinoma of the prostate.
2. Metastatic prostate cancer (positive bone scan and/or measurable disease)
3. Total testosterone < 50 ng/dL, except for subjects with prior orchiectomy, where testosterone does not need to be measured. Subjects should continue their LHRH agonist therapy.
4. Subjects receiving anti-androgen receptor therapy (e.g., Flutamide) may enroll if they have been on a stable dose for at least 2 months before enrollment (during the determination of eligibility) and must continue their therapy during their participation in the study. Subjects who choose to discontinue anti-androgen receptor therapy will complete an 8-week washout period before study drug administration to assess for a withdrawal response. Withdrawal responses typically occur in subjects who are treated with combined androgen blockade (a GnRH analog or orchiectomy in combination with continuous anti-androgen) as initial therapy for a prolonged period of time, or who have responded to adding a peripheral anti-androgen as second-line therapy. It is not necessary to wait the 8 weeks to assess for a withdrawal response in subjects who did not respond or who showed a decline in PSA for 3 months or less after an anti-androgen was administered as a second-line or later intervention.
5. Subjects receiving any herbal product known to decrease PSA levels (e.g., Saw Palmetto and PC-SPES), who have been on a stable dose for 2 or more months before enrollment and plan to continue the herbal product may remain on their regimen through the study. Subjects who have received the herbal products for less than 2 months, or do not plan to continue the products, must discontinue the agent for at least 4 weeks before screening. Progressive disease must be documented after discontinuation of these products.

6. Subjects receiving bisphosphonate therapy must have been on stable doses for at least 4 weeks with stable symptoms before enrollment.
7. Progressive disease despite castrate levels of testosterone:
 - For subjects with measurable disease, progression will be defined by the Response Evaluation Criteria in Solid Tumors (RECIST with modification). Subjects with stable measurable disease may be enrolled if there is evidence of PSA progression.
 - For subjects without progression in, or without any measurable disease, a positive bone scan and elevated PSA will be required.
 - PSA evidence for progressive prostate cancer consists of a PSA level that has risen on at least 2 successive occasions, obtained at least 1 week apart, and both must be obtained after the required wash out periods noted above. The final screening value must be at least 2 ng/mL.
 - For subjects with progression on bone scan only, progression is defined as the appearance of at least 2 or more new lesions compared with a prior scan. In situations where the scan findings are suggestive of a flare reaction, or apparent new lesion(s) may represent trauma, it may prove useful to confirm these results with other imaging modalities such as MRI or fine-cut CT.

Exclusion Criteria:

1. Bone pain due to metastatic bone disease that cannot be managed with a routine, stable dose of a narcotic analgesic.
2. Subjects with rising PSA only.

RENAL CANCER

Inclusion criteria:

1. Subjects must have histologically confirmed diagnosis of renal cell carcinoma (clear cell component) with advanced or recurrent and progressing disease that is not amenable to cure by surgery or other means, and must have failed at least 1 prior

- systemic therapy, including, but not limited to, treatment with Sunitinib, Temsirolimus, Sorafenib, IL-2, and/or chemotherapy.
2. Clinical evidence of or biopsy-proven metastatic disease to a site or sites distant from the primary tumor, that are not deemed to be surgically curative, or the subject is not a surgical candidate.
 3. Must have measurable disease with at least 1 measurable lesion per RECIST with modification.

Exclusion criteria:

1. The following histologies are not allowed: chromophobe, collecting duct, transitional cell carcinoma, or unclassified.

MELANOMA

Inclusion criteria:

1. Subjects must have a histologically confirmed diagnosis of melanoma with advanced disease (previously treated, therapy-refractory or recurrent Stage III (unresectable) or Stage IV); disease no longer controlled by surgery, chemotherapy, or radiotherapy; and disease refractory to or relapsed after standard therapy (including, but not limited to, chemotherapy and/or interleukin-2). All melanomas regardless of primary site of disease will be allowed.
2. Must have measurable disease with at least 1 measurable lesion per RECIST with modification.

Exclusion criteria:

1. No nitrosoureas (e.g., carmustine or lomustine) within the past 6 weeks and during study treatment.

NON-SMALL CELL LUNG CANCER

Inclusion criteria:

1. Subjects with refractory or recurrent histologically or cytologically confirmed non-small cell lung cancer (NSCLC).
2. Malignancy must be deemed unresectable.
3. Subjects should have failed at least one platinum- or taxane-based regimen.
4. Must have measurable disease with at least 1 measurable lesion per RECIST with modification.

COLORECTAL CANCER

Inclusion criteria:

1. Patients with histologically or cytologically confirmed recurrent or refractory colorectal carcinoma.
2. Tumor progression after prior therapy for colorectal cancer such as fluoroipyrimidine (5 FU or capecitabine), irinotecan, oxaplatin, or cetuximab.
3. Progressive disease as defined by any 1 of the following:
 - The appearance of 1 or more new lesions
 - At least a 20% increase in the sum of the longest diameters of the target lesions (taking as reference the smallest sum of the longest diameters recorded since the baseline measurements).

- Increasing carcinoembryonic antigen (CEA). Two values above baseline that are obtained at least 2 weeks apart are adequate to document progressive disease even in the absence of corroborating radiographs, and can also be followed for minor response indications.
4. Must have measurable disease with at last 1 measurable lesion per RECIST with modification.

APPENDIX 5 ECOG PERFORMANCE STATUS

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

³ Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, and Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.

APPENDIX 6 PRE-EXISTING AUTOIMMUNE DISEASES

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

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

Acute disseminated encephalomyelitis	Dermatomyositis	Ord's thyroiditis
Addison's disease	Diabetes mellitus type 1	Pemphigus
Alopecia universalis	Dysautonomia	Pernicious anemia
Ankylosing spondylitis	Eczema	Polyarteritis nodosa
Antiphospholipid antibody syndrome	Epidermolysis bullosa acqquista	Polyarthritis
Aplastic anemia	Gestational pemphigoid	Polyglandular autoimmune syndrome
Asthma	Giant cell arteritis	Primary biliary cirrhosis
Autoimmune hemolytic anemia	Goodpasture's syndrome	Psoriasis
Autoimmune hepatitis	Graves' disease	Reiter's syndrome
Autoimmune hypoparathyroidism	Guillain-Barré syndrome	Rheumatoid arthritis
Autoimmune hypophysitis	Hashimoto's disease	Sarcoidosis
Autoimmune myocarditis	IgA nephropathy	Scleroderma
Autoimmune oophoritis	Inflammatory bowel disease	Sjögren's syndrome
Autoimmune orchitis	Interstitial cystitis	Stiff-Person syndrome
Autoimmune thrombocytopenic purpura	Kawasaki's disease	Takayasu's arteritis
Behcet's disease	Lambert-Eaton myasthenia syndrome	Ulcerative colitis
Bullous pemphigoid	Lupus erythematosus	Vitiligo
Celiac disease	Lyme disease - chronic	Vogt-Kovanagi-Harada disease
Chronic fatigue syndrome	Meniere's syndrome	Vulvodynia
Chronic inflammatory demyelinating polyneuropathy	Mooren's ulcer	Wegener's granulomatosis
Chung-Strauss syndrome	Morphea	
Crohn's disease	Multiple sclerosis	
	Myasthenia gravis	
	Neuromyotonia	
	Opsoclonus myoclonus syndrome	
	Optic neuritis	

APPENDIX 7 LIST OF SYMPTOMS

Subjects should be questioned to elicit information regarding the occurrence of any of the following adverse events, as they may be indicators of immune-related adverse events such as cardiomyopathy, diabetes, thyroid deficiency, adrenal insufficiency, gastritis, lupus, hypersensitivity, or liver toxicity.

Body System	Adverse Event
Cardiovascular	Chest pain
Cardiovascular	Hypotension
Cardiovascular	Pale or purple fingers or toes from cold or stress (Raynaud's phenomenon)
Eyes	Blurry vision
Gastrointestinal	Abdominal bloating
Gastrointestinal	Abdominal pain
Gastrointestinal	Belching
Gastrointestinal	Black stool or blood in stool
Gastrointestinal	Blood in vomit
Gastrointestinal	Burning feeling in stomach
Gastrointestinal	Constipation
Gastrointestinal	Diarrhea
Gastrointestinal	Feeling of fullness
Gastrointestinal	Foul taste in mouth
Gastrointestinal	Mouth sores
Gastrointestinal	Mucosal pigmentation
Gastrointestinal	Nausea
Gastrointestinal	Stomach cramping
Gastrointestinal	Stomach upset
Gastrointestinal	Vomiting
General	Cold intolerance
General	Dizziness
General	Excessive thirst
General	Extreme hunger
General	Fatigue
General	Fever

General	Hypoglycemia
General	Lethargy
General	Loss of appetite
General	Swelling of the abdomen, legs, ankles, feet, face or around the eyes
General	Swollen glands
General	Weakness
General	Weight gain or increased difficulty losing weight
General	Weight loss
Musculoskeletal	Flu-like symptoms, aching muscles or joint pains.
Musculoskeletal	Painful or swollen joints and muscle pain
Nervous	Memory loss
Psychiatric	Decreased libido
Psychiatric	Depression
Psychiatric	Irritability
Reproductive	Abnormal menstrual cycles
Respiratory	Difficulty breathing
Skin	Blistering of the skin
Skin	Dry, rough pale skin
Skin	Hair loss
Skin	Itching
Skin	Rash
Skin	Sensitivity to the sun
Skin	Coarse, dry hair
Skin	Cutaneous pigmentation
Skin	Jaundice
Urinary	Frequent urination

MEDAREX

Page: 1 of 82
Protocol Number: MDX1106-03
Version: Original
Development Phase: Phase 1b
IND Number: 100,052
Document Status: Final
Date: 23 July 2008

Clinical Protocol MDX1106-03

A Phase 1b, Open-label, Multicenter, Multidose, Dose-escalation Study of MDX-1106 in Subjects with Selected Advanced or Recurrent Malignancies

Study Director/Medical Monitor

Israel Lowy, MD, PhD
Senior Director, Clinical Science
Office Phone Number: +1-908-479-2447
Office Fax Number: +1-908-479-2410
Mobile Phone Number: +1-908-770-6477
Email: ILowy@medarex.com

Clinical Operations Contact

Daniel McDonald, MBA
Manager, Clinical Operations
Office Phone Number: +1-908-479-2529
Office Fax Number: +1-908-479-2415
Mobile Phone Number: +1-908-797-0122
Email: DMcDonald@medarex.com

SAE Reporting FAX Number

+1-908-479-2408

Central Emergency Phone Number

+1-800-246-2912

If any Medarex contact information is changed during the course of the study, this will be done by Medarex, with written notification to the Investigator(s), and will not require (a) protocol amendment(s).

Property of Medarex, Inc.
519 Route 173 West
Bloomsbury, NJ 08804

Confidential

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be used, divulged, published, or otherwise disclosed without the written consent of Medarex, Inc. These restrictions on disclosure will apply equally to all future information supplied to you or generated by you in connection with the study.

TABLE OF CONTENTS

SYNOPSIS	5
ABBREVIATIONS	9
TIME AND EVENTS SCHEDULE	11
1. INTRODUCTION AND RATIONALE.....	17
1.1. Background.....	17
1.2. Programmed Death-1 (PD-1) and the Antitumor Immune Response	17
1.3. Summary of MDX-1106: Preclinical Studies	20
1.3.1. Summary	20
1.3.2. Preclinical Data with PD-1 Blockade or Deficiency and MDX-1106	22
1.4. Prior Experience with Similar Investigational Agents.....	23
1.4.1. CTLA-4 Blockade.....	23
1.4.2. Other Immunomodulatory Agents	23
1.5. Clinical Studies	24
1.5.1. Summary of Safety	24
1.5.2. Rationale for MDX-1106 Dosage Selection	25
2. STUDY OBJECTIVES.....	25
2.1. Primary Objective(s).....	25
2.2. Secondary Objective(s).....	26
3. OVERVIEW OF STUDY DESIGN	26
3.1. Overview.....	26
3.2. Administration of Additional Cycles	28
4. STUDY POPULATION	30
4.1. Inclusion Criteria	30
4.2. Exclusion Criteria	32
5. RANDOMIZATION AND BLINDING.....	32
6. ASSIGNMENT TO STUDY	32
7. DOSAGE AND ADMINISTRATION	33
7.1. Physical Description of Study Drug	33
7.2. Packaging and Labeling	33
7.3. Ordering Study Drug.....	33
7.4. Storage	33
7.5. Study Drug Preparation and Administration.....	33
7.6. Drug Accountability.....	34
7.7. Infusion Delays and Missed Doses	35
8. TOXICITY AND MANAGEMENT	35
8.1. Dose Escalation.....	35
8.2. Dose-limiting Toxicity.....	36
8.3. Stopping Rules for Dose-limiting Toxicity During Dose Escalation	36
8.4. Stopping Rules for Dose-Limiting Toxicities During the Expansion Phase	37

TABLE OF CONTENTS *(continued)*

8.5.	Possible Toxicities	37
8.6.	Infusion Reactions	38
8.7.	Stopping Rules for Clinical Deterioration	40
9.	COMPLIANCE.....	41
10.	CONCOMITANT THERAPY.....	41
11.	STUDY EVALUATIONS.....	42
11.1.	Study Procedures by Visit.....	42
11.1.1.	Overview	42
11.1.2.	Screening Period	42
11.1.3.	Treatment Period.....	44
11.1.3.1.	Cycle 1	44
11.1.3.2.	Cycle 2 to 12	46
11.1.4.	Follow-up Period	47
11.1.5.	Cycle 1 Treatment Completion.....	47
11.1.6.	Study Completion	47
11.2.	Efficacy Evaluations	48
11.2.1.	Primary Efficacy Parameter	48
11.2.2.	Secondary Efficacy Parameters	48
11.2.3.	Exploratory Evaluations of Immune Response.....	48
11.3.	Safety Evaluations	49
11.3.1.	Immune Safety Evaluations	49
11.3.2.	Immunogenicity	49
11.4.	Pharmacokinetic Evaluations.....	49
12.	ADVERSE EVENT REPORTING	50
12.1.	Definitions.....	50
12.2.	Serious Adverse Events	51
12.3.	Rapid Notification of Serious Adverse Events	52
12.3.1.	Reporting Responsibility	52
12.3.2.	Reporting Procedures.....	53
12.3.3.	Contact Persons and Numbers	53
12.4.	Overdose	53
12.5.	Pregnancy.....	53
12.6.	Immune-Related Adverse Events	54
12.7.	Rapid Notification of Adverse Events of Importance.....	55
13.	STATISTICAL METHODS	56
13.1.	Sample Size Determination.....	56
13.2.	Study Populations	56
13.2.1.	Safety Population	56
13.2.2.	Per-protocol Population	56
13.3.	Statistical Consideration	56
13.3.1.	Demographics and Baseline Characteristics.....	57
13.3.2.	Extent of Exposure.....	57

TABLE OF CONTENTS *(continued)*

13.3.3. Concomitant Medication.....	57
13.3.4. Efficacy	57
13.3.5. Safety	58
13.3.6. Pharmacokinetic Parameters	59
13.3.7. Immune Function	59
13.4. Missing Data Handling	59
13.5. Statistical Software	59
14. ETHICAL ASPECTS	60
14.1. Ethics and Good Clinical Practice	60
14.2. Confidentiality Regarding Study Subjects.....	60
14.3. Institutional Review Board/Independent Ethics Committee.....	60
14.4. Informed Consent.....	61
15. ADMINISTRATIVE REQUIREMENTS.....	61
15.1. Protocol Amendments.....	61
15.2. Monitoring Procedures.....	62
15.3. Recording of Data and Retention of Documents	62
15.4. Auditing Procedures.....	63
15.5. Publication of Results	63
15.6. Disclosure and Confidentiality	64
15.7. Discontinuation of Study	64
15.8. Data Management	64
15.8.1. Data Collection	64
15.8.2. Database Management and Quality Control	64
16. REFERENCES.....	66
17. APPENDICES	69
Appendix 1: RECIST With Modification	70
Appendix 2: Prostate Response Evaluation Criteria.....	75
Appendix 3: Tumor-Specific Inclusion/Exclusion Criteria	76
Appendix 4: ECOG Performance Status	79
Appendix 5: Pre-existing Autoimmune Diseases	80
Appendix 6: List of Symptoms.....	81

SYNOPSIS

TITLE

A Phase 1b, Open-Label, Multicenter, Multi-dose, Dose-escalation Study of MDX-1106 in Subjects with Selected Advanced or Recurrent Malignancies

PROTOCOL NUMBER

MDX1106-03

OBJECTIVES

The primary objective is to characterize the safety and tolerability of multiple doses of MDX-1106 in subjects with selected advanced or recurrent malignancies. The malignancies include: metastatic castration-resistant prostate cancer (mCRPC), renal cell carcinoma (RCC), malignant melanoma (MEL), and non-small cell lung cancer (NSCLC).

The secondary objectives are to: 1) assess the host immune response to MDX-1106 (immunogenicity); 2) characterize the pharmacokinetic profile of multiple doses of MDX-1106; 3) assess the efficacy of MDX-1106 monotherapy; and 4) explore the effects of MDX-1106 on humoral and cellular immune responses to tumor antigens and recall responses to a panel of non-tumor antigens.

OVERVIEW OF STUDY DESIGN

This is a Phase 1b, open-label, multicenter, multi-dose, dose-escalation study of MDX-1106, a fully human monoclonal IgG4 antibody, targeting the Programmed Death-1 (PD-1) membrane receptor on T lymphocytes and other cells of the immune system. The study will consist of 3 periods: Screening (up to 28 days), Treatment (up to 12 8-week cycles), and Follow-up (up to 46 weeks). Each treatment cycle is comprised of 4 doses of study drug administered on Days 1, 15, 29, and 43 with a response assessment between Days 52 and 56. The response assessment must be completed before the first dose in the next cycle.

Dose-escalation Phase

Three dose levels are planned: 1, 3, and 10 mg/kg. Subjects will be assigned to a dose level in the order of study entry. Initially, 3 subjects will be enrolled at the 1 mg/kg dose level. If no subject (0 of 3) in a dose cohort experiences a dose-limiting toxicity (DLT, see definition under SAFETY EVALUATIONS) during the first cycle, then the next dose cohort of 3 subjects will be enrolled at the next higher dose level. If 1 of 3 subjects in a dose cohort experiences a DLT during the first cycle, that cohort will be expanded to 6 subjects. Provided that no more than 1 of 6 subjects in the expanded dose cohort experiences a DLT within the first cycle, then the next dose cohort of 3 subjects will be enrolled at the next higher dose level. If ≥ 2 of up to 6 subjects in the 1 mg/kg dose cohort experiences a DLT during the first cycle, that cohort will have exceeded the maximum tolerated dose (MTD, which is defined as the highest tested dose at which no more than 1 of 6 subjects has experienced a DLT in Cycle 1), and a lower dose level (0.3 mg/kg) will be tested. If ≥ 2 of up to 6 subjects in the 3 or 10 mg/kg dose cohort experience a DLT during the first cycle, that cohort will have exceeded the MTD, and the following will occur:

- If no subjects (0 of 3) experienced a DLT at the previously tolerated dose level, 3 additional subjects will be dosed at that dose level.
- If ≤ 1 of 6 subjects experienced a DLT at the previously tolerated lower dose level, an intermediate dose level will be tested. The planned intermediate dose levels will be 2 and 7 mg/kg for the 3 and 10 mg/kg cohorts, respectively.

If 2 or more **delayed DLTs** (see definition under SAFETY EVALUATIONS) are noted within a dose cohort, further accrual will be held pending safety analysis of the event, and will be restarted only with Investigator and Sponsor (Medarex, Inc.) approval at all sites (with FDA and Institutional Review Board [IRB] notification).

No dose escalations or de-escalations are permitted within each subject's treatment. A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

Expansion Phase

To further characterize safety and efficacy, additional subjects will be enrolled at the MTD (or the highest dose studied if the MTD is not identified) in 3 tumor-specific expansion cohorts: NSCLC, mCRPC, and MEL+RCC. Up to 16 subjects will be enrolled in each of the NSCLC and mCRPC cohorts. For the MEL+RCC expansion cohort, 16 subjects are required in 1 of the 2 indications; up to 16 subjects may be enrolled in the 'other' indication (enrollment will be stopped in the 'other' indication at the time that the other 3 expansion cohorts [NSCLC, mCRPC and either MEL or RCC] each accrue 16 subjects). A total of 6 subjects must be enrolled at the MTD (or the highest dose studied where ≤ 1 of 6 subjects experiences a DLT if the MTD is not identified) and evaluated through the end of Cycle 1 before any new subject is dosed in the expansion cohorts. If none of the first 5 subjects have a DLT by the end of Cycle 1, enrollment to the expansion cohorts can begin immediately following enrollment of the 6th subject.

Enrollment will be stopped in all expansion cohorts if the rate of DLTs is $\geq 33\%$ across all indications (including subjects from the Dose-escalation Phase at the expansion dose) or if the rate of DLTs is $\geq 33\%$ in a specific indication after enrollment of the first 6 subjects in that indication (including subjects from the Dose-escalation Phase at the expansion dose). After safety analysis by the Investigators and Medarex (with FDA and IRB notification), a decision will be made whether to initiate a new expansion cohort of 16 subjects in 1 or more indications at a lower MDX-1106 dose (chosen according to the de-escalation rules above). For delayed DLTs, enrollment will be paused using the same rules as that for DLTs. After safety review of delayed DLTs by the Investigators and Medarex (with FDA and IRB notification), a decision will be made whether to resume enrollment at the current dose (with or without a limitation in the total number of allowed cycles) or to initiate a new expansion cohort in 1 or more of the indications at a lower dose (using the same de-escalation schedules as that for DLTs).

ADMINISTRATION OF ADDITIONAL CYCLES

The maximum number of cycles to be administered to an individual subject in this study is 12. Following each treatment cycle, the decision to treat a subject with additional cycles of MDX-1106 will be based on ongoing tumor response (evaluation performed between Days 52 and 56 and before the first dose in the next cycle). Day 1 of each cycle occurs upon completion of the previous cycle, and should be 56 days following Day 1 of the previous cycle.

Unless the subject develops a \geq Grade 3 Common Terminology Criteria for Adverse Events (CTCAE) adverse event or other adverse event related to MDX-1106 that precludes further treatment, subjects will be treated until confirmed complete response (CR) or progressive disease (PD) that is confirmed and worsens. If a subject is eligible to receive additional cycles, the first dose of the next cycle should be given 14 days after the last dose of the prior treatment cycle but should not be later than 28 days.

DURATION OF TREATMENT/STUDY PARTICIPATION

The maximum duration of study drug treatment for a subject is approximately 2 years.

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

STUDY POPULATION

Up to 76 subjects will be enrolled if only the planned dose levels are used. Subjects will be enrolled who have pathologically-verified mCRPC, RCC, MEL, or NSCLC that is clinically advanced or recurrent after prior treatment with other therapies, and for which no alternative curative option is available.

DOSAGE AND ADMINISTRATION

MDX-1106 (1, 3, or 10 mg/kg) will be administered as a single 60-minute intravenous (i.v.) infusion every 14 days for a total of 4 infusions in each cycle (up to 12 cycles).

EFFICACY EVALUATIONS

The primary efficacy endpoint is the best overall response rate (BORR) during the first 3 cycles (proportion of subjects with confirmed responses of CR or partial response [PR]) as determined by the results of Investigator evaluations for each indication. Tumor response status will be assessed using Response Evaluation Criteria in Solid Tumors (RECIST) with modifications. Independent confirmation of responses may be requested at the discretion of Medarex. The secondary efficacy parameters include the following: BORR during the entire study for each indication and across all indications (regardless of time to response), response categories (CR, PR, stable disease [SD], PD), disease control rate (sum of response rate for CR+PR+SD across subjects), and the time to response and duration of response for those subjects with confirmed responses.

Computed tomography/magnetic resonance imaging (CT/MRI [chest, abdomen, pelvis, and brain]) and bone scans will be performed at Screening and at the end of each cycle. Measurements of change in tumor burden must be reviewed and documented before initiating a new cycle of treatment with MDX-1106; response assessment determinations must be confirmed and documented by the end of the next treatment cycle. Tumor response status will be assessed using RECIST with modifications, as well as by prostate-specific antigen (PSA) levels for mCRPC.

Exploratory Immune-Function Evaluations

Samples will be collected and evaluated for lymphocyte phenotype, serum cytokines, and quantitative immunoglobulins, and additional research samples will be collected and stored for future research which may include disease-related biomarkers (or antibody responses to selected antigens), exploratory humoral and cellular immune responses to tumor antigens and a panel of recall non-tumor antigens.

Optional research-related tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) requiring specific agreement by the subject in the informed consent may be performed to assess morphology and the presence or absence of inflammatory infiltrates, and their cellular characterization. Available slides and tissue samples from tumor biopsies collected before enrollment in this study may also be examined for tumor markers and inflammatory infiltrates.

SAFETY EVALUATIONS

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

Dose-limiting Toxicity

A DLT is defined as a \geq Grade 3 drug-related adverse event (using National Cancer Institute [NCI] CTCAE Version 3.0) occurring during the first cycle (56 days) of dosing, excluding: Grade 3 adverse

event of tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor), Grade 3 rash, Grade 3 immune-related adverse event (irAE, defined below) that resolves to a Grade 1 or less within 28 days, or a transient (resolving within 6 hours of onset) Grade 3 infusion-related adverse event. A Grade 3 irAE that resolves to a Grade 1 or less within 28 days, while not constituting a DLT for dose escalation/expansion purposes, will preclude further administration of MDX-1106 to the subject.

Delayed DLTs are adverse events that meet the criteria of DLTs that occur after Cycle 1. Delayed DLTs will not be used to determine the MTD for dose escalation.

Immune-Related Adverse Events

Given the intended mechanism of action of MDX-1106, particular attention will be given to adverse events that may follow enhanced T-cell activation such as dermatitis and colitis, or other irAEs. An irAE is defined as a clinically significant adverse event of any organ that is associated with drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism. Serological and immunological data should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

PHARMACOKINETIC EVALUATIONS

Blood samples will be collected for pharmacokinetic evaluation of peak and trough levels of MDX-1106 on Days 1, 15, 29, and 43 of Cycle 1 and on Day 1 of Cycles 2-12. Single samples will also be collected to evaluate serum concentrations of MDX-1106 at the first 2 Follow-up Visits.

STATISTICAL METHODS

The sample size for this study is not determined from power analysis. A sample size of up to 76 subjects is based on the study design for dose escalation, 4 oncology indications, and the number of possible tumor-specific expansion cohorts for further safety and efficacy evaluation.

Efficacy and safety parameters will be summarized by dose and by indication using descriptive statistics. For some efficacy parameters, 95% confidence intervals will be determined. Time to response and duration of response will be summarized for those subjects with confirmed responses. For the expansion cohorts, efficacy estimates will only be applicable to cohorts that enroll 16 subjects. The incidence, relationship to therapy, and severity of adverse events will be summarized using descriptive statistics. Changes in clinical laboratory tests, immune safety assays, ECOG, physical examination, vital signs, ECGs, and immunogenicity results will be summarized using descriptive statistics.

ABBREVIATIONS

Abbreviation	Term
APC	Antigen-presenting cells
BORR	Best overall response rate
CRF	Case report form
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCF	Data clarification form
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
GCP	Good clinical practices
HIPAA	Health Information Portability and Accountability Act
ICF	Informed consent form
ICH	International Conference on Harmonisation
irAE	Immune-related adverse event
ITIM	immunoreceptor tyrosine inhibitory motif
ITSM	Immunoreceptor tyrosine-based switch motif
i.v.	Intravenous
IFN	Interferon
IRB/IEC	Institutional review board/independent ethics committee
mAb	Monoclonal antibody
mCRPC	Metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MEL	Metastatic melanoma
MRI	Magnetic resonance imaging
MTD	Maximum-tolerated dose
NCI	National Cancer Institute
NSCLC	Non small-cell lung cancer
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed death-1
PR	Partial response
PSA	Prostate-specific antigen

Abbreviation	Term
PVG	Pharmacovigilance
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RT	Radiation therapy
SAE	Serious adverse event
SD	Stable disease
SLD	Sum of longest diameters
SOP	Standard operating procedures
TCR	T-cell receptor
TEAE	Treatment-emergent adverse event
TNF	Tumor necrosis factor

TIME AND EVENTS SCHEDULE

Table 1: Time and Events Schedule

Period	Screening	Treatment										Follow-up	
		Cycle 1					Cycles 2-12						
Visit Name	Screening	C1:1	C1:2	C1:3	C1:4	C1:5	Cn:1	Cn:2	Cn:3	Cn:4	Cn:5	Follow-up 1	Follow-up 2-6
Timepoint Per Cycle (Day)	-28 to -1	1 ¹	15 ¹	29 ¹	43 ¹	56 ²	1 ³	15 ¹	29 ¹	43 ¹	56 ²	Last Cn:5 Visit + 1 to 7 Days	Previous Follow-up Visit + 56 Days ⁴
Informed consent/HIPAA ⁵	•												
Inclusion/exclusion criteria	•												
Demographics/medical history ⁶	•												
Diagnosis confirmation and stage	•												
Baseline signs and symptoms	• ⁷												
Tumor-specific therapy information	•												•
Hepatitis B and C testing ⁸	•												
Testosterone testing ⁹	•												
MDX-1106 infusion		•	•	•	•		•	•	•	•			
Serum sample for pharmacokinetics ¹⁰		•	•	•	•		•					•	• ¹¹
Serum sample for immunogenicity ¹²		•					• ¹³					•	• ¹⁴
Vital signs ¹⁵	•	•	•	•	•		•	•	•	•		•	•
Height	•												
Weight	•	•					• ¹⁶						
Complete physical exam ¹⁷	•						•					•	
Limited physical exam ¹⁸		•	•	•	•			•	•	•			•
ECOG performance	•	•	•	•	•		•	•	•	•		•	•
Hematology	•	• ¹⁹	• ¹⁹	• ¹⁹	• ¹⁹		• ¹⁹	• ¹⁹	• ¹⁹	• ¹⁹		•	•
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.													

continued

Table 1: Time and Events Schedule

Period	Screening	Treatment										Follow-up	
Visit Name	Screening	Cycle 1					Cycles 2-12					Follow-up 1	Follow-up 2-6
Timepoint Per Cycle (Day)	-28 to -1	1 ¹	15 ¹	29 ¹	43 ¹	56 ²	1 ³	15 ¹	29 ¹	43 ¹	56 ²	Last Cn:5 Visit + 1 to 7 Days	Previous Follow-up Visit + 56 Days ⁴
Serum chemistry	•	• ¹⁹	• ¹⁹	• ¹⁹	• ¹⁹		• ¹⁹	• ¹⁹	• ¹⁹	• ¹⁹		•	•
Urinalysis	•	•					•					•	• ¹¹
Immune safety assays		•					•					•	• ¹¹
Pregnancy test ²⁰	•	•	•	•	•		•	•	•	•		•	• ¹¹
Chest radiograph	•												
ECG (12-lead)	• ²¹						•					•	
CT/MRI (brain) ²²	• ²¹					• ^{2,23}					• ^{2,23}		• ²³
CT/MRI (chest, abdomen, pelvis) ²⁴	• ²¹					• ²					• ²		•
Bone scan ²⁵	• ²¹					• ²					• ²		•
PSA ²⁶	•	•					•					•	•
Response assessment						• ^{2,27}					• ^{2,27}	•	•
Tumor or other biopsy ²⁸	•												
Flow cytometry ¹²		•					• ¹³					•	
PBMC (cryopreserved) ¹²		•					• ¹³					•	
Serum for cytokine panel ¹²		•					• ¹³					•	
Serum for quantitative immunoglobulins ¹²		•					• ¹³					•	
Concomitant medications ²⁹	•	•	•	•	•		•	•	•	•		•	• ³⁰
Adverse events ²⁹		•	•	•	•		•	•	•	•		•	• ³⁰
Off-Study ³¹													
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.													

- ¹ To be done \pm 2 days of scheduled visit.
- ² This visit is NOT a clinic visit. The purpose of this visit is for radiologic assessment and subsequent evaluation of results by the Investigator (response assessment). Radiologic procedures and response assessments should occur between Days 52 and 56 and BEFORE administering the first dose of study drug in the next cycle.
- ³ Day 1 of each cycle should occur 56 days following Day 1 of the previous cycle, but no sooner than 14 days after the last dose of the previous cycle.
- ⁴ To be done \pm 7 days of scheduled visit.
- ⁵ Informed consent form and Health Information Portability and Accountability Act (HIPAA) authorization are to be provided before initiation of any Screening assessments and may be obtained before Day -28.
- ⁶ To include collection of prior medication and prior/concurrent medical conditions. For subjects with mCRPC, to include at least 3 PSA measurements over the preceding 6 months.
- ⁷ Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions CRF.
- ⁸ Hepatitis B surface antigen and Hepatitis C antibody (with reflex Hepatitis C RNA if antibody test is positive).
- ⁹ In subjects with mCRPC only. Testosterone level must be \leq 50 ng/dL.
- ¹⁰ Pharmacokinetic sampling to be performed according to Table 2.
- ¹¹ Follow-up Visit 2 only.
- ¹² To be collected before infusion.
- ¹³ Cycle 2 only.
- ¹⁴ Follow-up Visit 2 and 3 only.
- ¹⁵ Vital sign measurements to include temperature, pulse, and blood pressure. On the day of each infusion, vital signs will be obtained before the infusion, every 15 minutes during the infusion, at the end of the infusion, and 15 minutes after completion of the infusion. When slowing or re-starting an infusion due to an infusion reaction/adverse event, vital signs should be monitored every 15 minutes or as directed by the Investigator until the infusion is completed, and 15 minutes after completion of the infusion and/or the subject is stabilized.

(continued)

Table 1 Footnotes: *(continued)*

- ¹⁶ Dose adjustments are required to be made if there has been $\geq 10\%$ weight change since the previous cycle. [Weights should be determined at the onset of each new treatment cycle as a minimum, but may be done more frequently at sites whose standard dose administration procedures require weight determination before each dose.]
- ¹⁷ Complete physical examination includes assessment of the skin, head, eyes, nose, throat, neck, joints, lungs, heart, abdomen (including liver and spleen), lymph nodes, and extremities. A brief neurological examination should also be performed. All abnormal findings noted at the Screening physical examination should be recorded on the Medical History CRF, and any new or worse signs or symptoms are to be recorded on the Adverse Event CRF.
- ¹⁸ Limited physical examination includes assessment of the lungs, heart, abdomen, and skin. All abnormal findings noted at the Cycle 1/Day 1 evaluation should be recorded on the Medical History CRF. Abnormal findings of clinical significance that occur after the Cycle 1/Day 1 evaluation (or new adverse events) should be explicitly documented on the Adverse Event CRF.
- ¹⁹ During the study Treatment Period, hematology and serum chemistries will be evaluated by both local and central laboratories. The hematology and clinical chemistry laboratories **must be performed and reviewed before dosing**. Any new \geq Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the Medarex Medical Monitor should be contacted.
- ²⁰ Serum β -HCG pregnancy test within 7 days before the first infusion; urine pregnancy test at all other time points for women of childbearing potential. Urine pregnancy tests on days of study drug administration must be performed and negative before study drug administration.
- ²¹ Baseline imaging and 12-lead ECG done as part of the subject's previous routine care before signing the informed consent form and completed within 28 days prior to the administration of MDX-1106 need not be repeated. Whenever possible, baseline imaging should be done at the same institution/facility and with the same modality which will be used to measure response during the subject's participation in the study.
- ²² Brain scan required at Screening if not performed within the previous 2 months (and NOT required for subjects with mCRPC).
- ²³ Brain scans during Treatment and Follow-up Periods are required only if there is a prior history of lesions present at Screening, or as clinically indicated for new signs and symptoms that suggest central nervous system (CNS) involvement. The same technique (CT/MRI) used at baseline should be utilized throughout the study.
- ²⁴ Tumor imaging (CT/MRI of chest/abdomen/pelvis required). The same technique (CT/MRI) used at baseline should be utilized throughout the study.
- ²⁵ Bone scans must be done at all visits indicated for subjects with mCRPC. For subjects with MEL, RCC, and NSLC, bone scans at baseline or subsequent visits will be performed only if clinically indicated.

(continued)

Table 1 Footnotes: *(continued)*

- ²⁶ To be performed only in subjects with mCRPC.
- ²⁷ Tumor response status will be assessed by the Investigators using RECIST with modification. Response assessments must be performed by the Investigators at the end of each cycle to document eligibility for entry into the next treatment cycle. Copies of scans may be requested by Medarex for independent review.
- ²⁸ A tumor biopsy is required at baseline if there is no other record of histological diagnosis of tumor. Optional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed at Screening and at other times during the protocol as clinically indicated. Optional tumor or other biopsy requires specific agreement by the subject in the informed consent.
- ²⁹ All subjects who are withdrawn from the study should be followed until resolution and/or stabilization of any adverse event, and should be monitored for 70 days following the last dose of MDX-1106 for the occurrence of serious adverse events considered by the Investigator to be related to MDX-1106 treatment. Subjects should be contacted at least once within 70 days following the last dose of MDX-1106. Telephone contact is acceptable and should be within ± 10 days of the 70-day time point.
- ³⁰ For all follow-up periods beyond 70 days from the last dose of study drug, only adverse events deemed by the Investigator to be related to MDX-1106 and concomitant medication used to treat adverse events should be reported.
- ³¹ When a subject discontinues study drug treatment, the date and reason for study drug discontinuation should be documented on the CRF, all remaining visits of that treatment cycle should be completed (without infusions and with only a single pharmacokinetic sample taken at applicable visits), and the subject should enter the Follow-up Period. When a subject is withdrawn from the study (during the Treatment or Follow-up Period), all evaluations associated with that study visit should be performed and the date and reason for study discontinuation should be documented on the CRF.

Table 2: Pharmacokinetic Blood Sampling Schedule							
	Treatment Period¹					Follow-up Period	
	Cycle 1				Cycles 2-12	Visit 1	Visit 2
Time point	Day 1	Day 15	Day 29	Day 43	Day 1		
Non-infusion day						.	.
Infusion day (pre-infusion [within 2 hours of start of infusion])		
Infusion day (60 minutes [end of infusion]) ²		

¹ If a subject permanently discontinues study drug treatment, a single pharmacokinetic sample will be taken at each remaining visit for that cycle.

² In the event of a delay during the infusion, the sample will be taken at the END of the infusion.

1. INTRODUCTION AND RATIONALE

1.1. Background

Preclinical animal models of tumors and chronic infections have shown that blockade of Programmed death-1 (PD-1) by monoclonal antibodies (mAbs) can enhance the immune response and result in tumor rejection or control of infection. Studies of several human tumor types have suggested that the exploitation of the PD-1/PD-L1 pathway may permit immune evasion by tumors. MDX-1106 is a fully human, IgG4 (kappa) isotype, mAb that binds PD-1. PD-1 blockade by MDX-1106 is therefore proposed to be a promising avenue to pursue for immunotherapy of tumors.

An estimated 1,339,790 new cases of cancer and 564,830 deaths were seen in the United States in 2006.¹ Anti-tumor immunotherapy via PD-1 blockade is not limited in principle to any single tumor type, but may have activity in augmenting therapeutic immune response to a number of histologically distinct tumors. Four tumor types (metastatic castration-resistant prostate cancer [mCRPC], renal cell carcinoma [RCC], malignant melanoma [MEL], and non-small cell lung cancer [NSCLC]) were selected for the current study, as they are representative of tumors for which a high medical need for new therapies exist; those for which there is a precedent for clinical responses to other immunotherapies; and those for which there is supportive correlative pathologic data suggesting that the PD-1/PD-L1/2 pathway is important for tumor progression.

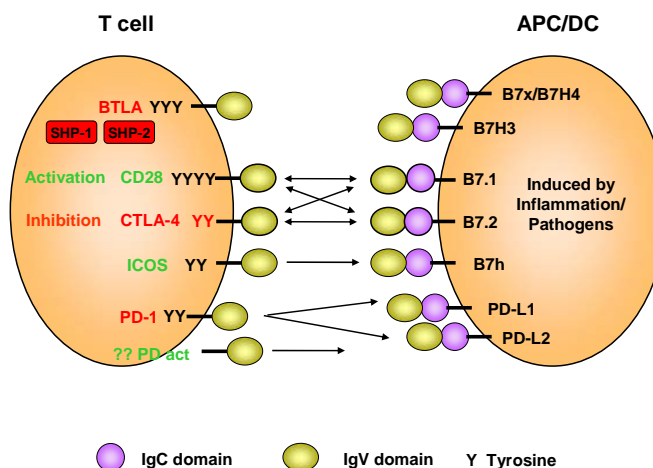
1.2. Programmed Death-1 and the Antitumor Immune Response

The antigen-specific T cell immune response initiates after the integration of 2 signals received by the T cell from the antigen-presenting cell (APC).² The first signal is antigen specific, from the T-cell receptor (TCR) interacting with the (peptide) antigen displayed on APC in the context of the Major Histocompatibility Complex Type I or Type II surface molecules, for CD8 and CD4 T cells, respectively. The second signal is not antigen specific, but is a costimulatory signal that arises from the interaction of the T cell CD28 surface molecule with the B7 molecule on the APC (either B7.1, CD80, or B7.2, CD86), and results in additional intracellular signals and secreted cytokines that drive an effective immune response. The absence of a costimulatory signal results in recognition without activation, or anergy, and may lead to death (by apoptosis) of antigen-specific T cells. Clearance of antigen is followed by the down regulation of the activated T-cell response, mostly by apoptosis. A subpopulation of the T cells matures into long-lived memory CD8 and CD4 cells that can then be promptly reactivated upon re-exposure to the antigen by APC. These regulatory mechanisms are likely to have arisen to maintain tolerance of the immune system to normal self antigens, while permitting it to effectively deal with abnormal or foreign antigens.

Immunotherapy of tumors rests on the premise that tumors can be recognized as foreign rather than as self, and effectively attacked. Many tumors express tumor-specific antigens, and ongoing immune surveillance may abort the emergence of many tumors as they arise. Tumor progression may depend upon acquisition of mechanisms to evade an effective immune response.³ Immune evasion may occur by exploiting any of the checkpoints that control the regulatory immune response, including display of antigens and control of costimulatory pathways. Current immunotherapy efforts focus on the effective introduction of cancer antigens via therapeutic vaccination, and the modulation of regulatory checkpoints by costimulation and cytokine manipulation in order to break the apparent tolerance of the immune system to tumor antigens.

CD28, CD80, and CD86 are members of the immunoglobulin superfamily of costimulatory receptors. It is now recognized that this family is quite large, and that 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 TCR (Figure 1).⁴ Collectively, these signals govern the balance between T-cell activation and tolerance to antigens.

Figure 1: T-cell Stimulation



PD-1 (or CD279) is a member of the CD28 family of T-cell costimulatory receptors that include CD28, CTLA-4, ICOS, PD-1, and BTLA. PD-1 is a 55 kD type I transmembrane protein that is part of the immunoglobulin gene superfamily.⁵ 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 (also known as B7-H1 or CD274) and PD-L2 (also known as B7-DC or 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.^{6,7,8} PD-1 delivers a negative signal by the recruitment

of SHP-2 to the phosphorylated tyrosine residue in the ITSM in its cytoplasmic region.^{9,10} PD-1 is primarily expressed on activated T cells, B cells, and myeloid cells.⁴

Further evidence for a negative regulatory role of PD-1 comes from studies of PD-1 null mice. PD-1-deficient mice develop various autoimmune phenotypes, including dilated cardiomyopathy, a lupus-like syndrome with arthritis and nephritis, and accelerated diabetes mellitus.^{11,12,13} 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. PD-1 deficiency on the C57BL/6 background results in development of a late-onset progressive arthritis and lupus-like glomerulonephritis,¹¹ while on the BALB/c background, it results in the development of a lethal dilated cardiomyopathy that shows incomplete penetrance, with concomitant evidence of autoantibodies to troponin-I.^{12,14}

In other murine models, PD-1 blockade has been found to play a role in the development of autoimmune diseases such as encephalomyelitis,¹⁵ graft-versus-host disease,¹⁶ and type I diabetes.¹³

The role of PD-1 and PD-L1 in viral immunity has recently been investigated. PD-1 expression has been found to be a critical mediator of T-cell unresponsiveness in the lymphocytic choriomeningitis virus model system.¹⁷ In addition, PD-1 deficiency enhances anti-viral immunity at effector sites, resulting in rapid clearance of adenovirus in the liver.¹⁸

Several published murine tumor studies using anti-PD-1 and anti-PD-L1 antibodies or PD-1 null mice support the role of this pathway for therapeutic intervention in cancer. Two metastatic models have been shown to be sensitive to PD-1 blockade.¹⁹ Utilizing CT26 (a colon carcinoma that metastasizes to the lung after intravenous [i.v.] injection), tumor growth was inhibited by 50% after treatment with anti-PD-1 antibody. This study also reports that B16 melanoma metastasis to the liver after intrasplenic injection of tumor cells, in which PD-L1 expression was found to be up-regulated in vivo, could be inhibited by anti-PD-1 treatment. Transfection of murine tumors with PD-L1 rendered them less susceptible to the specific T-cell antigen receptor-mediated lysis by cytotoxic T cells in vitro and markedly enhanced tumor growth and invasiveness in vivo.²⁰ Both effects could be reversed by blockade with anti-PD-L1 antibody.^{20,21} Transfection with PD-L1 was able to negate the enhanced immunogenicity conferred by transfection of P815 mastocytoma cells with CD80.²² The 4T1 mammary cell carcinoma is PD-L1 negative in culture but expresses PD-L1 in vivo (or can be induced to express PD-L1 in culture by interferon (IFN)- γ).²³ This tumor is refractory to tumor rejection mediated by an agonistic anti-41BB antibody, an activating receptor that is a member of the tumor necrosis factor (TNF) family of receptors. While treatment with anti-41BB results in a modest decrease in tumor growth, treatment with anti-41BB in combination with anti-PD-L1 results in dramatic tumor rejection. Murine myeloma cell lines naturally express PD-L1, and their growth in vivo

was also inhibited significantly, although transiently, by the administration of anti-PD-L1 antibody. A direct effect of the antibody on the growth of the tumor (by other mechanisms such as antibody-dependent cellular cytotoxicity) was not excluded. Their growth was suppressed completely in syngeneic PD-1-deficient mice.²⁰ In addition, PD-1^{-/-}CD8⁺ TCR transgenic T cells caused tumor rejection in an adoptive transfer model in which wild type and CTLA-4^{-/-} T cells failed to mediate rejection.²⁴ Studies reveal that antitumor activity by PD-1 blockade functions in PD-L1⁺ tumors as well as for tumors that are negative for the expression of PD-L1.¹⁸⁻²³ This suggests that host mechanisms, i.e., expression of PD-L1 in antigen-presenting cells, limits 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.^{21,25,26,27,28,29,30,31} PD-L1 expressed by tumor cells has been shown to enhance apoptosis of activated tumor-specific T cells in vitro.²¹ Moreover, the expression of PD-L1 may protect the tumor cells from the induction of apoptosis by effector T cells.³² In renal cell carcinoma, high surface expression levels of PD-L1 on tumor cells are related to tumor aggressiveness.²⁶ 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. It has been reported that PD-L1 and PD-L2 expression may be a significant prognostic marker in post-operative esophageal cancer subjects.²⁷

1.3. Summary of MDX-1106: Preclinical Studies

1.3.1. Summary

MDX-1106 has been shown to bind specifically to the PD-1 receptor of the CD28 family. In vitro assays have demonstrated that MDX-1106 does not react with the other members of this family. MDX-1106 has also demonstrated the ability to block binding of its ligands, PD-L1 and PD-L2, and to enhance T-cell proliferation and IFN- γ release in vitro. A surrogate anti-murine PD-1 antibody was effective in inhibiting tumor growth in several syngeneic tumor models.

In binding studies using fresh, frozen human tissues, MDX-1106 demonstrated reactivity with lymphocytes in a variety of tissues. There was also moderate to strong cytoplasmic staining of rare to occasional endocrine cells in the adenohypophysis. This was considered to be low affinity binding as the intensity was moderate to strong at 10 μ g/mL and was not present at 1 μ g/mL. This unexpected reactivity to endocrine cells is not expected to have physiological consequences due to the limited availability of cytoplasmic compartments in vivo. Similar staining patterns were observed in cynomolgus monkey tissues indicating that this is an appropriate animal

species to evaluate the potential toxicities of MDX-1106. In a cardiovascular, safety pharmacology study in cynomolgus monkeys, there were no significant effects of administration of 10 or 50 mg/kg of MDX-1106 on electrocardiographic parameters. MDX-1106 was also well tolerated when administered weekly at doses of 1, 10 or 50 mg/kg/dose for 5 weeks and when administered bi-weekly at doses of 10 and 50 mg/kg for 3 months. There were no adverse clinical findings or changes in clinical or anatomic pathology parameters in these studies.

In a study of cynomolgus monkeys which were administered multiple doses of ipilimumab, a fully human mAb to CTLA-4, in combination with MDX-1106, 1 monkey at the highest dose level (10 mg/kg ipilimumab/50 mg/kg MDX-1106) died 1 day following the fourth and last doses of ipilimumab and MDX-1106, respectively. This early death was attributed to acute gastric dilation, assessed as possibly related to administration of ipilimumab plus MDX-1106. Clinical observations in the days before death included persistent diarrhea, reduced food consumption, weight loss, decreased activity, dehydration, and hypothermia. Pathology findings included marked gas distention of the stomach and moderate gas dilatation of the duodenum, jejunum, ileum, cecum, and colon (correlated with decreased thickness of the gastric and intestinal wall, submucosal and muscularis), mottled, dark red, purple, tan discoloration of the lung (correlated with vascular congestion and a pulmonary granuloma), abnormal appearance of the lung due to atelectasis and hyperinflation (no microscopic correlate), decreased thymus size (correlated with marked, diffuse thymic atrophy), and purple discoloration of the neck and thorax (no microscopic correlate). One microscopic finding of uncertain relationship to ipilimumab plus MDX-1106 administration was identified in the kidney: mild multifocal tubular dilation and epithelial degeneration in the renal cortical tubules. Myeloid and eosinophil hypercellularity and erythroid hypocellularity were identified in the bone marrow. Myeloid and eosinophil hypercellularity were believed to be a secondary response to inflammation in the lung and not related to ipilimumab/MDX-1106 treatment. The cause of the erythroid hypocellularity was considered uncertain. Additional microscopic findings considered to be related to inappetence or physiological stress and not test article treatment included thymic involution/atrophy, pancreatic acinar cell degranulation, secretory depletion of the adrenal cortex, zona fasciculate and vascular congestion in several organs examined. All other gross observations or microscopic findings were considered incidental. There was no evidence of colitis upon gross or microscopic pathology evaluation of the gastrointestinal tract. The animal did develop diarrhea and this occurred in the cohort receiving the highest doses of the test articles. Therefore, the death may possibly be related to administration of ipilimumab and MDX-1106 and may be an immune-mediated gastrointestinal toxicity.

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

1.3.2. Preclinical Data with PD-1 Blockade or Deficiency and MDX-1106

PD-1:PD-L1/PD-L2 interactions play a role in the balance between immune activation and tolerance. Several preclinical studies in knockout mice, as well as mice treated with blocking mAbs have shown the ability to induce or aggravate an autoimmune type disease.^{10,11,12,14,15} The pattern of autoimmunity that develops in PD-1 knockout mice appears to be strain specific and develops with age, rather than appearing at birth. There is no evidence to date for a uniform type of immune-related toxicity. In contrast to CTLA-4-deficient mice, the phenotype of PD-1 null mice is variable and less uniformly dramatic. A variety of autoimmune perturbations have been observed that are strain dependent, not typically lethal, develop weeks or months after birth, and have variable genetic penetrance (ranging from 10% to 100%). Models with high penetrance are those done in backgrounds that are already predisposed to the underlying disease. PD-1 blockade experiments have been able to exacerbate some autoimmune disease in predisposed mouse strains.

Careful monitoring for immune-related adverse events (irAE) is a key part of the general safety monitoring of this protocol, and includes monitoring for specific patterns that have been seen in mice, such as cardiomyopathy, arthritis and diabetes, as well as a general heightened surveillance for immune-mediated pathology. The planned panel of laboratory markers for immune-mediated activation processes will monitor for adverse events that have been observed in these various model systems.

Preclinical evaluation of efficacy against multiple tumors and safety of MDX-1106, both in mouse and non-human primate species, have not shown any clear pattern of toxicity elicited by multiple doses of MDX-1106 at levels in excess of the doses used in ongoing clinical studies. A pattern of cross reactivity with a pituitary cytoplasmic determinant at high doses has been noted. Given the intracellular location, rare presence, and low affinity of the interaction, the lack of toxicity observed to date in the relevant preclinical model, and the non-complement activating subclass (IgG4) of the mAb, Medarex, Inc. believes the risk of pituitary toxicity to be very low, and it has not yet emerged in clinical studies (see below). Of note, pituitary dysfunction has emerged as an unexpected adverse event in the ipilimumab – anti-CTLA-4 program, another T-cell costimulatory molecule (that was not predicted by the preclinical data), where it has been successfully managed with hormone replacement therapy in the setting of durable clinical responses. Surveillance for altered pituitary function is included in the safety monitoring program.

1.4. Prior Experience with Similar Investigational Agents

1.4.1. CTLA-4 Blockade

As there is only limited data from human studies with MDX-1106, examination of the adverse events or other clinical safety issues associated with ipilimumab, an anti-CTLA4 investigational immunomodulatory mAb currently under development by Medarex may provide important background information for the clinical use of MDX-1106. Preclinical studies with CTLA-4 blockade revealed a severe and uniformly lethal neonatal phenotype in the knockout model associated with massive lymphoproliferation. Blockade with antibodies was shown to exacerbate disease in some autoimmune models in which there was either a genetic predisposition to autoimmunity or in which vaccination with self antigens resulted in enhanced autoimmunity. Clinical studies have shown an incidence of inflammatory adverse events, termed irAEs, which may be triggered by a loss of tolerance to enteric or self antigens. The primary irAEs have been rash, diarrhea, hepatitis, and an inflammatory colitis. Colitis has been a serious adverse event in 10% to 15% of subjects, and has been generally manageable with steroids without apparent abrogation of antitumor responses. Other related serious adverse events have included panhypophysitis and adrenal insufficiency; these have occurred in less than 5% of subjects.

1.4.2. Other Immunomodulatory Agents

Medarex has noted the reports of multi-organ failure in healthy volunteers receiving an activating anti-CD28 mAb (TGN 1412) in a Phase 1 study conducted in the United Kingdom. An interim report, published on 05 April 2006, by the Medicines and Healthcare Products Regulatory Agency identified the antibody TGN 1412, as being the cause of the life-threatening adverse event reactions that occurred in 6 healthy volunteers who experienced cytokine release syndrome, a type of severe systemic inflammatory response. Medarex has carefully considered whether an antibody to PD-1 could lead to similar issues, given that PD-1 is a CD28 family member.

Medarex has concluded that the occurrence of acute T-cell activation syndrome is unlikely for the reasons detailed below:

1. While PD-1 is related to CD28, it functions as an inhibitor of antigen-specific T-cell activation and not as a pan-specific activator.
2. MDX-1106 is designed to block the interaction of PD-1 with its ligands, PD-L1 and PD-L2. MDX-1106 is expected to augment T-cell activation in the presence of antigen-specific activating signals and PD-1 ligands. Non-specific activation of T cells should not occur as a consequence of PD-1 blockade in the absence of these signals.

3. While blocking PD-1 eliminates a negative regulatory signal, other homeostatic negative regulatory molecules for T-cell activation remain functional (i.e., CTLA-4).
4. The intended mechanism of action and its safety is supported by our preclinical studies. These preclinical models are carried out with antibodies that have high affinity interactions with the PD-1 molecule in the species employed.
5. Most importantly, and providing support for these conclusions, is the fact that, as of April 2008, MDX-1106 has been given as a single dose to 39 subjects at doses ranging from 0.3 to 10 mg/kg, including 21 subjects at a dose of 10 mg/kg, without any occurrence of an acute T-cell activation or cytokine storm syndrome.

1.5. Clinical Studies

1.5.1. Summary of Safety

Initial safety experience of single dose administration of MDX-1106 is available from ongoing Protocol MDX1106-01. Subjects with advanced or refractory malignancies (prostate, colorectal, melanoma, renal cell, and non-small cell lung cancer) received a single dose of MDX-1106 and were monitored for 12 weeks. Subjects without significant disease progression or toxicity during the 12-week observation following the first dose could receive 2 additional doses (at the same dose initially given), administered 4 weeks apart, and followed by another 12-week observation before repeating the 2-dose cycle. The dose levels, 0.3, 1.0, 3.0, and 10 mg/kg, were administered to cohorts of 6 subjects, with a cohort expansion of an additional 15 subjects at the 10 mg/kg dose level (the maximum dose studied). No dose-limiting toxicities (DLTs) have occurred in this study.

As of 15 April 2008, 17 subjects have experienced 40 serious adverse events; only 2 of these serious adverse events (diarrhea/colitis, spinal cord compression) were considered related to MDX-1106 treatment by the Investigator. Significant adverse events that are likely to be immune-related and that reflect on safety include polyarticular arthropathy (2 subjects, both low-grade adverse events) and diarrhea/colitis (1 subject).

There have been 2 cases of apparent flare of a syndrome of bilateral polyarticular arthropathy in subjects, both of whom had a prior history of similar type syndromes that was unknown to the Investigators at the time of enrollment (1 subject received MDX-1106 3 mg/kg and 1 received 10 mg/kg). These were not high-grade adverse events, and promptly responded to moderate corticosteroid treatment. These subjects are ineligible for re-treatment, despite 1 subject having had apparent shrinkage in pulmonary lung cancer lesions, and the other having had shrinkage in cutaneous melanoma lesions.

A serious adverse event of diarrhea/colitis has been reported in a subject with ocular melanoma. The subject developed colitis more than 5 weeks after receiving his 5th dose of MDX-1106 1 mg/kg over almost 8 months. The colitis has been managed with steroids and infliximab, administered according to treatment guidelines developed for the management of irAEs observed in the ipilimumab development program. This is the first instance of colitis in the MDX-1106 clinical program, and it is notable that the colitis did not occur until approximately 9 months after the subject's 1st dose of MDX-1106. It is also noteworthy that 21 subjects have each received at least a single dose of MDX-1106 10 mg/kg, and 3 of these subjects have received 3 doses of 10 mg/kg without such an adverse event. The potential for additional instances of colitis to emerge with repeated dosing will be closely monitored in this study.

1.5.2. Rationale for MDX-1106 Dosage Selection

The dose levels for the initial Phase 1 single-dose protocol (MDX1106-01) were selected based on an evaluation of in vivo activity data and toxicology data. Based on these studies, it was expected that an effective human dose of MDX-1106 would be in the range of 3 to 10 mg/kg. In ongoing Protocol MDX1106-01, transient shrinkage of lesions has been observed in subjects administered MDX-1106 at doses of 1, 3, and 10 mg/kg, and there has been 1 confirmed partial response (PR) at a dose of 3 mg/kg. The emergence of a related significant event of colitis after administration of 5 doses of 1 mg/kg of MDX-1106 has been noted above. Additional experience in this study, in which 21 subjects have received 10 mg/kg of single doses of MDX-1106, as well as 3 subjects who received 3 doses of 10 mg/kg over 16 weeks, suggests that MDX-1106 appears to be well-tolerated. In light of this data, 1 mg/kg has been chosen as the initial level for multiple dosing in this trial. Protocol MDX1106-03 will continue to provide safety monitoring for irAEs in general, and heightened surveillance for events of diarrhea or colitis in particular.

Preliminary pharmacokinetic analysis of single-dose administration of MDX-1106 indicates that the half-life of MDX-1106 is approximately 14 days. Thus, dosing of MDX-1106 every 2 weeks in this current study is expected to result in a gradual accumulation of drug levels, and is not likely to achieve steady state levels until after 5 to 6 doses (during the second cycle of treatment). The assessment of the best overall response rating (BORR) after 3 cycles of treatment was, therefore, selected as the primary efficacy endpoint.

2. STUDY OBJECTIVES

2.1. Primary Objective(s)

The primary objective is to characterize the safety and tolerability of multiple doses of MDX-1106 in subjects with selected advanced or recurrent malignancies. The malignancies include: mCRPC, RCC, MEL, and NSCLC.

2.2. Secondary Objective(s)

The secondary objectives are to: 1) assess the host immune response to MDX-1106 (immunogenicity); 2) characterize the pharmacokinetic profile of multiple doses of MDX-1106; 3) assess the efficacy of MDX-1106 monotherapy; and 4) explore the effects of MDX-1106 on humoral and cellular immune responses to tumor antigens and recall responses to a panel of non-tumor antigens.

3. OVERVIEW OF STUDY DESIGN

3.1. Overview

This is a Phase 1b, open-label, multi-dose, multicenter, dose-escalation study of MDX-1106, a fully human monoclonal IgG4 antibody, targeting the PD-1 membrane receptor on T lymphocytes and other cells of the immune system. The study will consist of 3 periods: Screening (up to 28 days), Treatment (up to 12 8-week cycles), and Follow-up (up to 46 weeks). Each treatment cycle is comprised of 4 doses of study drug administered on Days 1, 15, 29, and 43 with a response assessment between Days 52 and 56. The response assessment must be completed before the first dose in the next cycle.

Dose-escalation Phase

Three dose levels are planned: 1, 3, and 10 mg/kg. Subjects will be assigned to a dose level in the order of study entry. Initially, 3 subjects will be enrolled at the 1 mg/kg dose level. If no subject (0 of 3) in a dose cohort experiences a DLT during the first cycle, then the next dose cohort of 3 subjects will be enrolled at the next higher dose level. If 1 of 3 subjects in a dose cohort experiences a DLT during the first cycle, that cohort will be expanded to 6 subjects. Provided that no more than 1 of 6 subjects in the expanded dose cohort experiences a DLT within the first cycle, then the next dose cohort of 3 subjects will be enrolled at the next higher dose level. If ≥ 2 of up to 6 subjects in the 1 mg/kg dose cohort experiences a DLT during the first cycle, that cohort will have exceeded the maximum tolerated dose (MTD), which is defined as the highest tested dose at which no more than 1 of 6 subjects has experienced a DLT in Cycle 1, and a lower dose level (0.3 mg/kg) will be tested. If ≥ 2 of up to 6 subjects in the 3 or 10 mg/kg dose cohort experience a DLT during the first cycle, that cohort will have exceeded the MTD, and the following will occur:

- If no subjects (0 of 3) experienced a DLT at the previously tolerated dose level, 3 additional subjects will be dosed at that dose level.
- If ≤ 1 of 6 subjects experienced a DLT at the previously tolerated lower dose level, an intermediate dose level will be tested. The planned intermediate dose levels will be 2 and 7 mg/kg for the 3 and 10 mg/kg cohorts, respectively.

If 2 or more **delayed DLTs** are noted within a dose cohort, further accrual will be held pending safety analysis of the event, and will be restarted only with Investigator and Sponsor (Medarex) approval at all sites (with FDA and Institutional Review Board [IRB] notification).

A DLT is defined as a \geq Grade 3 drug-related adverse event (using National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events Version 3.0 [CTCAE]) occurring during the first cycle (56 days) of dosing, excluding: Grade 3 adverse event of tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor), Grade 3 rash, Grade 3 irAE (defined below) that resolves to a Grade 1 or less within 28 days, or a transient (resolving within 6 hours of onset) Grade 3 infusion-related adverse event. A Grade 3 irAE that resolves to a Grade 1 or less within 28 days, while not constituting a DLT for dose escalation/expansion purposes, will preclude further administration of MDX-1106 to the subject.

Delayed DLTs are adverse events that meet the criteria of DLTs that occur after Cycle 1. Delayed DLTs will not be used to determine the MTD for dose escalation.

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

No dose escalations or de-escalations are permitted within each subject's treatment. A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

Expansion Phase

To further characterize safety and efficacy, additional subjects will be enrolled at the MTD (or the highest dose studied if the MTD is not identified) in 3 tumor-specific expansion cohorts: NSCLC, mCRPC, and MEL+RCC. Up to 16 subjects will be enrolled in each of the NSCLC and mCRPC cohorts. For the MEL+RCC expansion cohorts, 16 subjects are required in 1 of the 2 indications; up to 16 subjects may be enrolled in the 'other' indication (enrollment will be stopped in the 'other' indication at the time that the other 3 expansion cohorts [NSCLC, mCRPC and either MEL or RCC] each accrue 16 subjects). A total of 6 subjects must be enrolled at the MTD (or the highest dose studied where ≤ 1 of 6 subjects experiences a DLT if the MTD is not identified) and evaluated through the end of Cycle 1 before any new subject is dosed in the expansion cohorts. If none of the first 5 subjects have a DLT by the end of Cycle 1, enrollment to the expansion cohorts can begin immediately following enrollment of the 6th subject.

Enrollment will be stopped in all expansion cohorts if the rate of DLTs is $\geq 33\%$ across all indications (including subjects from the Dose-escalation Phase at the expansion dose) or if the rate of DLTs is $\geq 33\%$ in a specific indication after enrollment of the first 6 subjects in that indication (including subjects from the Dose-escalation Phase at the expansion dose). After safety analysis by the Investigators and Medarex (with FDA and IRB notification), a decision will be made whether to initiate a new expansion cohort of 16 subjects in 1 or more indications at a lower MDX-1106 dose (chosen according to the de-escalation rules above). For delayed DLTs, enrollment will be paused using the same rules as that for DLTs. After safety review of delayed DLTs by the Investigators and Medarex (with FDA and IRB notification), a decision will be made whether to resume enrollment at the current dose (with or without a limitation in the total number of allowed cycles) or to initiate a new expansion cohort in 1 or more of the indications at a lower dose (using the same de-escalation schedules as that for DLTs).

3.2. Administration of Additional Cycles

The maximum number of cycles to be administered to an individual subject in this study is 12. Following each treatment cycle, the decision of whether to treat a subject with additional cycles of MDX-1106 will be based on ongoing tumor response evaluation. The response assessment must be completed before the first dose in the next cycle. Unless the subject develops a \geq Grade 3 (CTCAE) adverse event or other adverse event related to MDX-1106 that precludes further treatment, subjects will be treated until confirmed clinical response (CR) or progressive disease (PD) that is both confirmed and then further progresses as described below. If a subject is eligible to receive additional cycles, the first dose of the next cycle should be given 14 days after the last dose of the prior treatment cycle but no later than 28 days.

- Unconfirmed CR: Subject will receive an additional cycle of treatment until confirmation of the CR at the next scheduled imaging time point.
- Confirmed CR: Subjects will stop treatment and enter the Follow-Up Period.
- Confirmed CR in mCRPC: Subjects will stop treatment and enter the Follow-up Period if at the end of a treatment cycle they have a confirmed complete prostate-specific antigen (PSA) response (PSA <0.5 ng/mL for 2 consecutive measurements separated by at least 3 weeks) AND either a confirmed radiologic CR (subjects with measurable disease) OR a radiological response of SD or better (subjects with only non-measurable bony disease).
- PR or stable disease (SD): Subjects will continue to receive MDX-1106 therapy until confirmed CR, PD (under the conditions defined below), toxicity (as defined below), or the maximum number of cycles allowed have been administered. Subjects will then enter the Follow-up Period.

- PD: Accumulating evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological (or PSA – for mCRPC) progression, or the appearance of new lesions or some enlarging lesions while certain target lesions are regressing (“mixed response”). It is thus reasonable, in the absence of clinical deterioration, to continue to treat these subjects until radiologic progression is **both confirmed and** at a subsequent imaging assessment is found to have progressed further. Evidence of PD will be based on a comparison with baseline (or nadir) scans, in which there is either an increase of 20% or more in the sum of the longest diameters (SLD) of target lesions taking as reference the smallest sum of the longest diameters (nadir) recorded since Screening, unequivocal progression of non-target lesions, with or without the development of 1 or more new lesions (at least 2 new bone lesions for mCRPC). The appearance of 1 or more new lesions will not in itself (in the absence of increased size of target/non-target lesions) constitute PD for this study. PD should be confirmed by repeat scans at the next scheduled imaging evaluation 8 weeks later (but no sooner than 4 weeks).

PD seen at the end of Cycle 1, in the absence of clinical deterioration, will NOT count as one of these PD findings to determine further progression. Subjects with stable or improved clinical status, but evaluation at the end of Cycle 2 or later demonstrates evidence of PD, will continue to be treated with study drug until their next scheduled imaging evaluation. If, at each subsequent imaging evaluation, there is no further increase in the SLD and no additional new lesions develop, and the subject’s clinical status remains stable or has improved, treatment will be continued, even if PD is confirmed. If, after confirmation of PD, there is further increase in the SLD or development of additional new lesions at a subsequent imaging evaluation, then the subject should stop treatment and return for 1 final visit, Follow-up Visit 1.

For mCRPC, isolated PSA progression in the absence of radiologic or clinical deterioration will **not** be used to determine PD. Stopping treatment for clinical deterioration should be guided by clinical observations outlined in Section 8.7 and Investigator judgment.

- Development of a \geq Grade 3 (CTCAE) intolerability or adverse event related to MDX-1106 that precludes further treatment with the study drug, but subject does not have confirmed progression: Subjects will complete the remaining visits of their current treatment cycle (without infusions) if possible. Subjects will then enter the Follow-Up Period until progression or completion of all (6) Follow-up Visits.

4. STUDY POPULATION

Up to 76 subjects will be enrolled if only the planned dose levels are used. Subjects must have pathologically-verified mCRPC, RCC, MEL, or NSCLC that is clinically advanced or recurrent after prior treatment with other therapies, and for which no alternative curative option is available.

As soon as the subject is considered for this study and before conducting any study procedures, the subject will have the nature of the study explained to them and will be asked to sign an informed consent form (ICF) and provide Health Insurance Portability and Accountability Act (HIPAA) authorization. The ICF and HIPAA authorization must be obtained before conducting any procedures that do not form a part of the subject's normal care. After signing the ICF and HIPAA Authorization, subjects will be evaluated for study eligibility during the Screening Period (no more than 28 days before study drug administration) according to the following inclusion/exclusion criteria.

4.1. Inclusion Criteria

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

1. Adults at least 18 years of age;
2. Life expectancy \geq 12 weeks;
3. Subjects must have mCRPC, RCC, MEL, or NSCLC, confirmed by available pathology records or current biopsy, that is advanced (non-resectable), or recurrent and for which no alternative, curative standard therapy exists. Indication-specific criteria are detailed in Appendix 3;
4. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2 (Appendix 4);
5. Must have at least 1 measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) with modification (see Appendix 1). The measurable lesion(s) must be outside the field of radiation therapy (RT) if there was prior treatment with RT. Subjects with mCRPC and with only non-measurable bone lesions must have either progression with 2 or more new lesions or have PSA progression within the 6-week period before study drug administration;
6. At least 1 and up to 5 prior systemic therapies for advanced/recurrent disease (unlimited hormonal therapies allowed);

7. Prior chemotherapy or immunotherapy (tumor vaccine, cytokine, or growth factor given to control the cancer) must have been completed at least 4 weeks before study drug administration, and all adverse events have either returned to baseline or stabilized;
8. Prior treated brain or meningeal metastases must be without MRI evidence of progression for at least 8 weeks and off immunosuppressive doses of systemic steroids (> 10 mg/day prednisone or equivalent) for at least 2 weeks before study drug administration;
9. Prior systemic radiation therapy must have been completed at least 4 weeks before study drug administration. Prior focal radiotherapy completed at least 2 weeks before study drug administration. No radiopharmaceuticals (strontium, samarium) within 8 weeks before study drug administration;
10. Immunosuppressive doses of systemic medications, such as steroids or absorbed topical steroids (doses > 10 mg/day prednisone or equivalent) must be discontinued at least 2 weeks before study drug administration;
11. Prior surgery that required general anesthesia must be completed at least 4 weeks before study drug administration. Surgery requiring local/epidural anesthesia must be completed at least 72 hours before study drug administration and subjects should be recovered;
12. Screening laboratory values must meet the following criteria:

WBC	$\geq 2000/\mu\text{L}$
Neutrophils	$\geq 1500/\mu\text{L}$
Platelets	$\geq 100 \times 10^3/\mu\text{L}$
Hemoglobin	≥ 9.0 g/dL
Creatinine	≤ 2 mg/dL
AST	$\leq 2.5 \times \text{ULN}$ without, and $\leq 5 \times \text{ULN}$ with hepatic metastasis
ALT	$\leq 2.5 \times \text{ULN}$ without, and $\leq 5 \times \text{ULN}$ with hepatic metastasis
Bilirubin	$\leq 2 \times \text{ULN}$ (except subjects with Gilbert's syndrome, who must have total bilirubin < 3.0 mg/dL)
13. Women must meet 1 of the following criteria: post-menopausal for at least 24 consecutive months; surgically incapable of bearing children (i.e., have had a hysterectomy or bilateral oophorectomy); or utilizing a reliable form of contraception. Women of child bearing potential must agree to use a reliable form of contraceptive during the study Treatment Period and for at least 70 days following the last dose of study drug; and
14. Men must agree to the use of male contraception during the study Treatment Period and for at least 180 days after the last dose of study drug.

4.2. Exclusion Criteria

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

1. History of severe hypersensitivity reactions to other mAbs;
2. Prior malignancy active within the previous 2 years except for locally curable cancers that have been adequately treated, such as basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix or breast;
3. Subjects with any active autoimmune disease (Appendix 5) or a documented history of autoimmune disease, or history of syndrome that required systemic steroids or immunosuppressive medications, except for subjects with vitiligo or resolved childhood asthma/atopy;
4. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PDL-2, or anti-CTLA-4 antibody (or any other antibody targeting T cell co-stimulation pathways);
5. Known history of Human Immunodeficiency Virus;
6. Active infection requiring therapy, positive tests for Hepatitis B surface antigen or Hepatitis C ribonucleic acid (RNA);
7. Underlying medical conditions that, in the Investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of toxicity determination or adverse events;
8. Concurrent medical condition requiring the use of immunosuppressive medications, or immunosuppressive doses of systemic or absorbable topical corticosteroids;
9. Use of other investigational drugs (drugs not marketed for any indication) within 28 days or at least 5 half-lives (whichever is longer) before study drug administration; or
10. Pregnant or nursing.

5. RANDOMIZATION AND BLINDING

Not applicable as this is an open-label study.

6. ASSIGNMENT TO STUDY

The investigative site will contact Medarex for treatment assignment once a subject is determined to be eligible for enrollment. Subjects who meet all eligibility requirements will be assigned to the next available dose level, as determined by Medarex. Once assigned, numbers for any screening failures, non-treated, non-evaluable, or discontinued subjects will not be re-used.

7. DOSAGE AND ADMINISTRATION

7.1. Physical Description of Study Drug

MDX-1106 is supplied in a single-use 10 mL vial. Each vial contains a concentrated solution with the equivalent of 100 mg of MDX-1106 (10 mg/mL).

7.2. Packaging and Labeling

The study drug will be packaged and labeled according to current good clinical practices (GCP). Details of the packaging and labeling of clinical supplies may be found in the Pharmacy Manual.

7.3. Ordering Study Drug

Clinical supplies may be requested by completing a Request Form and faxing it to the Clinical Operations Contact at Medarex.

7.4. Storage

MDX-1106 vials must be stored at a temperature of 2°C to 8°C and should be protected from light. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of MDX-1106 include laboratory coats and gloves. Note: once MDX-1106 has been prepared for administration, the total storage time (combination of refrigeration and room temperature) is not to exceed 24 hours.

Stability data for MDX-1106 supports 6 hours at room temperature/under room light and 18 hours at 2°C to 8°C in the refrigerator following dilution and transfer to the i.v. bag. Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent.

7.5. Study Drug Preparation and Administration

MDX-1106 (1, 3, or 10 mg/kg) will be administered as a single 60-minute i.v. infusion every 14 days for a total of 4 infusions in each cycle (up to 12 cycles).

1. Allow the appropriate number of vials of MDX-1106 to stand at room temperature for approximately 5 minutes before preparation.
2. Ensure that the MDX-1106 solution is clear, colorless and essentially free from particulate matter on visual inspection.
3. Aseptically withdraw the required volume of MDX-1106 solution into a syringe, and dispense into an i.v. bag. (If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall and so on.)

4. The total dose to be administered will be diluted to a total volume of 60 mL in sterile normal saline (0.9% sodium chloride). In cases where the total volume is more than 60 mL, no additional dilution is necessary.
5. Prepare the MDX-1106 solution for infusion per the example provided below:

Total dose should be calculated as follows:

Subject body weight in kg x 3 mg (for the 3 mg/kg cohort) = total dose, mg

For example, a subject with a body weight of 70 kg would be administered 210 mg of MDX-1106 (70 kg x 3.0 mg/kg = 210 mg). Twenty-one (21) mL of MDX-1106 and 39 mL of normal saline would be mixed in the i.v. bag and the solution would be infused over 60 minutes.

6. Mix by GENTLY inverting several times. DO NOT shake.
7. Visually inspect the final solution. If the infusion is not clear or the contents appear to contain precipitate, the solution should be discarded (according to the instructions in Section 7.6) and documented on the Drug Accountability Log.
8. Record the time MDX-1106 was prepared on the i.v. bag label.
9. Attach the i.v. bag containing the MDX-1106 solution to the infusion set, 0.2 µM in-line filter, and infusion pump.
10. The infusion rate of the infusion pump should be adjusted to allow for a total infusion time of 60 minutes.
11. At the end of the infusion period, flush the line with a sufficient quantity of normal saline.

Do not enter into each vial more than once.

Do not prepare MDX-1106 for infusion in glass syringes.

Do not administer study drug as an i.v. push or bolus injection.

7.6. Drug Accountability

Medarex is the manufacturer and provider of the study drug supply. All study drug(s) will be supplied to the Investigator by Medarex or its designee. Study drug supplies must be kept in an appropriate, secure locked area and stored in accordance with the conditions specified on the labels.

The Investigator or designated study person must maintain an accurate record of dispensing the study drug in a Drug Accountability Log, a copy of which must be given to Medarex at the end of the study. The Drug Accountability Log will record the study drugs received, dosages

prepared, time prepared, doses dispensed, and doses and/or vials destroyed. The Drug Accountability Log will be reviewed by the field monitor during site visits and at the completion of the study.

All used and partially used study drug will be destroyed by the site, in accordance with the site's standard operating procedures (SOPs) or at a central depot.

7.7. Infusion Delays and Missed Doses

There must be a minimum of 14 days between study drug infusions. In the case that an infusion cannot be administered at a scheduled visit, it has to be administered as soon as possible. If the delay is between 1 and 7 days, the procedures at the original scheduled visit should be performed. If the delay is more than 7 days, the procedures at the next visit should be performed, and subsequent visits will follow every 2 weeks (the infusion at the original scheduled visit will be considered a missed dose). Subjects with infusion delays >35 days (i.e., 2 missed doses + 7 days) should discontinue treatment and enter the Follow-up Period.

8. TOXICITY AND MANAGEMENT

8.1. Dose Escalation

Three dose levels are planned: 1, 3, and 10 mg/kg. Subjects will be assigned to a dose level in the order of study entry. Initially, 3 subjects will be enrolled at the 1 mg/kg dose level. If no subject (0 of 3) in a dose cohort experiences a dose-limiting toxicity (DLT, see definition under Section 8.2) during the first cycle, then the next dose cohort of 3 subjects will be enrolled at the next higher dose level. If 1 of 3 subjects in a dose cohort experiences a DLT during the first cycle, that cohort will be expanded to 6 subjects. Provided that no more than 1 of 6 subjects in the expanded dose cohort experiences a DLT within the first cycle, then the next dose cohort of 3 subjects will be enrolled at the next higher dose level. If ≥ 2 of up to 6 subjects in the 1 mg/kg dose cohort experiences a DLT during the first cycle, that cohort will have exceeded the MTD, which is defined as the highest tested dose at which no more than 1 of 6 subjects has experienced a DLT in Cycle 1, and a lower dose level (0.3 mg/kg) will be tested. If ≥ 2 of up to 6 subjects in the 3 or 10 mg/kg dose cohorts experience a DLT during the first cycle, that cohort will have exceeded the MTD, and the following will occur:

- If no subjects (0 of 3) experienced a DLT at the previously tolerated dose level, 3 additional subjects will be dosed at that dose level.
- If ≤ 1 of 6 subjects experienced a DLT at the previously tolerated lower dose level, an intermediate dose level will be tested. The planned intermediate dose levels will be 2 and 7 mg/kg for the 3 and 10 mg/kg cohorts, respectively.

No dose escalations or de-escalations are permitted within each subject's treatment.

8.2. Dose-limiting Toxicity

A DLT is defined as a \geq Grade 3 drug-related adverse event (using NCI CTCAE Version 3.0) occurring during the first cycle (56 days) of dosing, excluding:

- Grade 3 adverse event of tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor),
- Grade 3 rash,
- Grade 3 irAE that resolves to a Grade 1 or less within 28 days, or
- a transient (resolving within 6 hours of onset) Grade 3 infusion-related adverse event.

A Grade 3 irAE that resolves to a Grade 1 or less within 28 days, while not constituting a DLT for dose escalation/expansion purposes, will preclude further administration of MDX-1106 to the subject. A DLT will be considered related to study drug unless there is a clear, well-documented, alternative explanation for the toxicity. Delayed DLTs are adverse events that meet the criteria of DLTs that occur after Cycle 1. Delayed DLTs will not be used to determine the MTD for dose escalation.

All adverse events that meet DLT or delayed DLT criteria, as well as any Grade 3 or 4 infusion reactions whether or not the event is a DLT, must be reported to Medarex, within 24 hours using the rapid notification procedures described in Section 12.3.

8.3. Stopping Rules for Dose-limiting Toxicity During Dose Escalation

Two or more DLTs in a dose escalation cohort will exceed the MTD.

Delayed DLTs will be evaluated on a case-by-case basis. If 2 or more delayed DLTs are noted within a dose escalation cohort, further accrual will be held pending safety analysis of the adverse events, and will be restarted only with Investigator and Medarex, approval at all sites (with FDA and IRB notification).

If there is a previous DLT in a cohort followed by a Grade 3 irAE, further enrollment and treatment of subjects in the cohort should be paused for up to 28 days while awaiting the outcome of the Grade 3 irAE. If the Grade 3 irAE does not resolve to Grade 1 or less within 28 days, it will be considered a DLT.

Initial analyses of pharmacokinetic samples from protocol MDX1106-01 indicate that the half life of MDX-1106 is approximately 14 days. Dose-related toxicity is therefore most likely to occur during treatment or within the 10 to 14 days following treatment.

8.4. Stopping Rules for Dose-Limiting Toxicities During the Expansion Phase

Enrollment will be stopped if either the rate of DLTs is $\geq 33\%$ across all indications (including subjects from the Dose-escalation Phase at the expansion dose) **or** if the rate of DLTs is $\geq 33\%$ for a specific indication after enrollment of the first 6 subjects in that indication (including subjects from the Dose-escalation Phase at the expansion dose). After safety analysis by the Investigators and Medarex (with FDA and IRB notification), a decision will be made whether to initiate a new expansion cohort of 16 subjects in each of 1 or more of the indications at a lower MDX-1106 dose (chosen according to the de-escalation rules above). For delayed DLTs, enrollment will be stopped using the same rules as that for DLTs. After which, the Investigators and the Medarex Medical Monitor (with FDA and IRB notification) will review the delayed DLTs, and a decision will be made whether to resume enrollment at the current dose (with or without a limitation in the total number of allowed cycles) or initiate a new expansion cohort in 1 or more of the indications at a lower dose (using the same de-escalation schedules as that for DLTs).

8.5. Possible Toxicities

There is not enough clinical experience with MDX-1106 to define expected toxicities. Possible toxicities could affect the immune system, hematologic, cardiovascular, hepatic, musculoskeletal, and other systems, and may include the following:

- **Allergic reaction/hypersensitivity:** Fever, chills, shakes, itching, rash, hyper- or hypotension, difficulty breathing. It is likely that most infusion-related adverse events will occur within the first 24 hours after beginning the infusion, and may be treated by slowing or interruption of the infusion, or with supportive treatment as indicated.
- **Widespread immune activation/cytokine storm:** Cytokine storm adverse events may initially look like allergic reaction/hypersensitivity, but are distinguished by more sustained and profound hemodynamic disturbances related to the widespread release of cytokines such as IL-1 and TNF. Symptoms may include fever, myalgia, change in mental status, hypotension, pulmonary infiltrates, metabolic acidosis and acute renal failure. Cytokine storm has been observed with an agonistic anti-CD28 antibody (TGN1412), but is not expected with MDX-1106, and has not been seen in preclinical testing nor in human subjects with cancer treated to date.
- **Tumor lysis syndrome:** Rapid lysis of tumors may result in asymptomatic laboratory abnormalities to clinical changes secondary to electrolyte disturbances, including cardiac arrhythmias, neuromuscular irritability, tetany, seizures, and mental status changes (hypocalcemia), acute renal failure (hyperuricemia and hyperphosphatemia), and metabolic acidosis (acute renal failure and lactic acidosis).

- **Immune-related adverse events:** It is possible that syndromes may develop that are most consistent with an underlying enhanced immune response as the driving factor. Such events may consist of persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, or cardiomyopathy. Experience with other immunomodulatory mAbs indicates that irAEs are typically low grade and self limited, more often occur after multiple doses, and most frequently involve the gastrointestinal tract (diarrhea/colitis), skin (rashes), liver (hepatitis), and endocrine systems (a variety of endocrinopathies).
 - **Gastrointestinal system:** Colitis, characterized by new onset of diarrhea, which may be accompanied by abdominal pain and or GI bleeding. Events of Grade 3 or Grade 4 diarrhea as well as Grade 2 diarrhea with blood in stool should be evaluated for colitis. **Any \geq Grade 2 diarrhea/colitis must be reported to Medarex, within 24 hours using the rapid notification procedures described in Section 12.3.**
- **Immune suppression:** Subjects should be monitored for signs of new infection or return of a previous infection, with rash, fever, chills, other localizing symptoms, or sepsis that could require antibiotics either as prevention or treatment.
- **Musculoskeletal system:** Muscle or joint aches or swelling, weakness
- **Blood:** A decrease in blood components (platelets, white or red cells) that could lead to infection, bleeding, or anemia.
- **Skin:** The most likely adverse events are rash and pruritus, which generally resolve when drug therapy is discontinued.

8.6. Infusion Reactions

Since MDX-1106 contains only human protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. Since this antibody specifically binds to PD-1, this makes it less likely that such a reaction would occur. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions will be evaluated as to whether or not the event is a DLT and should be reported within 24 hours using the rapid notification procedures described in Section 12.3.

Prophylactic premedication may be given anytime after the first dose of Cycle 1.

Infusion reactions should be graded according to NCI CTCAE (Version 3.0) guidelines. Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

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

- Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic pre-medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol (acetaminophen) at least 30 minutes before additional MDX-1106 administrations.

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

- Stop the MDX-1106 infusion, begin an i.v. infusion of normal saline, and treat the subject with diphenhydramine 50 mg i.v. (or equivalent) and/or paracetamol/acetaminophen; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further MDX-1106 will be administered at that visit. Administer diphenhydramine 50 mg i.v., and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the case report form (CRF). The following prophylactic pre-medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent), paracetamol (acetaminophen) and/or corticosteroids should be administered at least 30 minutes before additional MDX-1106 administrations.

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

- Immediately discontinue infusion of MDX-1106. Begin an i.v. 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 i.v. administration, and/or diphenhydramine 50 mg i.v. with methylprednisolone 100 mg i.v. (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. MDX-1106 will be

permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms.

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

8.7. Stopping Rules for Clinical Deterioration

Accumulating evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological (or PSA – for mCRPC) progression, or appearance of new lesions or some enlarging lesions while certain target lesions are regressing (“mixed response”). It is thus reasonable to allow for these possibilities and continue to treat the subject until progression is confirmed and found to be advancing and continuing at the next imaging assessment. These considerations should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment.

Such deterioration will be assessed to have occurred after a clinical event that, in the Investigator’s opinion, is attributable to disease progression, is unlikely to reverse with continued study treatment and therefore indicates that the subject is not benefiting from study treatment **and** can not be managed by the addition of supportive care (such as bisphosphonates and/or bone directed radiotherapy, thoracentesis or paracentesis of accumulating effusions).

For example:

- Performance status decrease of at least 2 points from baseline
- Skeletal related events defined by the following:
 - pathologic bone fracture in the region of cancer involvement
 - cancer related surgery to bone
 - spinal cord or nerve root compression
- Bladder outlet or urethral obstruction
- Development of new central nervous system (CNS) metastases
- Or any setting where the initiation of new anti-neoplastic therapy has been deemed beneficial to the subject even in the absence of any such documented clinical events.

9. COMPLIANCE

The Investigator or their designated study personnel will maintain a log of all study drugs received, dispensed, destroyed, and returned. Drug supplies will be inventoried and accounted for throughout the study.

The Investigator and the study personnel will ensure that each subject receives the calculated dose of the study drug based on body weight.

10. CONCOMITANT THERAPY

All medications taken within 28 days before the administration of study drug and all concomitant therapy administered during the study will be recorded on the relevant CRF, along with the reason for and details of therapy use.

1. Prophylactic premedication with acetaminophen and diphenhydramine and steroids may be given if indicated by previous experience with MDX-1106 in an individual subject.
2. Inhaled or intranasal corticosteroids (with minimal systemic absorption) may be continued if the subject is on a stable dose. Non-absorbed intra-articular steroid injections will be permitted. Systemic corticosteroids required for the control of infusion reactions or irAEs must be tapered and be at non-immunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) for at least 2 weeks before the next study drug administration.
3. Use of new herbal remedies, other marketed anti-cancer chemo/immunotherapy drugs, or investigational drugs (drugs not marketed for any indication) is not permitted.
4. New chemotherapy or immunotherapy is not permitted. Other palliative/therapeutic therapies (e.g., focal radiotherapy for pain, thoracocentesis or paracentesis for comfort) may be administered.

All subjects should be maintained on the same concomitant medications throughout the study period, as medically feasible. Any new concomitant medications prescribed for the subject or changes to dosing/schedule of concomitant medications should be recorded on the appropriate CRF page. The addition of a new concomitant medication for which there is a concern that it may not be permitted should be first reviewed with the Medarex Medical Monitor.

11. STUDY EVALUATIONS

11.1. Study Procedures by Visit

11.1.1. Overview

The study is divided into periods with associated evaluations and procedures that must be performed at specific time points. The Time and Events Schedule (Table 1) summarizes the frequency and timing of efficacy, safety, and other study measurements. The Pharmacokinetic Blood Sampling Schedule (Table 2) delineates the frequency and timing of serum sampling for pharmacokinetic assessment.

As soon as the subject is considered for this study and before performing any study procedures, the subject will have the nature of the study explained to him/her, and will be asked to give written informed consent and HIPAA authorization. Informed consent/HIPAA authorization must be obtained before any procedures that do not form a part of the subject's normal care. Baseline imaging and ECG performed as part of the subject's previous routine care before signing the informed consent form and completed within 28 days before the administration of MDX-1106 need not be repeated.

All subjects (withdrawn or completed) will have final evaluations and procedures performed.

11.1.2. Screening Period

Subjects will be evaluated for entry criteria during the Screening Period within 28 days before administration of study drug. The following procedures and evaluations will be completed for each subject before Day 1 and before inclusion in the study:

- Informed consent/HIPAA may be obtained greater than 28 days before receiving study drug, before any Screening procedures
- Inclusion/exclusion criteria
- Demographics and medical history (to include collection of prior medications administered to the subject during the Screening Period, prior and concurrent medical conditions, and baseline signs and symptoms). For subjects with mCRPC, medical history will include at least 3 PSA measurements over the preceding 6 months.
- Baseline signs and symptoms: Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions CRF.
- Diagnosis confirmation and stage
- Tumor-specific therapy

- Hepatitis B and C testing, including Hepatitis B surface antigen and Hepatitis C antibody (with reflex Hepatitis C RNA if antibody test is positive).
- Testosterone testing in subjects with mCRPC only. Testosterone level must be ≤ 50 ng/dL.
- Vital sign measurements including temperature, pulse, and blood pressure
- Height
- Weight
- Complete physical examination (including examination of skin, head, eyes, nose, throat, neck, joints, lungs, heart, abdomen [including liver and spleen], lymph nodes, and extremities). A brief neurological examination should also be performed.
- ECOG performance status
- Clinical laboratory tests ([central laboratory]):
 - Hematology: Complete blood count (CBC) with differential (including absolute lymphocyte count) and direct platelet count.
 - Chemistry: Albumin
SGOT (AST)
SGPT (ALT)
Alkaline phosphatase
Bilirubin (direct and total)
Calcium
Creatinine
Glucose
Lactate dehydrogenase (LDH)
Total protein
Urea nitrogen (BUN)
Uric acid
Electrolytes (including sodium, phosphorous, potassium, chloride, and bicarbonate)
 - Urinalysis: Gross examination including specific gravity, protein, glucose, and blood.

Microscopic examination including WBC/HPF, RBC/HPF, and any additional findings
- Serum β -HCG pregnancy test (before the first infusion; for all women of childbearing potential; serum pregnancy test must be negative to continue).

- Chest radiograph
- 12-lead Electrocardiogram (ECG)
- A brain CT/MRI scan is required at Screening if not performed within the previous 2 months (and NOT required for subjects with mCRPC).
- Tumor imaging (CT/MRI chest/abdomen/pelvis). The same imaging modality technique must be used throughout the protocol.
- Bone scans for subjects with mCRPC and as clinically indicated in subjects in other indications.
- PSA (for mCRPC only) including at least 3 PSA measurements over the preceding 6 months.
- Tumor biopsy required if there is no other record of histological diagnosis of tumor.
- Optional research-related tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed at Screening and at other times during the protocol as clinically indicated. Optional tumor or other biopsy for research purposes requires specific agreement by the subject in the informed consent.
- Concomitant medications

11.1.3. Treatment Period

The Treatment Period of the study is divided into cycles with associated evaluations and procedures that must be performed at specific time points (see Table 1). Subjects who meet selection criteria may start MDX-1106 treatment within 0 to 28 days of Screening. Subjects will receive 4 doses of MDX-1106 every 14 days during each cycle. Following Cycle 1, the decision whether to treat a subject with additional cycles of MDX-1106 will be determined as summarized in Section 3.2. Results of assessments must be reviewed before administering the first dose of the next cycle. No subject will be permitted dose escalations. The maximum number of cycles to be administered to an individual subject in this study is 12.

Every effort should be made to schedule visits within the protocol-specified windows. For infusion delays (i.e., by 1 to 13 days) or missed doses, see Section 7.7 for administration details.

A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

11.1.3.1. Cycle 1

Cycle 1 will begin with the first i.v. infusion of MDX-1106 (Day 1) and will continue through to completion of evaluations by Day 56. The subject will be given a 60-minute i.v. infusion every

14 days for a total of 4 infusions (Days 1, 15, 29, and 43) with a response assessment between Days 52 and 56.

During Cycle 1, the following evaluations will be performed as indicated in Table 1, and the results will be recorded on the CRF:

- MDX-1106 infusions (after all other evaluations for the visit according to the Time and Events Table have been completed except for the post-infusion pharmacokinetic samples)
- Serum sample for pharmacokinetics as outlined in Table 2. (Post-infusion samples should be drawn from a site other than the infusion site [i.e., contralateral arm] on infusion days.)
- Serum sample for immunogenicity (collected prior to infusion)
- Vital sign measurements to include temperature, pulse, and blood pressure will be obtained as defined in the Time and Events Schedule (Table 1).
- Weight
- Limited physical examination (including measurement of vital signs as well as pulmonary, heart, abdomen, and skin assessments)
- ECOG performance status
- Clinical laboratory tests ([local and central laboratories]; Hematology and clinical chemistry laboratories **must be performed and reviewed before dosing.**)
- Any new \geq Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the Medarex Medical Monitor should be contacted. Samples should be drawn from a site other than the infusion site [i.e., contralateral arm]) on the days of infusion:
 - Hematology with differential (as outlined in Section 11.1.2)
 - Clinical chemistry (as outlined in Section 11.1.2)
 - Urinalysis
- Immune Safety Assays: Rheumatoid Factor (RF), Thyroid Stimulating Hormone (TSH), Free T4 Level, C-Reactive Protein (CRP), Antinuclear Antibody (ANA) titer and pattern.

The following tests, may also be performed on selected stored samples at a later date: anti-DNA antibody, anti-phospholipid antibody, anti-SSA antibody (Ro), anti-islet cell antibody; anti-SSB antibody (La), anti-neutrophil cytoplasm antibody, antithyroglobulin antibody, C3 and C4, anti-LKM antibody, and CH50.

Abnormal endocrine results will be followed up with prolactin and a.m. cortisol tests, and may require an endocrine consult.

- Urine pregnancy test to be performed locally (for all women of childbearing potential; urine pregnancy test must be negative before study drug administration to continue)
- CT/MRI Brain (not required for mCRPC, or for subjects with other indications with a normal screening CT/MRI Brain, unless clinically indicated by the development of new symptoms that suggest new CNS involvement)
- Tumor imaging (CT/MRI chest/abdomen/pelvis).
- Bone scan (for all subjects with mCRPC, or if clinically indicated or positive at baseline for other indications)
- PSA (only for subjects with mCRPC)
- Response assessment and documentation
- The following tests will be performed for research purposes:
 - Flow cytometry: Fresh whole blood will be sent to the central laboratory. Phenotypic markers to be tested include: CD3, CD4, CD8, CD19, CD4+CD25, CD4+CD25+CD45RO, CD8+CD25, CD4+HLA-DR, CD8+HLA-DR, CD4+45RO, and CD8+45RO.
 - Cryopreserved peripheral blood mononuclear cells (PBMCs): Samples will be subsequently analyzed for immunoreactivity to a panel of peptide recall antigens (Cytomegalovirus, Epstein Barr Virus, and Influenza virus [CEF]). Tumor-specific antigen reactivity testing will be governed by type of tumor and availability of test antigens.
 - Serum for subsequent cytokine panel assays: may include: IL-1, 4, 5, 6, 10, 13 and IFN gamma, TNF alpha, and TGF beta.
 - Serum for quantitative immunoglobulins: Samples will be analyzed for IgM, IgG1, IgG2, IgG3, IgG4, IgA
- Concomitant medications
- Adverse event assessment including specific elicitation of symptoms (see Appendix 6) that may be indicative of irAEs.

11.1.3.2. Cycle 2 to 12

Following Cycle 1, subjects may receive up to 11 additional cycles of therapy. Day 1 of each cycle is 56 days following Day 1 of the previous cycle. During each of these cycles, subjects will be given a 60-minute i.v. infusion every 14 days for a total of 4 infusions on Days 1, 15, 29, and 43 of each cycle with a response assessment between Days 52 and 56. Following each cycle, the decision whether to treat a subject with additional cycles of MDX-1106 will be determined as

summarized in Section 3.2. The maximum number of cycles to be administered to an individual subject in this study is 12.

The evaluations performed in Cycle 1 will be repeated during Cycle 2 and subsequent cycles as indicated in Table 1, and the results will be recorded on the CRF. The following additional evaluations will also be performed as indicated in Table 1:

- Complete physical examination (as outlined in Section 11.1.2)
- ECG

11.1.4. Follow-up Period

Up to 6 follow-up visits will be conducted after completion of the Treatment Period or as indicated in Section 3.2. Subjects whose PD is confirmed and who have further progression at a subsequent imaging evaluation will only complete Follow-up Visit 1. The evaluations performed in Cycles 2 to 12 (with the exception of MDX infusions, weight, and urine pregnancy test) will be repeated during the Follow-up Visits as indicated in Table 1, and the results will be recorded on the CRF.

The following additional evaluation will also be performed as indicated in Table 1:

- Tumor-specific therapy

11.1.5. Cycle 1 Treatment Completion

Whether or not each subject completed study drug treatment through the first cycle will be documented on the CRF, including how many doses in Cycle 1 were received. Subjects will be considered to have completed Cycle 1 treatment if they:

- Completed 4 doses of MDX-1106 in Cycle 1, and
- Completed all evaluations at the end of Cycle 1.

11.1.6. Study Completion

Subjects who complete all 6 Follow-up Visits will be considered to have completed the study. Whether or not each subject completed the clinical study will be documented, including how long he/she was followed, and if withdrawn, the reason for withdrawal.

If for any reason, either study treatment or observations were discontinued, the reason will be recorded. The primary reasons for discontinuation will be documented:

- Adverse event(s)
- Protocol violation
- Disease progression

- Subject withdrew consent
- Subject is lost to follow-up
- Death
- Other

Subjects who discontinue from the study should be followed until resolution and/or stabilization of any adverse event. All subjects who discontinue from the study should be monitored for 70 days following the last dose of MDX-1106 for the occurrence of serious adverse events considered by the Investigator to be related to MDX-1106 treatment. Subjects should be contacted at least once within 70 days following the last dose of MDX-1106. Telephone contact is acceptable and should be within ± 10 days of the 70-day time point.

11.2. Efficacy Evaluations

11.2.1. Primary Efficacy Parameter

The primary efficacy parameter is the BORR during the first 3 cycles (proportion of subjects with confirmed responses of CR or PR) as determined by the results of Investigator evaluations for each indication. Tumor response status will be assessed using RECIST with modification (as detailed in Appendix 1) as well as by PSA for mCRPC. PSA responses will be graphically described using waterfall diagrams (Appendix 2).

11.2.2. Secondary Efficacy Parameters

The secondary efficacy parameters include BORR during the entire study for each indication and across all indications (regardless of time to response), response categories (CR, PR, SD, PD), disease control rate (sum of response rate for CR+PR+SD across subjects), and the time to response and duration of response for those subjects with a confirmed response. Tumor response status will be assessed using RECIST with modification (Appendix 1) as well as by PSA for mCRPC (Appendix 2).

11.2.3. Exploratory Evaluations of Immune Response

Additional efficacy evaluations may be performed to measure the impact of MDX-1106 upon the potency of the immune response that may ultimately be associated with beneficial clinical responses.

- Samples (including serum and PBMCs) for evaluation of cytokines, lymphocyte phenotype, quantitative immunoglobulins, disease-related biomarkers (or antibody responses to selected antigens), cellular immune responses to tumor antigens, and a panel of recall non-tumor antigens may be assessed.

- Readily accessible tissue from the optional research-related biopsies may be collected at the time of apparent inflammatory infiltrate or clinical event of note at the tumor or other site. Tissue samples from these tumor biopsies, as well as from any other clinically indicated and consented biopsies conducted during the study will be collected, to assess morphology and the presence or absence of inflammatory infiltrates, and their cellular characterization. Available slides and tissue samples from tumor biopsies collected before enrollment in this study may also be examined for tumor markers and inflammatory infiltrates.
- Additional sample collections and analyses may be performed at selected study sites with a site-specific amendment. All samples collected for these exploratory analyses will be stored, and may be used for subsequent research relevant to tumor immune response.

11.3. Safety Evaluations

The following evaluations will be performed during the study to measure the safety and tolerability of MDX-1106: clinical laboratory tests (blood and urine sampling for clinical laboratory parameters), pregnancy testing, ECOG performance status, physical examinations including vital sign measurements, ECG, and the incidence and severity of treatment-emergent adverse events. Safety assessment will also include evaluations of immune safety and immunogenicity.

11.3.1. Immune Safety Evaluations

Immune safety assays refer to clinical laboratory tests that measure the emergence of auto-immune or other unintended reactivities that the subject may develop as a consequence of MDX-1106-mediated stimulation of the immune system. The presence of these new reactivities may or may not be associated with clinical consequences, and are being monitored as part of the safety surveillance in this protocol.

11.3.2. Immunogenicity

Immunogenicity refers to the development of an immune response to the MDX-1106 drug itself, and is characterized by antibodies that the subject may develop that react with MDX-1106. These may result in more rapid clearance of MDX-1106 from the bloodstream, or predispose the subject to an infusion reaction if the subject is to be retreated with MDX-1106 at a later date.

11.4. Pharmacokinetic Evaluations

Blood samples will be collected for pharmacokinetic evaluation of peak and trough levels of MDX-1106 on infusion days according to the schedule in Table 2 of the Time and Events Schedule. Single samples will also be collected to evaluate serum concentrations of MDX-1106 as indicated in Table 2. Serum samples should be drawn from a site other than the infusion site

(i.e., contralateral arm) on days of infusion. If the infusion was interrupted, the reason for interruption will also be documented on the CRF.

12. ADVERSE EVENT REPORTING

Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions CRF.

12.1. Definitions

An adverse event is any undesirable sign, symptom, clinically significant laboratory abnormality, or medical condition occurring after starting study treatment, even if the event is not considered to be treatment-related. Each adverse event is to be reported on an Adverse Event CRF page. Adverse events are graded using the Cancer Therapy Evaluation Program (CTEP) CTCAE, Version 3.0.³³ If CTCAE grading does not exist for an adverse event, the severity of mild (1), moderate (2), severe (3), life-threatening (4), and death related to an adverse event (5) will be used. Information about all adverse events, whether volunteered by the subject, discovered by Investigator questioning, or detected through physical examination, laboratory testing, or other means, will be collected and recorded on the Adverse Event CRF page and followed as appropriate. Adverse event monitoring should be continued until adverse event resolution/stabilization (whichever is later).

Medical conditions/diseases present before the infusion of study drug are only considered adverse events if they worsen after receiving any study drug. Clinical events occurring before the administration of study drug but after signing the ICF and providing HIPAA authorization are to be recorded on the Medical History/Current Medical Conditions CRF page. All laboratory values are to be reviewed by the Investigator and abnormal values will be graded according to CTCAE Version 3 and reported in the study report. A laboratory abnormality is considered an adverse event if it results in discontinuation from study drug, necessitates therapeutic medical intervention, or if the Investigator assesses the abnormality as an adverse event. These adverse events will be recorded on the Adverse Events CRF page and will include all signs, symptoms, or diagnosis associated with them.

As far as possible, each adverse event will also be described by:

1. Description
2. Duration (start and end dates)
3. CTCAE Grade 1 through 5 or severity if CTCAE is not available
4. Relationship to the study drug – related or not related

5. Action(s) taken with study drug
6. Whether event was serious
7. Whether event is ongoing

Relationship to Study Drug

The relationship of each adverse event to study drug will be defined as “not related” or “related”. The Investigator is responsible for determining the study drug relationship for each adverse event that occurs during the study. Assessments are to be recorded on the appropriate CRF page.

Not related

The temporal relationship of the clinical event to study drug administration **makes a causal relationship unlikely**, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

Related

The temporal relationship of the clinical event to study drug administration **makes a causal relationship possible**, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

Action(s) Taken

The actions taken in response to an adverse event are described on a numerical scale that covers the various possibilities. One or more of these are to be selected:

- 0 No action taken
- 2 Study drug permanently discontinued due to this adverse event
- 6 Study drug temporarily interrupted

12.2. Serious Adverse Events

A serious adverse event is defined in general as an untoward (unfavorable) adverse event which:

1. is fatal or life-threatening;
2. requires or prolongs hospitalization;
3. is significantly or permanently disabling or incapacitating;
4. constitutes a congenital anomaly or a birth defect; or
5. may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Hospitalizations occurring under the following circumstances are not considered serious adverse events: admission to a hospice for respite care; hospitalizations planned before entry into the clinical study; hospitalization for elective treatment of a condition unrelated to the studied indication or its treatment; hospitalization on an emergency, outpatient basis that does not result in admission (unless fulfilling the criteria above); hospitalization as part of the normal treatment or monitoring of the studied indication; hospitalization to facilitate the work up of a \leq Grade 2 adverse event, including overnight hospitalization following study drug administration for non-medical reasons.

12.3. Rapid Notification of Serious Adverse Events

12.3.1. Reporting Responsibility

Any serious adverse event occurring in a subject after he/she has provided informed consent and HIPAA authorization, and while receiving study treatment must be reported. All subjects who withdraw from the study should be monitored for 70 days following the last dose of MDX-1106 for the occurrence of serious adverse events considered by the Investigator to be related to MDX-1106 treatment. Subjects should be contacted at least once within 70 days following the last dose of MDX-1106. Telephone contact is acceptable and should be within ± 10 days of the 70-day time point. After 70 days following the last dose of MDX-1106, any serious adverse events considered by the Investigator to be related to MDX-1106 treatment must also be reported. The timeframe for reporting after discontinuation of study drug may be extended if there is a strong suspicion that the study drug has not yet been eliminated or the pharmacodynamic effects of the study drug persist beyond 70 days. All serious adverse events must also be reported for the timeframe in which the study drug interferes with the standard medical treatment given to a subject.

Each serious adverse event must be reported by the Investigator to the Medarex Pharmacovigilance (PVG) Desk, or designee, within 24 hours of learning of its occurrence, even if it is not felt be related to study drug. Serious adverse events occurring after 70 days from the last dose of MDX-1106 must be reported if deemed related to study drug. The report must include the adverse event term, subject identifier, attribution, description, concomitant medication used to treat the adverse event, and any other relevant information. Follow-up information about a previously reported serious adverse event must also be reported to Medarex within 24 hours of receiving the information. Medarex, or its designee, may contact the Investigator to obtain further information about a reported serious adverse event. If warranted, an Investigator Alert may be issued to inform all Investigators involved in any study with the same study drug that a serious adverse event has been reported.

12.3.2. Reporting Procedures

The Investigator must complete the Serious Adverse Event Report Form in English, assess the causal relationship to study drug, and send the completed form to the **SAE Reporting FAX Number** within 24 hours, to Medarex or its designee. The study monitor will review the Serious Adverse Event Report Form and the supporting source documents during monitoring visits.

Follow-up information should be sent to the same PVG Desk that received the original Serious Adverse Event Form, within 24 hours of the time the information is known. Either a new Serious Adverse Event Report Form is faxed (indicating that the information is a follow-up), or the original form may be re-faxed (with the new information highlighted and a new date provided). The follow-up report should describe whether the serious adverse event has resolved or is continuing, if and how it was treated, and whether the subject continued or permanently discontinued study participation. The form(s) and FAX confirmation sheet(s) must be retained in the investigational site study file.

The Investigator is responsible for informing the Institutional Review Board/Independent Ethics Committee (IRB/IEC) of the serious adverse event and providing them with all relevant initial and follow-up information about the event. Medarex or designee will communicate serious adverse events to the study sites as required by regulatory authorities.

12.3.3. Contact Persons and Numbers

The Medarex Central Emergency Contact telephone and SAE telefax numbers are listed on the cover page of the protocol.

12.4. Overdose

An overdose is defined as the accidental or intentional ingestion/infusion of any excessive dose of a product. For reporting purposes, Medarex considers an overdose, regardless of adverse outcome, as a serious adverse event (see Section 12.3, Serious Adverse Events).

12.5. Pregnancy

Pregnancy testing must be performed in all women of childbearing potential throughout the study as specified in the Time and Event Schedule table, and the results of all pregnancy tests (positive or negative) are to be recorded on the CRF. All women of childbearing potential must have a negative pregnancy test before each infusion. If the pregnancy test is positive, the subject must not receive MDX-1106 and must not continue in the study. The subject will be followed to determine the outcome of the pregnancy.

In addition, all women of childbearing potential 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 the study Treatment Period phase of the study or during the 70-day period following their last dose of study drug.

Male subjects should contact the Investigator immediately if they suspect they may have fathered a child during the study Treatment Period phase of the study or during the 180-day period following their last dose of study drug. When possible, such pregnancies should be followed (to term) to determine the outcome.

12.5.1. Reporting of Pregnancy

Initial information on a pregnancy (during or after the study as defined above) must be reported immediately to Medarex and the outcome information provided once the outcome is known. The Serious Adverse Event Form must be faxed to Medarex according to Serious Adverse Event reporting procedures described in Section 12.3.

For female subjects, protocol-required procedures for study discontinuation and follow-up must be performed unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome must be reported. Infants should be followed for a minimum of 8 weeks.

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

12.6. Immune-Related Adverse Events

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

Given the expected mechanism of action of MDX-1106, namely disinhibition of cellular immune responses, it is possible that syndromes may develop that are most consistent with an underlying enhanced immune response as the driving factor. Such events may consist of persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, or cardiomyopathy. The spectrum of irAEs is currently hypothetical, as very few human subjects have been treated to date, and are based upon preclinical studies in mice deficient in PD-1, as well as experience with other monoclonal antibodies that act by disinhibiting the immune response. Such irAEs may resolve with time, or may require institution of counteracting immunosuppressive therapies.

Medarex has observed irAEs in another development program with an immunostimulatory antibody, ipilimumab (anti-CTLA-4). Ipilimumab-induced irAEs are typically low grade and self

limited, more often occur after multiple doses, and most frequently involve the gastrointestinal tract (diarrhea/colitis), skin (rashes), liver (hepatitis), and endocrine systems (a variety of endocrinopathies). In addition, the known animal and human toxicity profiles of anti-CTLA-4 antibodies such as ipilimumab include colitis as an expected adverse event. Based on these considerations, MDX-1106 may also cause immune-mediated colitis.

Colitis is characterized by new onset of diarrhea, which may be accompanied by abdominal pain and or gastrointestinal bleeding. Events of Grade 3 or Grade 4 diarrhea as well as Grade 2 diarrhea with blood in stool should be evaluated for colitis.

Management Algorithms for High Grade irAEs

Management algorithms for high grade irAEs have been established for ipilimumab, where timely application of defined immunosuppressive regimens appear to be effective in limiting the morbidity and mortality from such events without compromising therapeutic efficacy. A management algorithm with recommended guidelines for the treatment and monitoring of diarrhea/colitis is provided in the Investigator Brochure. **All incidents of diarrhea should be managed according to this algorithm.** Additional clinical experience will be required to define the spectrum of irAE-like events that may emerge in the MDX-1106 program, and these algorithms are useful guides towards establishing an effective management approach as experience accumulates.

All adverse events of colitis \geq Grade 2 are deemed to be of special interest, and should be reported using the serious adverse event reporting procedures, even if the adverse event itself is not deemed as serious. In all cases, drug-related \geq Grade 2 diarrhea/colitis will be managed with regular communication between the Investigator and the Medarex Medical Monitor, and with a minimum of at least 1 in-person visit per week until the diarrhea/colitis is $<$ Grade 2. Any Grade 2 adverse event of colitis (per CTCAE) that also results in additional medical requirements, such as more than 2 weeks of immunosuppressive doses of steroids (> 10 mg/day of prednisone or equivalent), blood transfusion, or i.v. hyperalimentation, will be defined as a Grade 3 adverse event. Subjects are to be carefully monitored until recovery of the colitis to \leq Grade 1.

12.7. Rapid Notification of Adverse Events of Importance

In addition to serious adverse events, the following adverse events will be reported within 24 hours using the same rapid notification procedures that are used for serious adverse events (described in Section 12.3), even if the nature of the adverse event is not deemed serious:

- adverse events that potentially meet DLT criteria
- adverse events that potentially meet the delayed DLT criteria

- Grade 3 or 4 infusion reactions whether or not the event is a DLT
- \geq Grade 2 diarrhea/colitis

13. STATISTICAL METHODS

13.1. Sample Size Determination

A sample size of up to 76 subjects is based on the study design for dose escalation, 4 oncology indications, and the number of possible tumor-specific expansion cohorts for further safety and efficacy evaluation.

13.2. Study Populations

13.2.1. Safety Population

The safety population includes subjects who receive at least 1 dose or any partial dose of MDX-1106.

13.2.2. Per-protocol Population

The per-protocol population includes all subjects dosed at the MTD (or the highest dose tested if the MTD is not determined) in the safety population who have the correct disease diagnosis, valid baseline tumor assessment, and at least 1 valid post-baseline tumor assessment. Any subject who has a major inclusion/exclusion violation, major dosing violation, or major protocol conduct violation will be excluded from the per-protocol population. A subject who withdraws from the study during Cycle 1 for reasons other than a DLT will be replaced, hence will be excluded from per-protocol population.

13.3. Statistical Consideration

The Biostatistics group at Medarex or its designees will analyze the data collected in this study.

All data will be listed individually by subject. Continuous variables will be summarized using the following descriptive statistics: number of observed values, mean, standard deviation, median, and minimum and maximum. Categorical variables will be summarized using frequencies and percentages.

The baseline value for analysis variable is the last measurement before study drug administration.

13.3.1. Demographics and Baseline Characteristics

Subject demographics and baseline characteristics including age, sex, race, ethnicity, weight, disease information, and medical conditions will be summarized by dose level using descriptive statistics.

13.3.2. Extent of Exposure

The dose of MDX-1106 taken by subjects will be summarized by dose level. A by-subject listing of treatment exposure will be generated.

13.3.3. Concomitant Medication

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODD). Concomitant medications will be summarized. Tabulation will be made with respect to the proportion of subjects taking at least 1 concomitant medication for each preferred term during the study. A listing of concomitant medications by subject will be provided.

13.3.4. Efficacy

The primary efficacy parameter is BORR during the first 3 cycles (proportion of subjects with confirmed responses of CR or PR) as determined by the results of Investigator evaluations for each indication. The secondary efficacy parameters include BORR during the entire study for each indication and across all indications, response categories (CR, PR, SD, PD), disease control rate (sum of response rate for CR+PR+SD across subjects), and the time to response and duration of response for those subjects with confirmed responses.

All efficacy parameters will be summarized by dose and indication using descriptive statistics. Response will be defined according to RECIST with modification (Appendix 1) or PSA (Appendix 2).

Waterfall diagrams for PSA changes will be generated at time points to be specified in Statistical Analysis Plan.

The greatest percent change in PSA will be plotted for Cycle 1 through Cycle 3, and for the study overall. The PSA at the end of each cycle will be obtained from either the next cycle Day 1 assessment for subjects continuing treatment or from Follow-up Visit 1 for subjects who are not continuing treatment. The best outcome will be plotted based on the results in Cycles 1 through 3 and overall (i.e., the best reduction from baseline whenever it occurred for a subject no matter what cycle).

The efficacy analysis will be conducted on the per-protocol population. For the expansion cohorts, efficacy estimates will only be applicable to cohorts that enroll 16 subjects.

13.3.5. Safety

The safety analysis will be conducted on the safety population. The following safety parameters will be evaluated:

Adverse Events

A treatment-emergent adverse event (TEAE) is defined as a sign or symptom that emerges during treatment or within 70 days of the last dose of the study drug, having been absent pre-treatment or that has worsened relative to the pre-treatment state. Any adverse event deemed related to study drug will also be considered a TEAE regardless of elapsed time since last study drug dose.

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

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) to categorize a system organ class and a preferred term for each adverse event. The number of subjects who experienced at least 1 adverse event, treatment-related adverse event, severe (Grade 3 or above) adverse event, serious adverse event, irAE, immune-related serious adverse event, and the number of subjects withdrawn due to adverse events will be summarized. For each system organ class and preferred term, summaries will be made with respect to the number and proportion of subjects having at least 1 occurrence of an adverse event during the study. The incidence of adverse events will be presented overall, by system organ class and preferred term, intensity (based on NCI CTCAE Version 3.0), irAEs, TEAEs, and additional grouping by severity and relationship to study drug. Individual listings of adverse events will be provided.

DLTs and study drug-related Grade ≥ 2 adverse events will be listed individually.

Physical Examination

Abnormal findings in physical examinations will be provided using descriptive statistics in the data listings and will be summarized by dose level using descriptive statistics.

Vital Signs

Vital signs measurements will be summarized by dose level using descriptive statistics.

ECGs

12-lead ECG results will be summarized by dose level.

Clinical Laboratory Tests

Clinical laboratory test values outside the normal range will be flagged in the data listing.

Laboratory data will be summarized by dose level using descriptive statistics. The results of the immune safety tests will be summarized appropriately.

NCI CTCAE Version 3.0 Grade will be assigned to some of the laboratory parameters, which are included in “CTCAE Version 3.0”. Laboratory values will be listed. The laboratory values which are outside normal range will be flagged as H (above high normal limit), L (below lower normal limit), or A (abnormal) in the data listings. The NCI CTCAE Version 3.0 Grade will also be flagged in the data listings.

ECOG Performance Status

ECOG performance status will be summarized by dose level using descriptive statistics.

Immunogenicity

Immunogenicity results will be summarized by dose level using descriptive statistics.

13.3.6. Pharmacokinetic Parameters

Pharmacokinetic parameters will be summarized by dose level using descriptive statistics.

Serum concentration of study drug will be determined by a validated method according to assessment schedules. The concentrations will be summarized by visit and schedule sample time using descriptive statistic for the safety population by dose level. The mean concentration will be plotted against scheduled sample time.

13.3.7. Immune Function

The effects of MDX-1106 on humoral and cellular immune responses to tumor antigens (when available) and a panel of recall nontumor antigens will be assessed. Parameters to be examined will include lymphocyte phenotype, activation and response to antigens, quantitative immunoglobulins, changes in cytokine levels or other markers of interest, and where tumor tissue is available, the extent of lymphocytic infiltration before and after treatment will be assessed. These parameters will be summarized by dose level using descriptive statistics.

13.4. Missing Data Handling

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

13.5. Statistical Software

All statistical analyses will be performed using SAS[®] Version 9.13 or higher.

14. ETHICAL ASPECTS

14.1. Ethics and Good Clinical Practice

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

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

14.2. Confidentiality Regarding Study Subjects

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

Personal medical information may be reviewed and/or copied for research, quality assurance, and/or data analysis. This review may be conducted by the study monitor, properly authorized persons on behalf of Medarex, an independent auditor, IRBs/IECs or regulatory authorities. Personal medical information will always be treated as confidential.

14.3. Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed ICF, and other information provided to subjects must be reviewed by an IRB/IEC. A signed and dated statement that the protocol and ICF have been approved by the IRB/IEC must be given to Medarex before study initiation. The name and occupation of the chairperson and the members of the IRB/IEC (preferred) or the IRB's Health and Human Safety Assurance number must be supplied to Medarex or its designee. Any amendments to the protocol which need formal approval, as required by local law or procedure, will be approved by this committee. The IRB/IEC will also be notified of all other administrative amendments (i.e., administrative changes).

14.4. Informed Consent

The Investigator, or designee, will explain to each subject (or legally authorized representative) the nature of the research study, its purpose, the procedures involved, the expected duration of subject participation, alternative treatment, potential risks and benefits involved, and any discomfort which may occur during the subject's participation in the study. Each subject will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it and should be given a copy of the signed document. No subject can enter the study and no study-related procedures can be done before his/her informed consent has been obtained.

The ICF must be submitted by the Investigator with the protocol for IRB/IEC approval. Medarex supplies a proposed ICF template that complies with regulatory requirements and is considered appropriate for the study. Any changes to the proposed ICF suggested by the Investigator must be agreed to by Medarex or its designee before submission to the IRB/IEC, and a copy of the approved version must be provided to the Medarex study monitor after IRB/IEC approval.

15. ADMINISTRATIVE REQUIREMENTS

15.1. Protocol Amendments

Any change or modification to this protocol requires a written protocol amendment that must be approved by Medarex before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the IRB/IEC of all centers and, in some countries, by the regulatory authority. A copy of the written approval of the IRB/IEC must be given to the Medarex study monitor, or their designee. Examples of amendments requiring such approval are:

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

These requirements for approval should in no way prevent any immediate action from being taken by the Investigator or by Medarex in the interests of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt by the Investigator to be

necessary and is implemented by him/her for safety reasons, Medarex should be notified and the IRB/IEC for the center should be informed within 1 working day.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC approval; however, the IRB/IEC for each center must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB/IEC approval that can be treated as administrative amendments include, but are not limited to:

1. Changes in the staff used to monitor studies (e.g., Medarex staff versus a contract research organization); and
2. Minor changes in the packaging or labeling of study drug.

15.2. Monitoring Procedures

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Medarex representative will review the protocol, CRFs, and other study documents with the Investigators and their staff. During the study, the Medarex study monitor, or designee, will visit the site regularly to check the completeness of subject records, accuracy of entries on the CRFs, adherence to the protocol and to GCP, progress of enrollment, and also to ensure that study drug is being stored, dispensed, and accounted for according to specifications.

The Investigator must give the study monitor access to relevant hospital or clinical records to confirm their consistency with the CRF entries. No information in these records about the identity of the subjects will leave the study center. Medarex monitoring standards require full verification for the presence of informed consent, HIPAA authorization, adherence to the inclusion/exclusion criteria, documentation of serious adverse events, and recording of efficacy and safety variables. Additional checks of the consistency of source data with the CRFs are performed according to the study-specific monitoring plan.

15.3. Recording of Data and Retention of Documents

All information required by the protocol should be provided; any omissions or corrections should be explained. All CRFs should be completed and available for collection within a timely manner, preferably no more than 10 days after the subject's visit (except for the last visit of the last subject, which should be completed in a timely manner, preferably within 5 working days), so that the study monitor may check the entries for completeness, accuracy and legibility, ensure the CRF is signed by the Investigator and transmit the data to Medarex or its designee.

All entries to the CRF must be made clearly in black ball-point pen to ensure the legibility of self-copying or photocopied pages. Corrections will be made by placing a single horizontal line

through the incorrect entry, so that the original entry can still be seen, and placing the revised entry beside it. The revised entry must be initialed and dated by a member of the Investigator's research team authorized to make CRF entries. Correction fluid must not be used.

The Investigator must maintain source documents for each subject in the study. All information on CRFs will be traceable to these source documents, which are generally maintained in the subject's file. The source documents will contain all demographic and medical information, including laboratory data, ECGs, etc., and also a copy of the signed informed consent/HIPAA authorization, which should indicate the study number and title of the study.

Essential documents, as listed below, will be retained by the Investigator for as long as needed to comply with national and international regulations. Medarex will notify the Investigator(s)/institution(s) when study-related records are no longer required to be retained. The Investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include:

1. Signed protocol and all amendments;
2. IRB/IEC approvals for the study protocol and all amendments;
3. All source documents and laboratory records;
4. CRF copies;
5. Subjects' ICF/HIPAA authorization; and
6. Any other pertinent study documents.

15.4. Auditing Procedures

In addition to the routine monitoring procedures, Medarex, or its designees, may conduct audits of clinical research activities in accordance with internal SOPs to evaluate compliance with the principles of GCP. Medarex, its designee, or a regulatory authority may wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority, the Investigator will inform Medarex immediately that this request has been made.

15.5. Publication of Results

Any formal presentation or publication of data collected from this study will be considered as a joint publication by the Investigator(s) and the appropriate personnel of Medarex. Authorship will be determined by mutual agreement. For multicenter studies, it is mandatory that the first publication be based on data from all centers, analyzed as stipulated in the protocol by Medarex statisticians, and not by the Investigators themselves. Investigators participating in multicenter

studies agree not to present data gathered from one center or a small group of centers before the full, initial publication, unless formally agreed to by all other Investigators and Medarex.

Medarex must receive copies of any intended communication in advance of submission (at least 30 working days for a journal submission and 15 days for an abstract or oral presentation). Medarex will review the communications for accuracy (thus avoiding potential discrepancies with submissions to health authorities), verify that confidential information is not being inadvertently disclosed, and provide any relevant supplementary information. Authorship of communications arising from pooled data may include members from each of the contributing centers, as well as Medarex personnel.

15.6. Disclosure and Confidentiality

By signing the protocol, the Investigator agrees to keep all information generated in connection with the study or provided by Medarex or its designee in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC. Study documents provided by Medarex (protocols, Investigators' Brochures, CRFs, and other material) will be stored appropriately to ensure their confidentiality. Such confidential information may not be disclosed to others without direct written authorization from Medarex, except to the extent necessary to obtain informed consent/HIPAA authorization from subjects who wish to participate in the study.

15.7. Discontinuation of Study

Medarex reserves the right to discontinue any study for any reason at any time.

15.8. Data Management

15.8.1. Data Collection

Investigators must enter the information required by the protocol onto the Medarex CRFs that are printed on "no carbon required" paper. Medarex study monitors or designees will review the CRFs for completeness and accuracy, and instruct site personnel to make any required corrections or additions. The CRFs will be forwarded to Medarex, or its designee, with one copy retained at the study site.

If Electronic Data Capture (EDC) system is deployed, eCRF will be completed by the authorized study site personnel. An electronic version of the final eCRF book for each patient will be forwarded to the study sites for record keeping at the study site closure.

15.8.2. Database Management and Quality Control

Data items from the CRFs will be entered into the study database using double data entry with verifications.

Subsequently, the information entered into the database will be systematically checked by Data Management staff following Medarex, or its designee, data management procedures. Obvious errors will be corrected by Medarex personnel, or its designee. Other errors, omissions, or requests for clarification will be queried; queries will be returned to the study site for resolution using a Data Clarification Form (DCF). A copy of the signed DCF will be kept with the CRFs. After receipt in Data Management, the resolutions will be entered into the database. Quality control audits of all key safety and efficacy data in the database will be conducted as agreed upon by relevant team members.

If EDC is deployed, data will be entered into the EDC system by the authorized study site personnel. Electronic queries will be used to communicate eligible discrepant data with the study sites.

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by joint written agreement of the Medarex study team.

16. REFERENCES

- ¹ Cancer Facts and Figures (2006). American Cancer Society. Atlanta GA. 2006.
- ² Bernard A, Lamy L, Alberti I. The Two-signal model of T-cell activation after 30 years. *Transplant* 2002;73:S31-35.
- ³ Pardoll D. Does the immune system see tumors as foreign or self? *Annu Rev Immunol* 2003;21:807-39.
- ⁴ Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. *Annu Rev Immunol* 2004;23:515-48.
- ⁵ Nishimura H, Honjo T. PD-1: an inhibitory immunoreceptor involved in peripheral tolerance. *Trends Immunol* 2001;22(5):265-8.
- ⁶ Freeman GJ, Long AJ, Iwai Y, Bourque K, Chernova T, Nishimura H, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. *J Exp Med* 2000;192(7):1027-34.
- ⁷ Latchman Y, Wood CR, Chernova T, Chaudhary D, Borde M, Chernova I, et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. *Nat Immunol* 2001;2(3):261-8.
- ⁸ Carter LL, Fouser LA, Jussif J, Fitz L, Deng B, Wood CR, et al. PD-1:D-L inhibitory pathway affects both CD4+ and CD8+ T cells and is overcome by IL-2. *Eur J Immunol* 2002;32(3):634-43.
- ⁹ Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. *J Immunol* 2004;173(2):945-54.
- ¹⁰ Sheppard KA, Fitz LJ, Lee JM, Benander C, George JA, Wooters J. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. *FEBS Letters* 2004 Sep 10;574(1-3):37-41.
- ¹¹ Nishimura H, Nose M, Hiai H, Minato N, Honjo T. Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. *Immunity* 1999;11(2):141-51.
- ¹² Nishimura H, Okazaki T, Tanaka Y, Nakatani K, Hara M, Matsumori A, et al. Autoimmune dilated cardiomyopathy in PD-1 receptor-deficient mice. *Science* 2001;291(5502):319-22.
- ¹³ Wang J, Yoshida T, Nakaki F, Hiai H, Okazaki T, Honjo T. Establishment of NOD-Pdcd1-/- mice as an efficient animal model of type I diabetes. *Proc Natl Acad Sci USA* 2005;102(33):11823-8.
- ¹⁴ Okazaki T, Tanaka Y, Nishio R, Mitsuiye T, Mizoguchi A, Wang, J, et al. Autoantibodies against cardiac troponin I are responsible for dilated cardiomyopathy in PD-1-deficient mice. *Nat Med* 2003;9(12):1477-83.

(continued)

REFERENCES (*continued*)

- ¹⁵ Salama AD, Chitnis T, Imitola J, Ansari MJ, Akiba H, Tushima F, et al. Critical role of the programmed death-1 (PD-1) pathway in regulation of experimental autoimmune encephalomyelitis. *J Exp Med* 2003;198(1):71-8.
- ¹⁶ Blazar BR, Carreno BM, Panoskaltsis-Mortari A, Carter L, Iwai Y, Yagita H, et al. Blockade of programmed death-1 engagement accelerates graft-versus-host disease lethality by an IFN- γ -dependent mechanism. *J Immunol* 2003;171(3):1272-7.
- ¹⁷ Barber DL, Wherry EJ, Masopust D, Zhu B, Allison JP, Sharpe AH, et al. Restoring function in exhausted CD8 T cells during chronic viral infection. *Nature* 2006;439:682-7.
- ¹⁸ Iwai Y, Terawaki S, Ikegawa M, Okazaki T, Honjo T. PD-1 inhibits antiviral immunity at the effector phase in the liver. *J Exp Med* 2003;198(1):39-50.
- ¹⁹ Iwai Y, Terawaki S, Honjo T. PD-1 blockade inhibits hematogenous spread of poorly immunogenic tumor cells by enhanced recruitment of effector T cells. *Int Immunol* 2004;17(2):133-44.
- ²⁰ Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo H, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade, *Proc Natl Acad Sci USA* 2002;99(19):12293-7.
- ²¹ Strome SE, Dong H, Tamura H, Voss SG, Flies DB, Tamada K, et al. B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma. *Cancer Res* 2003;63:6501-5.
- ²² Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. *Nat Med* 2002;8(8):793-800.
- ²³ Hirano F, Kaneko K, Tamura H, Dong H, Wang S, Ichikawa M, et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. *Cancer Res* 2005;65(3):1089-96.
- ²⁴ Blank C, Brown I, Peterson AC, Spiotto M, Iwai Y, Honjo T, et al. PD-L1/B7H-1 inhibits the effector phase of tumor rejection by T cell receptor (TCR) transgenic CD8⁺ T cells. *Cancer Res* 2004;64:1140-45.
- ²⁵ Konishi J, Yamazaki K, Azuma M, Kinoshita I, Dosaka-Akita H, Nishimura M. B7-H1 Expression on non-small cell lung cancer cells and its relationship with tumor-infiltrating lymphocytes and their PD-1 expression. *Clin Cancer Res* 2004;10(15):5094-100.
- ²⁶ Thompson RH, Gillett MD, Cheville JC, Lobse CM, Dong H, Webster WS, et al. Costimulatory B7-H1 in renal cell carcinoma subjects: indicator of tumor aggressiveness and potential therapeutic target. *Proc Natl Acad Sci USA* 2004;101(49):17174-9.

(*continued*)

REFERENCES (*continued*)

- ²⁷ Ohigashi Y, Sho M, Yamada Y, Tsurui Y, Hamada K, Ikeda N, et al. Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand-2 expression in human esophageal cancer. *Clin Cancer Res* 2005;11(8):2947-53.
- ²⁸ Tsushima F, Tanaka K, Otsuki N, Youngnak P, Iwai H, Omura K, et al. Predominant expression of B7-H1 and its immunoregulatory roles in oral squamous cell carcinoma. *Oral Oncol* 2005 (article in press).
- ²⁹ Thompson RH, Webster WS, Cheville JC, Lohse CM, Dong H, Leibovich BC, et al. B7-H1 glycoprotein blockade: a novel strategy to enhance immunotherapy in subjects with renal cell carcinoma. *Urology* 2005;66(5A):10-14.
- ³⁰ Thompson RH, Gillett MD, Cheville JC, Lohse CM, Dong H, Webster WS, et al. Costimulatory Molecule B7-H1 in primary and metastatic clear cell renal cell carcinoma. *Cancer* 2005 Nov 15;104(10):2084-91.
- ³¹ Dong H, Chen L. B7-H1 pathway and its role in the evasion of tumor immunity. *J Mol Med* 2003;81(5):281-7.
- ³² Azuma T, Yao S, Zhu G, Flies A, Flies S, Chen L. B7-H1 is a ubiquitous antiapoptotic receptor on cancer cells. *Blood* 2008;111(7) 3635-3643.
- ³³ Cancer Therapy Evaluation Program (CTEP) Common Terminology Criteria for Adverse Event (CTCAE), Version 3.0, Division of Cancer Treatment and Diagnosis (DCTD), NCI, National Institute of Health (NIH), Department of Health and Human Services (DHHS), 16 April 2003 (located on the internet at <<http://ctep.cancer.gov>>).

17. APPENDICES

Appendix 1: RECIST With Modification

Solid Tumor Response

Measurable disease/target lesions and non-measurable disease/non-target lesions are to be evaluated according to the new standardized RECIST established by the NCI. Each category (measurable and non-measurable lesions) will be assessed and reported independently. (Adapted from Therasse, Arbuck et al. 2000).

Method

CT scans (or MRI) will be performed to evaluate tumor response. All measurements should be taken and recorded in metric notation (mm) using a ruler or calipers.

CT and MRI are the best currently available and reproducible methods to measure target lesions and qualitatively assess non-target lesions selected for response assessment. Conventional CT (non-spiral or non-helical) and conventional MRI (MRI performed without fast scanning techniques) should produce images contiguously reconstructed at 10 mm or less. Spiral (helical or multidetector) CT should produce images contiguously reconstructed between 5 and 8 mm.

Lesions identified on a chest x-ray should be imaged by a CT or MRI scan.

The same method of assessment and the same technique should be used to characterize each site of disease at baseline and during follow-up evaluations.

Documentation of Target and Non-target Lesions

All measurable or target lesions, up to a maximum of 5 lesions per organ and 10 lesions total, representative of all sites of disease, will be identified and measured at baseline and followed as target lesions throughout the study. Target lesions should be selected on the basis of their size (longest diameter) and suitability for accurate reproducibility and measurement on follow-up imaging. The SLD for all target lesions will be calculated and reported as the baseline SLD. The baseline SLD will be used as a reference by which to characterize the objective tumor response at each subsequent tumor assessment point (timepoint). The smallest sum of the longest diameters recorded since baseline will be used as reference when evaluating for progression. All other lesions (or sites of disease) should be identified as non-target lesions and should be recorded at baseline. Measurement of these lesions is not required, but the presence, absence, or worsening of each should be noted throughout follow-up.

Response Confirmation

To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive repeat assessments that should be performed no less than 28 days after the criteria

for response are first met. **For this study, the next scheduled tumor assessment can meet this requirement.**

Overall Timepoint Responses (RECIST) for all Possible Combinations of Tumor Responses in Target and Nontarget Lesions With or Without the Appearance of New Lesions

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR/NA	No	CR
CR	SD	No	PR
CR	UE/ND	No	UE
PR	Non-PD/NA	No	PR
PR	UE/ND	No	UE
SD	Non-PD/NA	No	SD
SD	UE/ND	No	UE
PD	Any	Yes or no*	PD
Any	PD	Yes or no*	PD
Any	Any	Yes*	PD
UE	Non-PD/NA	No	UE
ND	Non-PD/NA	No	UE
NA	SD	No	SD
NA	CR	No	CR

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease

UE = unable to evaluate (any target or non-target lesion present at baseline which was not assessed or unable to be evaluated leading to an inability to determine the status of that particular tumor for that timepoint)

NA = not applicable (no target or nontarget lesions identified at baseline)

ND = not done (scans not performed at this timepoint)

* See study specific definition of progressive disease below with regard to assessment of new lesions.

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time are to be classified as having “symptomatic deterioration.” (See Section 8.7)

Definitions

Measurable lesions	Target lesions that can be measured accurately in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques, or as ≥ 10 mm with spiral (helical) computed tomography (CT) scan or two (2) times the reconstruction interval (RI) when using spiral (helical) or multidetector CT, but not less than 10 mm. The greatest diameter of a lymph node must measure at least 2 cm by spiral CT to be considered a target lesion.
Nonmeasurable lesions	Non-target lesions not classified as measurable lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan) and truly nonmeasurable lesions. These include bone lesions on BS, effusions, and leptomeningeal disease. Any measurable lesions that were not classified as target lesions will be classified as non-target lesions.
Target lesions	<p>All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, are to be identified as target lesions and recorded and measured. Target lesions are to be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).</p> <ul style="list-style-type: none"> • Longest diameter for target lesions – The sum of the longest diameter for all target lesions (SLD). • Complete response – Disappearance of all target lesions. • Partial response – At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the Screening sum longest diameter. • Stable disease – Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease. • Progressive disease – At least a 20% increase in the sum of the longest diameters of target lesions (with addition of diameters of any newly emergent measurable lesions), taking as reference the smallest sum of the longest diameters (nadir) recorded since screening. The appearance of 1 or more new lesions will not in itself constitute PD for this study. For this study PD must be confirmed by an additional scan at the next therapeutic assessment. After confirmation, if a subsequent therapeutic assessment shows further progression (i.e., further increase in SLD or additional new lesion[s]), the subject will stop study drug treatment. A subject with confirmed progression who does not have further progression on subsequent assessment will remain in the study and will be re-evaluated at the completion of the next cycle unless the subject has rapid clinical deterioration (as defined in Section 8.7). • UE/ND/NA

continued

Definitions (continued)

Nontarget lesions	<p>All lesions other than target lesions (or sites of disease) are to be identified as nontarget lesions and are to be recorded. Measurements of these lesions are not required, but the presence or absence of each is to be noted.</p> <ul style="list-style-type: none"> • Complete response – Disappearance of all nontarget lesions. • Incomplete response/stable disease – Persistence of one or more nontarget lesion(s). • Progressive disease – Unequivocal progression of a nontarget lesion or appearance of 1 or more new lesions. . The appearance of 1 or more new lesions will not in itself constitute PD for this study. For this study PD must be confirmed by an additional scan at the next therapeutic assessment. After confirmation, if a subsequent therapeutic assessment shows further progression (i.e., further increase in SLD or additional new lesion[(s)], the subject will stop study drug treatment. A subject with confirmed progression who does not have further progression on subsequent assessment will remain in the study and will be re-evaluated at the completion of the next cycle unless the subject has rapid clinical deterioration (as defined in Section 8.7). • UE/ND/NA
Best overall response	<p>The best overall response is the confirmed overall response. To be assigned a best overall response of partial response or complete response, change in tumor measurements must be confirmed by repeat assessment no less than 4 weeks after the criteria for response of CR or PR are first met.</p>
Methods of measurements	<p>The same imaging modality, method of assessment, and technique must be used throughout the study to characterize each identified and reported lesion. All measurements are to be made with a ruler or calipers; measurements are to be recorded in metric notation.</p>
Clinical examination	<p>Clinically detected lesions are only to be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For skin lesions, documentation by color photography—including a ruler to estimate the size of the lesion—is recommended.</p>
Chest X-ray	<p>Lesions on the chest X-ray are to be acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. Chest X-ray is to be performed in full inspiration in the poster-anterior projection. The film to tube distance is to remain constant between examinations. If subjects with advanced disease are not well enough to fulfill these criteria, such situations are to be reported together with the measurements. Lesions bordering the thoracic wall, and lesions bordering or involving the mediastinum, are not suitable for measurements by chest x-ray.</p>

continued

Definitions (continued)

Computed Tomography and Magnetic Resonance Imaging	<p>CT is the imaging modality of choice. Conventional CT and magnetic resonance imaging (MRI) are to be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT is to be performed by use of a 5 mm contiguous reconstruction algorithm. CT scans of the thorax, abdomen, and pelvis are to be contiguous throughout the anatomic region of interest. The minimum size of the lesion is to be no less than double the slice thickness. The longest diameter of each target lesion is to be selected in the axial plane only. For spiral CT scanners, the minimum size of any given lesion at Screening may be 10 mm, provided the images are reconstructed contiguously at 5 mm intervals. For conventional CT scanners, the minimum-sized lesion is to be 20 mm by use of a contiguous slice thickness of 10 mm.</p> <p>In subjects in whom the abdomen and pelvis have been imaged, oral contrast agents are to be given to accentuate the bowel against other soft-tissue masses. Intravenous contrast agents are also to be given, unless contraindicated for medical reasons such as allergy. An adequate volume of a suitable contrast agent is to be given so that the metastases are demonstrated to best effect. All images from each examination are to be included and not "selected" images of the apparent lesion.</p> <p>All window settings are to be included, particularly in the thorax, where the lung and soft-tissue windows are to be considered. Lesions are to be measured on the same window setting on each examination.</p> <p>When MRI is used, lesions are to be measured in the same anatomic plane by use of the same imaging sequences on subsequent examinations. Wherever possible, the same scanner is to be used.</p>
Bone scan	Bone scans are to be used for the assessment of non-target lesions only.
Ultrasound	Ultrasound is not to be used to measure tumor lesions that are clinically not easily accessible.

Appendix 2: Prostate Response Evaluation Criteria

PSA Assessment

PSA Assessment will be evaluated according to the recommendations of the Prostate cancer Clinical Trials Working Group¹ with modification.

- **PSA Complete Response** is defined as a PSA concentration <0.5 ng/mL for 2 consecutive measurements separated by at least 3 weeks
- **PSA Progression** is defined as follows:
 - In subjects where no decline in PSA from baseline is documented, PSA progression is a $\geq 25\%$ increase from the baseline value along with an increase in absolute value of 2 ng/mL or more after 12 weeks of treatment. It should be confirmed by a second value obtained 3 or more weeks later.
 - In patients whose PSA nadir is <100% of the baseline value, PSA progression is $\geq 25\%$ increase from the nadir and an absolute increase of 2 ng/mL or more from the nadir, confirmed by a second value obtained 3 or more weeks later.

Subjects should be kept on study until confirmed radiographic or symptomatic response, which is a better reflection of a change in clinical status than PSA measurements, is documented, and an effort should be made not to discontinue therapy solely on the basis of a rise in PSA in the absence of other indicators of disease progression.

Radiographic Assessment

- **Bone lesions**
 - Progression is defined as the appearance of 2 or more new lesions.
 - Progression should be confirmed by a repeat measurement at least 6 weeks later demonstrating additional new lesions.
- **Soft tissue lesions**
 - Soft tissue lesions should be assessed according to the modified RECIST (Appendix 1).

¹ Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, et al. Design and End Points of Clinical Trials for Patients With Progressive Prostate Cancer and Castrate Levels of Testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008; 26:1148-1159.

Appendix 3: Tumor-Specific Inclusion/Exclusion Criteria

PROSTATE CANCER

Inclusion criteria:

1. Histologic diagnosis of adenocarcinoma of the prostate.
2. Metastatic prostate cancer (positive bone scan and/or measurable disease)
3. Total testosterone <50 ng/dL, except for subjects with prior orchiectomy, where testosterone does not need to be measured. Subjects should continue their LHRH agonist therapy.
4. Subjects receiving anti-androgen receptor therapy (e.g., Flutamide) may enroll if they have been on a stable dose for at least 2 months before enrollment (during the determination of eligibility) and must continue their therapy during their participation in the study. Subjects who choose to discontinue anti-androgen receptor therapy will complete an 8-week washout period before study drug administration to assess for a withdrawal response. Withdrawal responses typically occur in subjects who are treated with combined androgen blockade (a GnRH analog or orchiectomy in combination with continuous anti-androgen) as initial therapy for a prolonged period of time, or who have responded to adding a peripheral anti-androgen as second-line therapy. It is not necessary to wait the 8 weeks to assess for a withdrawal response in subjects who did not respond or who showed a decline in PSA for 3 months or less after an anti-androgen was administered as a second-line or later intervention.
5. Subjects receiving any herbal product known to decrease PSA levels (e.g., Saw Palmetto and PC-SPES), who have been on a stable dose for 2 or more months before enrollment and plan to continue the herbal product may remain on their regimen through the study. Subjects who have received the herbal products for less than 2 months, or do not plan to continue the products, must discontinue the agent for at least 4 weeks before screening. Progressive disease must be documented after discontinuation of these products.
6. Subjects receiving bisphosphonate therapy must have been on stable doses for at least 4 weeks with stable symptoms before enrollment.
7. Progressive disease despite castrate levels of testosterone:
 - For subjects with measurable disease, progression will be defined by the Response Evaluation Criteria in Solid Tumors (RECIST with modification). Subjects with stable measurable disease may be enrolled if there is evidence of PSA progression.
 - For subjects without progression in, or without any measurable disease, a positive bone scan and elevated PSA will be required.

- PSA evidence for progressive prostate cancer consists of a PSA level that has risen on at least 2 successive occasions, obtained at least 1 week apart, and both must be obtained after the required wash out periods noted above. The final screening value must be at least 2 ng/mL.
- For subjects with progression on bone scan only, progression is defined as the appearance of at least 2 or more new lesions compared with a prior scan. In situations where the scan findings are suggestive of a flare reaction, or apparent new lesion(s) may represent trauma, it may prove useful to confirm these results with other imaging modalities such as MRI or fine-cut CT.

Exclusion Criteria:

1. Bone pain due to metastatic bone disease that cannot be managed with a routine, stable dose of a narcotic analgesic.
2. Subjects with rising PSA only.

RENAL CANCER

Inclusion criteria:

1. Subjects must have histologically confirmed diagnosis of renal cell carcinoma (clear cell component) with advanced or recurrent disease that is not amenable to cure by surgery or other means, and must have failed at least 1 prior systemic therapy, including, but not limited to, treatment with Sunitinib, Temsirolimus, Sorafenib, IL-2, and/or chemotherapy.
2. Clinical evidence of or biopsy-proven metastatic disease to a site or sites distant from the primary tumor, that are not deemed to be surgically curative, or the subject is not a surgical candidate.
3. Must have measurable disease with at least 1 measurable lesion per RECIST with modification.

Exclusion criteria:

1. The following histologies are not allowed: chromophobe, collecting duct, transitional cell carcinoma, or unclassified.

MELANOMA

Inclusion criteria:

1. Subjects must have a histologically confirmed diagnosis of melanoma with advanced disease (previously treated, therapy-refractory or recurrent Stage III (unresectable) or Stage IV);

disease no longer controlled by surgery, chemotherapy, or radiotherapy; and disease refractory to or relapsed after standard therapy (including high-dose interleukin-2). All melanomas regardless of primary site of disease will be allowed.

2. Must have measurable disease with at least 1 measurable lesion per RECIST with modification.

Exclusion criteria:

1. No nitrosoureas (e.g., carmustine or lomustine) within the past 6 weeks and during study treatment.

NON-SMALL CELL LUNG CANCER

Inclusion criteria:

1. Subjects with refractory or recurrent histologically or cytologically confirmed non-small cell lung cancer (NSCLC).
2. Malignancy must be deemed unresectable.
3. Subjects should have failed at least one platinum- or taxane-based regimen.
4. Must have measurable disease with at least 1 measurable lesion per RECIST with modification.

Appendix 4: ECOG Performance Status

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

¹ Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, and Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.

Appendix 5: Pre-existing Autoimmune Diseases

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

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

Acute disseminated encephalomyelitis	Autoimmune myocarditis	Dermatomyositis
IgA nephropathy	Neuromyotonia	Reiter's syndrome
Addison's disease	Autoimmune oophoritis	Diabetes mellitus type 1
Inflammatory bowel disease	Opsoclonus myoclonus syndrome	Rheumatoid arthritis
Alopecia universalis	Autoimmune orchitis	Dysautonomia
Interstitial cystitis	Optic neuritis	Sarcoidosis
Ankylosing spondylitis	Autoimmune thrombocytopenic purpura	Eczema
Lambert-Eaton myasthenia syndrome	Ord's thyroiditis	Scleroderma
Antiphospholipid antibody syndrome	Behcet's disease	Sjögren's syndrome
Lupus erythematosus	Pemphigus	Epidermolysis bullosa acqvista
Aplastic anemia	Bullous pemphigoid	Stiff-Person syndrome
Lyme disease - chronic	Pernicious anemia	Gestational pemphigoid
Asthma	Celiac disease	Takayasu's arteritis
Meniere's syndrome	Polyarteritis nodosa	Giant Cell arteritis
Autoimmune hemolytic anemia	Chronic fatigue syndrome	Ulcerative colitis
Mooren's ulcer	Polyarthritis	Goodpasture's syndrome
Autoimmune hepatitis	Chronic inflammatory demyelinating polyneuropathy	Vitiligo
Morphea	Polyglandular autoimmune syndrome	Graves' disease
Autoimmune hypophysitis	Chung-Strauss syndrome	Vogt-Kovanagi-Harada disease
Multiple sclerosis	Primary biliary cirrhosis	Guillain-Barré syndrome
Autoimmune hypoparathyroidism	Crohn's disease	Vulvodynia
Myasthenia gravis	Psoriasis	Hashimoto's disease
		Wegener's granulomatosis
		Kawasaki's disease

Appendix 6: List of Symptoms

Subjects should be questioned to elicit information regarding the occurrence of any of the following adverse events, as they may be indicators of immune-related adverse events such as cardiomyopathy, diabetes, thyroid deficiency, adrenal insufficiency, gastritis, lupus, hypersensitivity, or liver toxicity.

Body System	Adverse Event
Cardiovascular	Chest pain
Cardiovascular	Hypotension
Cardiovascular	Pale or purple fingers or toes from cold or stress (Raynaud's phenomenon)
Eyes	Blurry vision
Gastrointestinal	Abdominal bloating
Gastrointestinal	Abdominal pain
Gastrointestinal	Belching
Gastrointestinal	Black stool or blood in stool
Gastrointestinal	Blood in vomit
Gastrointestinal	Burning feeling in stomach
Gastrointestinal	Constipation
Gastrointestinal	Diarrhea
Gastrointestinal	Feeling of fullness
Gastrointestinal	Foul taste in mouth
Gastrointestinal	Mouth sores
Gastrointestinal	Mucosal pigmentation
Gastrointestinal	Nausea
Gastrointestinal	Stomach cramping
Gastrointestinal	Stomach upset
Gastrointestinal	Vomiting
General	Cold intolerance
General	Dizziness
General	Excessive thirst
General	Extreme hunger
General	Fatigue
General	Fever

Body System	Adverse Event
General	Hypoglycemia
General	Lethargy
General	Loss of appetite
General	Swelling of the abdomen, legs, ankles, feet, face or around the eyes
General	Swollen glands
General	Weakness
General	Weight gain or increased difficulty losing weight
General	Weight loss
Musculoskeletal	Flu-like symptoms, aching muscles or joint pains.
Musculoskeletal	Painful or swollen joints and muscle pain
Nervous	Memory loss
Psychiatric	Decreased libido
Psychiatric	Depression
Psychiatric	Irritability
Reproductive	Abnormal menstrual cycles
Respiratory	Difficulty breathing
Skin	Blistering of the skin
Skin	Dry, rough pale skin
Skin	Hair loss
Skin	Itching
Skin	Rash
Skin	Sensitivity to the sun
Skin	Coarse, dry hair
Skin	Cutaneous pigmentation
Skin	Jaundice
Urinary	Frequent urination

Page: 1
Protocol Number: CA209003/MDX1106-03
IND Number: IND 100,052
EUDRACT Number: Not Applicable
Date: 23-Jan-2012

Protocol CA209003: A Phase 1, Open-label, Multicenter, Multidose, Dose-escalation Study of BMS-936558 (MDX-1106) in Subjects with Selected Advanced or Recurrent Malignancies

Amendment Number 05
Site Number: All

Study Director / Central Medical Monitor

Ashok Gupta, MBBS, MD, PhD
Route 206 & Province Line Road, Princeton, NJ 08543
Telephone (office): +1 (609) 252-3464
Fax: +1 (609) 252-6816
E-mail: Ashok.Gupta@bms.com

24-hr Emergency Telephone Number:

USA: 1-866-470-2267

International: +1-248-844-7390

Bristol-Myers Squibb Research and Development

Oncology Clinical Research and Development
Route 206 & Province Line Road
Lawrenceville, NJ 08543

This protocol amendment contains information that is confidential and proprietary to Bristol-Myers Squibb (BMS).

This amendment must be maintained with the referenced protocol.

Amendment Rationale:

Preliminary data generated from the CA209-003/MDX1106-03 study protocol has demonstrated objective responses (OR) as measured by RECIST 1.0 in multiple tumor types including malignant melanoma, renal cell carcinoma, and non-small cell lung cancer. To date OR appear durable. It is therefore of clinical interest for the development of BMS-936558 to collect survival data as an exploratory endpoint. Collecting survival data on the number of subjects that have enrolled in this study will allow for some exploratory correlations on safety, efficacy, biomarker with survival data and enable decision making on subsequent clinical studies.

In addition to inclusion of an exploratory objective of overall survival, additional exploratory objectives have been added to evaluate PDL-1 expression in tumors as well as to evaluate the level of PD-1 receptor occupancy in peripheral blood.

Changes to the Protocol:

- 1) Protocol cover page, the revised date was updated to 23-Jan-2012, the revised protocol and amendment number was revised to 05, and updated confidentiality agreement.
- 2) Protocol synopsis, Objectives, exploratory objectives for survival, evaluation of PDL-1 expression in tumors, and evaluation of PD-1 receptor occupancy.
- 3) Protocol synopsis, Overview of Study Design, the inclusion of collection of survival data was specified
- 4) Protocol synopsis, Survival Follow-up Phase, section was added to the protocol describing the survival follow-up phase
- 5) Protocol synopsis, Duration of Treatment/Study Participation, section was revised to include the additional duration due to the additional survival component of the study
- 6) Protocol synopsis, Efficacy Evaluations, section was revised to include an exploratory analysis for overall survival
- 7) Protocol synopsis, Statistical Methods, Efficacy Analyses, section was updated to include an analysis for overall survival by Kaplan-Meier
- 8) Protocol synopsis, Statistical Methods, Exploratory Biomarker, section was updated to further clarify the types of biomarkers that will be evaluated as well as clarification on the expectation for exploratory interim analyses for decision making
- 9) Protocol synopsis, Table 2: Time and Events, table was updated to include survival visits as well as oxygen saturation levels. Updates to footnotes were included based on these time and event procedure changes.

- 10) Protocol Section 2.3, Exploratory Objectives, section was added to include exploratory objectives for survival, evaluation of PDL-1 expression in tumors, and evaluation of PD-1 receptor occupancy
- 11) Protocol Section 3, Overview of Study Design, the inclusion of collection of survival data was specified
- 12) Protocol Section 3.6, Survival Follow-up Phase, section was added to the protocol describing the survival follow-up phase
- 13) Protocol Section 3.7, Post-Study Access to Study Therapy, section was revised to clarify the post-study access to study therapy
- 14) Protocol Section 7.6, Storage, section was revised for new storage requirements for BMS-936558 based on revised stability data
- 15) Protocol Section 11.1.3.1, Cycle 1, section was revised to include language which further specifies types of exploratory biomarker analyses which may be conducted with tumor and blood specimen collected under subjects enrolled under amendment 4
- 16) Protocol Section 11.1.6, Survival Follow-up, section was added to the protocol describing the survival follow-up phase and the types of data/assessments that will be collected
- 17) Protocol Section 11.2.2, Additional Efficacy Parameters, section was revised to include an exploratory analysis for overall survival
- 18) Protocol Section 11.3, Exploratory Biomarkers of Immune Response, section was revised to clarify the types of exploratory biomarker analyses that will be conducted to support the exploratory objectives under newly added section 2.3
- 19) Protocol Section 13.2.3, Per Protocol Population, section was deleted
- 20) Protocol Section 13.2.4, Response Evaluation Data Set, section was revised to clarify the definition of response evaluable
- 21) Protocol Section 13.3.4, Efficacy, section was revised to include the analyses for overall survival and to clarify how efficacy analyses will be presented by tumor type and dose group. In addition, the section was updated to specify that interim analyses may be conducted in the future to support clinical development decisions for BMS-936558
- 22) Protocol Section 13.3.5, Safety, the section was updated to specify that interim analyses may be conducted in the future to support clinical development decisions for BMS-936558
- 23) Protocol Section 13.3.6, Immunogenicity, the section was updated to specify that interim analyses may be conducted in the future to support clinical development decisions for BMS-936558

- 24) Protocol Section 13.3.7, Pharmacokinetic, the section was updated to specify that interim analyses may be conducted in the future to support clinical development decisions for BMS-936558
- 25) Protocol Section 13.3.8, Exploratory Biomarker, the section was updated to clarify the types of exploratory biomarkers that will be conducted, especially those supporting the exploratory objectives. In addition, the section was updated to specify that interim analyses may be conducted in the future to support clinical development decisions for BMS-936558

Please maintain a copy of this amendment with your protocol. Please provide a copy to your Investigational Review Board / Ethics Committee, unless agreed otherwise with BMS.

AMENDMENT ACKNOWLEDGMENT

I have read this Amendment and agree that it contains all necessary details for carrying out the changes described. I understand that it must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and approved or given favorable opinion before implementation unless to eliminate an immediate hazard to subjects.

If this Amendment substantially alters the study design or increases potential risk to subjects, the consent form will be revised and submitted to the Institutional Review Board/Independent Ethics Committee for approval/positive opinion. I will use the new consent form for any new subjects prior to enrollment, and for subjects currently enrolled in the study if they are affected by the Amendment.

Investigator's printed name and signature

Date

Medical Monitor/Study Director
(If required by applicable regulations and guidelines.)

Date

Protocol Number: CA209003/MDX1106-03

Site Number:

Amendment Number: 05

Page: 1
Protocol Number: CA209003
IND Number: IND 100,052
EUDRACT Number: Not Applicable
Date: 08-Oct-2010

Protocol CA209003: A Phase 1, Open-label, Multicenter, Multidose, Dose-escalation Study of BMS-936558 (MDX-1106) in Subjects with Selected Advanced or Recurrent Malignancies

Amendment Number 04
Site Number: All

Study Director / Central Medical Monitor

Ashok Gupta, MBBS, MD, PhD
Route 206 & Province Ling Road, Princeton, NJ 08543
Telephone (office): +1 (609) 252-3464
Fax: +1 (609) 252-6816
E-mail: Ashok.Gupta@bms.com

24-hr Emergency Telephone Number:

USA: 1-866-470-2267
International: +1-248-844-7390

Bristol-Myers Squibb Research and Development

Oncology Clinical Research and Development
Route 206 & Province Line Road
Lawrenceville, NJ 08543

This protocol amendment contains information that is confidential and proprietary to Bristol-Myers Squibb (BMS).

This amendment must be maintained with the referenced protocol.

Amendment Rationale:

The primary purpose of this amendment is to add additional expansion cohorts in subjects with non-small cell lung cancer (NSCLC), melanoma (MEL) or renal cell carcinoma of clear cell histology (RCC) in order to gain additional clinical experience on safety/tolerability and clinical activity in these tumor types with BMS-936588 administered as monotherapy.

Preliminary observations from safety and activity data from this study thus far are summarized in the most recent version of the Investigator Brochure. In this study (CA209003), as of the clinical data cut off date (28 May 2010), 113 subjects with advanced melanoma (MEL), renal cell carcinoma, clear cell histology (RCC), non-small cell lung cancer (NSCLC), colorectal cancer, or prostate cancer have been treated with BMS-936558 at 1, 3, or 10 mg/kg doses administered every 14 days. A significant level of clinical activity has been observed in 88 response-evaluable subjects, with clinical responses observed in MEL, RCC and NSCLC subjects across all dose levels tested to-date. Specifically, a complete response (CR) was reported in 1 subject with RCC, partial response (PR) was reported in 25 subjects (5 RCC, 17 MEL, and 3 NSCLC), and stable disease was reported in 26 subjects. In subjects with NSCLC, responses have been observed in tumors with both squamous as well as non-squamous histology. All doses of BMS-936558 tested to date continue to demonstrate adequate tolerability with no clear or consistent pattern in the incidence, severity or relationship of adverse events related to the dosage level of BMS-936558.

The following seven (7) additional cohorts will be accrued under this amendment;

- Three (3) additional expansion cohorts (N = 32/cohort) in subjects with NSCLC administered BMS-936558 every 14 days at 1, 3, and 10 mg/kg respectively. Each cohort will accrue approximately equal numbers of subjects with squamous and non-squamous histologies. These cohorts will provide expanded safety, tolerability, and preliminary efficacy data in subjects with NSCLC with pre-specified tumor histologies at multiple dose levels.
- Three (3) additional expansion cohorts (N = 16/cohort) in subjects with MEL administered BMS-936558 every 14 days at 0.1, 0.3, and 1 mg/kg respectively. Based on the prolonged estimated half-life of BMS-936558 and the prolonged estimated receptor occupancy of BMS-936558 on T cell receptors, it is reasonable to expect that the range of clinically active doses includes dose levels lower than

the original protocol's lowest tested dose of 1 mg/kg. Clinical activity in MEL at doses ranging from 1 mg/kg to 10 mg/kg has already been established in this study. Additional MEL cohorts at 0.1 and 0.3 mg/kg dose levels will expand the clinical experience in this tumor type at the lower end of the dose range tested to-date. An additional MEL cohort at 1 mg/kg will also be included to allow for randomization across MEL dose cohorts.

- One (1) expansion cohort (N = 16) in subjects with clear cell renal cell carcinoma (RCC). This cohort will provide additional safety and preliminary activity data in subjects with RCC at dose levels other than 10 mg/kg

Other changes to the protocol include the following: 1) inclusion of extensive PK samples for 16 patients in each cohort; 2) inclusion of an exploratory analysis using an immune-based response criteria based on modifications to the Response Evaluation Criteria In Solid Tumors (v 1.0); 3) an allowance for reinitiating study therapy for subjects that demonstrate disease progression during the follow-up phase either after having achieved a confirmed complete response to therapy or after completion of all 12 treatment cycles with an ongoing stable disease (SD) or partial response (PR); 4) modification and clarification to the allowable on-study treatments to isolated/symptomatic lesions; 5) modification to stopping rules for clinical deterioration for the development of new CNS metastases; and 6) modification to the drug preparation and administration guidelines to include instructions for the 0.1 and 0.3 mg/kg dose levels.

Changes to the Protocol:

- 1) Protocol cover page, the study phase in the protocol title was changed from Phase 1b to Phase 1.
- 2) Protocol cover page, the study director/medical monitor name and contact information on the cover page was changed from Israel Lowy, MD, PhD to Ashok Gupta, MBBS, MD, PhD.
- 3) Protocol header, the word "confidential" was replaced with "Anti-PD-1 Monoclonal Antibody" on each page.
- 4) Synopsis, Study Objectives, the secondary objectives were modified to include the word preliminary under secondary objective #3, and a new secondary objective was included to assess the dose response relationship in MEL and NSCLC.
- 5) Synopsis, Overview of Study Design, the maximum duration of study therapy was changed from 12 8-week cycles to 3 years.

- 6) Synopsis, Overview of Study Design, language was added describing the allowance for subjects entering the follow-up phase to restart study medication upon disease progression.
- 7) Synopsis, Dose Escalation, language was added specifying that the 0.1 and 0.3 mg/kg dose levels did not impact the dose escalation plan for this study.
- 8) Synopsis, Dose Escalation, language was added qualifying that subjects in the 0.1 and 0.3 mg/kg dose levels will not be subject to the no inpatient dose escalations.
- 9) Synopsis, Expansion Cohorts, language was added specifying the inclusion of 7 new expansion cohorts (3 cohorts in NSCLC, 3 cohorts in MEL, and 1 cohort in RCC). The language also clarified using an inserted table and figure which cohorts had completed enrollment prior to this amendment and which cohorts were added as a direct result of this amendment.
- 10) Synopsis, Expansion Cohorts, language was included specifying that the NSCLC cohorts and the MEL cohorts will each be randomized during enrollment.
- 11) Synopsis, Expansion Cohorts, language was added clarifying how the various expansion cohorts were initiated. The primary expansion cohorts were considered the primary MTD expansion cohorts. The initial melanoma expansion cohorts were considered the non-MTD expansion cohorts. The newly added cohorts under this amendment are considered the additional expansion cohorts. Language was added to describe the initiation of the new expansion cohorts.
- 12) Synopsis, Administration of Additional Treatment Cycles, the language describing the maximum duration of study therapy and the criteria by which subjects are allowed to continue therapy was clarified by removing redundant text relating to the treatment windows.
- 13) Synopsis, Re-initiation of Study Therapy for Subjects in Follow-up Period, this new section of the protocol synopsis was added.
- 14) Synopsis, Study Population, the total number of expected subjects was revised. Also, the number of subjects that have enrolled to date and the number expected to enroll under this amendment was specified.
- 15) Synopsis, Dosage and Administration, section was modified to include new protocol instructions for all anticipated dose levels.
- 16) Synopsis, Efficacy Evaluations, section was revised based on the inclusion of additional cohorts and inclusion of an immune-related response criteria analysis.
- 17) Synopsis, Exploratory Immune Function Evaluations, section was revised to clarify that some of the previously collected samples will not be collected under this amendment.
- 18) Synopsis, Safety Evaluations, Inflammatory events regardless of causality were added as part of the safety evaluations section.

- 19) Synopsis, Immunogenicity, the section was added to the protocol synopsis describing the purpose and timing of immunogenicity sample collection and analysis.
- 20) Synopsis, Pharmacokinetic Evaluations, section was modified include the anticipated time points for collection and the parameters under evaluation.
- 21) Synopsis, Statistical Methods, section was revised based on the anticipated analyses and the number of expansion cohorts and tumor types.
- 22) Synopsis, Abbreviations, section was revised to include the newly added abbreviations identified under this amendment.
- 23) Synopsis, Time and Events Schedule (Table 1), modified to clarify which samples would no longer be collected under this amendment and also to specify what new samples will be collected under this amendment.
- 24) Synopsis, Pharmacokinetic Blood Sampling Schedule (Table 2), modified to include newly specified PK collection time points.
- 25) Protocol Section 1.5.1, Summary of Safety, section was modified to include a reference to updated safety information in the Investigator's Brochure.
- 26) Protocol Section 1.5.2, Rationale for BMS-936558 (MDX-1106) Dosage Selection, section was modified to include updates to the rationale for dose selection and a correction to the PK half-life of BMS-936558.
- 27) Protocol Section 2.2, Secondary Objectives, secondary objective #3 was modified to include the word preliminary, and a new secondary objective was included to assess the dose response relationship in MEL and NSCLC.
- 28) Protocol Section 3, Overview of Study Design, section was modified to change the maximum duration of study therapy from 12 8-week cycles to 3 years.
- 29) Protocol Section 3.1, Dose Escalation, section was modified to add language specifying that the 0.1 and 0.3 mg/kg dose levels did not impact the dose escalation plan for this study.
- 30) Protocol Section 3.2, Expansion Cohorts was modified to include language specifying the inclusion of 7 new expansion cohorts (3 cohorts in NSCLC, 3 cohorts in MEL, and 1 cohort in RCC). The language (including a new figure and table) also clarified which cohorts had completed enrollment prior to this amendment and which cohorts were added as a direct result of this amendment and specifying that the NSCLC cohorts and the MEL cohorts will each be randomized during enrollment.
- 31) Protocol Section 3.2.1, Initiation of the Primary MTD Expansion Cohorts, the title to this protocol section was changed to include the descriptor MTD.
- 32) Protocol Section 3.2.2, Initiation of the Additional Non-MTD Melanoma Expansion Cohorts, the title to this protocol section was changed to include the descriptor Non-MTD.

- 33) Protocol Section 3.2.3, Initiation of Additional Expansion Cohorts, this protocol section was added to specify how the newly added cohorts under amendment 4 would will be initiated.
- 34) Protocol Section 3.3, Administration of Additional Treatment Cycles, the language describing the maximum duration of study therapy and the criteria by which subjects are allowed to continue therapy was clarified by removing redundant text relating to the treatment windows.
- 35) Protocol Section 3.4, Follow-up Period, section was modified to allow the 1st follow-up visit to occur 0-7 days following the last dose of study therapy and language was added to specify that there will be additional analyses for subjects that reinstate study therapy after entering follow-up.
- 36) Protocol Section 3.5, Re-Initiation of Study Therapy For Subjects in Follow-up Period, this new protocol section was added.
- 37) Protocol Section 4, Study Population, this section was modified to include the revised total number of expected subjects. Also, the number of patients that have enrolled to date and the number expected to enroll under this amendment was specified.
- 38) Protocol Section 4.1, Inclusion Criteria, inclusion criterion #3 was added requiring availability of archival tumor samples in order to enroll under amendment #4.
- 39) Protocol Section 4.1, Inclusion Criteria, inclusion #4 was modified to eliminate inclusion of subjects with baseline ECOG of 2.
- 40) Protocol Section 4.2, Exclusion Criteria, exclusion criterion #10 was added requiring a 4 week wash-out from any vaccinations prior to initiating study drug.
- 41) Protocol Section 5, Randomization and Blinding, section was modified to specify that subjects enrolled to the new NSCLC and new MEL cohorts will be randomized to one of the specified dose levels included under this amendment.
- 42) Protocol Section 6, Assignment to Study, section was modified to specify that subjects will not be enrolled into the next available dose level, but assigned to a specified treatment group as determined by BMS.
- 43) Protocol Section 7.5, Ordering Study Drug, section was modified to clarify the correct contact person for ordering of clinical supplies.
- 44) Protocol Section 7.7, Study Drug Preparation and Administration, section was modified to include instructions and guidance for study drug preparation for all anticipated dose levels included under this amendment.
- 45) Protocol Section 7.9, Dose Adjustments, Infusion Delays, and Missed Doses, section was modified to include additional language about maximum dosing delays and the allowance for subjects in the 0.1 and 0.3 mg/kg dose levels to be escalated to 1 mg/kg as described earlier in the amendment.

- 46) Protocol Section 8.1, Dose Escalation, section was modified to add language specifying that the 0.1 and 0.3 mg/kg dose levels did not impact the dose escalation plan for this study.
- 47) Protocol Section 8.2, Dose-Limiting Toxicity, section was modified to include language specifying that clinical sites need to seek input/approval/agreement by the BMS medical monitor prior to rechallenge of any subjects that experience a grade 3 irAE.
- 48) Protocol Section 8.3, Stopping Rules for Dose-limiting Toxicity During Dose Escalation, section was modified to correct the estimated PK half-life of BMS-936558.
- 49) Protocol Section 8.6, Infusion Reactions, section was modified to include the current infusion reaction experience with BMS-936558.
- 50) Protocol Section 8.7, Stopping Rules for Clinical Deterioration, section was modified to include language the rules for stopping study drug in the setting of newly identified CNS metastases.
- 51) Protocol Section 10, Concomitant Therapy, section was modified to include language regarding clinically indicated infectious disease vaccinations and to clarify language allowing other palliative treatments.
- 52) Protocol Section 10.1, Treatment of Isolated Lesions, this new protocol section was added.
- 53) Protocol Section 11.1.2, Screening Period, section was modified to include language specifying that peripheral blood samples should be collected for subjects that consent to optional research related biopsies.
- 54) Protocol Section 11.1.3, Treatment Period, section was modified to correct protocol section references and change the maximum duration of study therapy to 3 years.
- 55) Protocol Section 11.1.3.1, Cycle 1, section was modified to specify that certain laboratory tests will not be collected in subjects enrolled under this amendment and to specify the inclusion of a baseline blood sample for performing SNP analyses.
- 56) Protocol Section 11.1.3.1, Cycle 1, section was modified to specify that any remaining tumor and blood samples that are available after completion of designated analyses may be used in the future for identification of potential predictive and/or pharmacodynamic markers.
- 57) Protocol Section 11.1.3.2, Cycle 2+, the title to protocol section was modified and the text revised to correct for the maximum duration of study therapy.
- 58) Protocol Section 11.1.4, Follow-up Period, section was modified to include clarifying text and corrected references.
- 59) Protocol Section 11.1.5, Cycle 1 Treatment Completion, section was modified to clarify the criteria for completion of cycle 1.

- 60) Protocol Section 11.2.1, Primary Efficacy Parameters, section was modified to include corrected primary efficacy parameters based on the modified sample size.
- 61) Protocol Section 11.2.2 was modified to include corrected secondary efficacy parameters.
- 62) Protocol Section 11.3, Exploratory Biomarkers of Immune Response, the title of this section was modified and the text clarified to clarify the types of biomarker analyses that will be conducted.
- 63) Protocol Section 11.4.2, Immunogenicity, section was modified to include clarifying language on the timing and rationale for immunogenicity analyses.
- 64) Protocol Section 11.5, Pharmacokinetic Evaluations, this section was modified to include description of sample processing and PK parameters under evaluation.
- 65) Protocol Section 12.7, Rapid Notification of Adverse Events of Special Interest (EOSI), this section was modified to change the contact person to which clinical site report adverse events of special interest and to include an additional type of event that requires reporting to BMS within 24 hours.
- 66) Protocol Section 13.1, Sample Size Determination, this section was revised to include sample size estimates based on the anticipated toxicity and the number of anticipated expansion cohorts.
- 67) Protocol Section 13.2.1, All Enrolled Population, this section was added to define the All Enrolled study population.
- 68) Protocol Section 13.2.2, All Treated Population, this section was added to define the All Treated study population.
- 69) Protocol Section 13.3.2, Per-protocol Population, this section was modified to include clarifying the analyses that will be conducted on this population.
- 70) Protocol Section 13.2.4, Pharmacokinetic Data Set, this section was added.
- 71) Protocol Section 13.2.5, Response Evaluable Data Set, this section was added.
- 72) Protocol Section 13.2.6, Exploratory Immune Function Biomarkers, this section was added.
- 73) Protocol Section 13.3, Statistical Considerations, the existing text under this protocol section was deleted.
- 74) Protocol Section 13.3.1, Demographics and Baseline Characteristics, this section was modified to specify the data types that constitute these parameters, and how they will be summarized.
- 75) Protocol Section 13.3.4, Efficacy, this section was modified to clarify the efficacy parameters that will be conducted including the addition of the immune-related response criteria.
- 76) Protocol Section 13.3.5, Safety, this section was modified to include language regarding Adverse Event definitions and the different sub-types of adverse events.

- 77) Protocol Section 13.3.6, Immunogenicity, this section was modified to include correcting and clarifying text on how immunogenicity data will be presented/summarized.
- 78) Protocol Section 13.3.7, Pharmacokinetic Parameters, this section was modified to include correcting and clarifying text on the types of analyses and pharmacokinetic parameters that will be summarized under this amendment.
- 79) Protocol Section 13.3.8, Exploratory Biomarkers of Immune Response, this section was modified to include correcting and clarifying text on the parameters to be analyzed and the types of analyses to be conducted.
- 80) Protocol Section 13.4, Missing Data Handling, this section under the previous version of the protocol was deleted.
- 81) Protocol Section 13.5, Statistical Software, this section under the previous version of the protocol was deleted.
- 82) Protocol Section 16, References, reference #33 was added to the protocol reference section.
- 83) Protocol Appendices, appendix #2 (Immune-related RECIST) was inserted into the protocol appendices.

Please maintain a copy of this amendment with your protocol. Please provide a copy to your Investigational Review Board / Ethics Committee, unless agreed otherwise with BMS.

AMENDMENT ACKNOWLEDGMENT

I have read this Amendment and agree that it contains all necessary details for carrying out the changes described. I understand that it must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and approved or given favorable opinion before implementation unless to eliminate an immediate hazard to subjects.

If this Amendment substantially alters the study design or increases potential risk to subjects, the consent form will be revised and submitted to the Institutional Review Board/Independent Ethics Committee for approval/positive opinion. I will use the new consent form for any new subjects prior to enrollment, and for subjects currently enrolled in the study if they are affected by the Amendment.

Investigator's printed name and signature

Date

Medical Monitor/Study Director
(If required by applicable regulations and guidelines.)

Date

Protocol Number: CA209003

Site Number:

Amendment Number: 04

Page: 1
Protocol Number: CA209003
(MDX1106-03)
IND Number: 100,052
EUDRACT Number NA
Date: 08-Feb-2010

Protocol CA209003 (MDX1106-03): A Phase 1b, Open-label, Multicenter,
Multidose, Dose-escalation Study of BMS-936558 (MDX-1106) in Subjects with
Selected Advanced or Recurrent Malignancies

Amendment Number 03
Site Number: All

Study Director/Central Medical Monitor

Israel Lowy, MD, PhD
Route 206 & Province Line Road
Lawrenceville, NJ 08543
Telephone (office): +1-609-252-7601
Fax: +1-609-252-6163

24-hr Emergency Telephone Number:

USA: 1-866-470-2267
International: +1-248-844-7390

Bristol-Myers Squibb Research and Development

Oncology Clinical Research and Development
Route 206 & Province Line Road
Lawrenceville, NJ 08543

**This protocol amendment contains information that is confidential and proprietary
to Bristol-Myers Squibb (BMS).**

This amendment must be maintained with the referenced protocol.

Amendment Rationale:

The protocol was amended to incorporate information and processes resulting from the acquisition of Medarex, Inc. by Bristol-Myers Squibb Co (BMS). New and revised protocol sections were incorporated to provide more clarity to investigators and where applicable to provide investigators with new instructions.

Changes to the Protocol:

- 1) Cover page, new contact information was provided for the Medical Monitor, Israel Lowy, MD, PhD.
- 2) In all sections of the protocol including the protocol title, “MDX-1106” was replaced with “BMS-936558 (MDX-1106)”.
- 3) In all sections of the protocol, “MDX1106-03” was replaced with “CA209003 (MDX1106-03)”.
- 4) “Medarex, Inc.” was replaced with “Bristol-Myers Squibb”.
- 5) On page 12 in the abbreviations section, the abbreviation for events of special interest was modified from “ESI” to “EOSI”.
- 6) In the abbreviations section on page 13, the abbreviation for WOCBP (Women of Child Bearing Potential) was added to the abbreviation list.
- 7) On page 36, Section 3.5 Post Study Access to Therapy was added. New included text states: At the end of the study, the sponsor will not continue to supply study drug to subjects/investigators unless the sponsor chooses to extend the study. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.”
- 8) On page 36-37, in Section 4, additional text was added. The added text states: Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria. If there is a question about the inclusion or exclusion criteria listed below, the investigator should consult with the sponsor’s Medical Monitor, or designee, before enrolling the subject into the study. For entry into the study, the following criteria **MUST** be met.
- 9) On page 38, Section 4.1, Inclusion Criterion #13 was revised to include the following: In general, the decision for appropriate methods to prevent pregnancy should be determined by discussions between the investigator and the study subject. Women must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to the start of investigational product.
- 10) On page 39, Section 4.2 Exclusion Criteria. The following 2 exclusion criteria were added:

- 11. Prisoners or subjects who are involuntarily incarcerated; or
- 12. Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

- 11) On page 40, Section 7, the following text was added: All protocol-specified investigational and noninvestigational products are considered study drug.
- 12) On page 40, Section 7.1 Investigational Product. The following section/text was added: An investigational product, also known as investigational medicinal product in some regions, is defined as follows: A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form. The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations. In this protocol, investigational product(s) is: BMS-936558 (MDX-1106).
- 13) On page 40, Section 7.2 Noninvestigational Product was added: 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: Not applicable for this study.
- 14) On page 41, Section 7.6, the text was expanded to include the following: The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the sponsor. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately.
- 15) On page 43, Section 7.10 Destruction of Study Drug was added: If study drugs (those supplied by the sponsor or sourced by the investigator) are to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor.
- 16) On page 44, Section 7.11 Return of Study Drug was added: Study drug will not be returned. All unused and/or partially used study drug may be destroyed on site providing the site has an applicable standard operating procedure on file.

- 17) On page 50, Section 10, the use of steroids while on study was clarified in include the following statement: The use of steroids as prophylactic treatment for subjects with contrast allergies to diagnostic imaging contrast dyes will be permitted.
- 18) On page 57-58, Section 11.1.7 Discontinuation of Subjects from Treatment was added: Subjects MUST discontinue investigational product (and noninvestigational product at the discretion of the investigator) for any of the following reasons:
- Withdrawal of informed consent (subject's decision to withdraw for any reason)
 - Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
 - Pregnancy
 - Termination of the study by Bristol-Myers Squibb (BMS)
 - Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
 - Inability to comply with protocol.
 - Discretion of the investigator.
 - Disease progression or clinical deterioration as defined in section 3.3
 - Dosing delays greater than the maximum allowed dosing delays as defined in section 7.9

All subjects who discontinue should comply with protocol specified follow-up procedures as outlined in Section 11.1.6. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

- 19) On page 60, Section 12.1 was expanded to include the following text “any laboratory test that is clinically significant or meets the definition of an SAE. It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value)”.
- 20) On page 62, Section 12.1.1 was expanded to include the following text: A nonserious adverse event is an AE not classified as serious. The collection of nonserious AE information should begin at initiation of study drug and should conclude 70 days after last dose of study drug. Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 12.3). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

21) On page 62, Section 12.2 was expanded include the following text: (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);

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

- Suspected transmission of an infectious agent (eg, any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.
- Although pregnancy, overdose and cancer are not always serious by regulatory definition, these events must be handled as SAEs for data transmission purposes (See Section 12.5.1 or reporting pregnancies).

NOTE:

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

Hospitalizations occurring under the following circumstances are not considered serious adverse events: admission to a hospice for respite care; hospitalizations planned before entry into the clinical study; hospitalization for elective treatment of a condition unrelated to the studied indication or its treatment; hospitalization on an emergency, outpatient basis that does not result in admission (unless fulfilling the criteria above); hospitalization as part of the normal treatment or monitoring of the studied indication; or hospitalization to facilitate the work up of a Grade 1 adverse event, including overnight hospitalization following study drug administration for non medical reasons.

- 22) On page 64, Section 12.3.1 was expanded to include the following text: ; or within 30 days of the last visit for screen failures
- The investigator should collect any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.
 - An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

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

- 23) On page 65, Section 12.3.2 was revised to include the following text: SAEs must be recorded on the BMS SAE Report Form; pregnancies on a BMS Pregnancy Surveillance Form. These original BMS Forms are to remain on site. SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours via confirmed facsimile (fax) transmission, or scanned and reported via electronic mail to: SAE Email Address: Worldwide.Safety@BMS.com SAE Facsimile Number: See Contact Information list. SAE Telephone Contact (required for pregnancy reporting): See Contact Information list. If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.) If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.
- 24) On page 66, Section 12.5.1 was revised to include the following text: If, following initiation of the investigational product, it is subsequently discovered that a study subject or a female partner of a male study participant 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 for the female study participant in an appropriate manner (eg, dose tapering if necessary for subject safety). Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. The investigator must immediately notify the BMS Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS within 24 hours and in accordance with SAE reporting procedures described in Section 12.5.1. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form. Infants should be followed for a minimum of 8 weeks.

- 25) On page 68, Section 12.8 Other Safety Considerations was added as follows: Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.
- 26) On page 73, Section 14.1 was revised to include the following text: All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.
- 27) On page 73-74, Section 14.3 was revised to include the following text: Before implementing this study, the protocol, the proposed ICF, and other information provided to subjects must be reviewed by an IRB/IEC. A signed and dated statement that the protocol, and ICF, subject recruitment materials/process (eg, advertisements), and any other written information to be provided to subjects have been approved by the IRB/IEC must be given to BMS before study initiation. The name and occupation of the chairperson and the members of the IRB/IEC (preferred) or the IRB's Health and Human Safety Assurance number must be supplied to BMS or its designee. Any amendments to the protocol which need formal approval, as required by local law or procedure, will be approved by this committee. The IRB/IEC will also be notified of all other administrative amendments (i.e., administrative changes). The investigator or sponsor should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects and any updates. The investigator or sponsor should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments and administrative letters) according to regulatory requirements or institution procedures.
- 28) On page 74-75, Section 14.4 was revised to include the following text: Investigators must ensure that subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representatives, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. The ICF must be submitted by the Investigator with the protocol for IRB/IEC approval. BMS supplies a proposed ICF template that complies with regulatory requirements, includes all elements required by ICH, GCP and applicable regulatory requirements, and is considered appropriate for the study. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki. Any changes to the proposed ICF suggested by the Investigator must be agreed to by BMS or its designee before submission to the IRB/IEC, and a copy of the approved version must be provided to the BMS study monitor after IRB/IEC approval.

Investigators must:

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

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records. Subjects unable to give their written consent (eg, stroke patients, or subjects with severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with the subjects' understanding, and should they become capable, personally sign and date the consent form as soon as possible. The explicit wish of a subject unable to give his or her written consent, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator. The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

- 29) On page 76, Section 15.1 was revised to include the following text: These requirements for approval should in no way prevent any immediate action from being taken by the Investigator or by BMS in the interests of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt by the Investigator to be necessary and is implemented by him/her for safety reasons, BMS

should be notified and the IRB/IEC for the center should be informed within 1 working day. Any significant deviation must be documented in the CRF.

- If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:
- IRB/IEC for review and approval/favorable opinion
- Bristol-Myers Squibb
- Regulatory Authority(ies), if required by local regulations

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

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

- 30) On page 77, Section 15.2 was revised to include the following text: Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential. The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.
- 31) On page 78, Section 15.2.1 Investigational Site Training was added: Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.
- 32) On page 78, Section 15.3 was revised to include the following text: Essential documents, as listed below, will be retained by the Investigator for the maximum period required to comply with national and international regulations, or institutional procedures, or for the period specified by the sponsor, whichever is longer. BMS. will notify the Investigator(s)/institution(s) when study-related records are no longer required to be retained. The Investigator agrees to adhere to the document retention procedures by signing the protocol. The investigator must contact BMS prior to

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

33) On page 79, Section 15.3.1 Study Drug Records was added: It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by the sponsor) is maintained at each study site where study drug is inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label ID number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- non-study disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to the sponsor
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product (IP) dispensing/accountability, as per the Delegation of Authority Form.

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

34) On page 80, Section 15.3.2 Case Report Forms was added: An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained. For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the SAE form and Pregnancy Surveillance form, respectively Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by the sponsor. The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s). The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or

- corrections on CRFs. The completed CRF, including any paper SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by a qualified physician who is an investigator or subinvestigator. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections. Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by the sponsor. User accounts are not to be shared or reassigned to other individuals.
- 35) On page 81, Section 15.5 was revised to include the following text: The data collected during this study are confidential and proprietary to the sponsor. Any publications or abstracts arising from this study require approval by the sponsor prior to publication or presentation and must adhere to the sponsor's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to the sponsor at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. Sponsor shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application. BMS must receive copies of any intended communication in advance of submission (at least 30 working days for a journal submission and 15 days for an abstract or oral presentation). BMS will review the communications for accuracy (thus avoiding potential discrepancies with submissions to health authorities), verify that confidential information is not being inadvertently disclosed, and provide any relevant supplementary information. Authorship of communications arising from pooled data may include members from each of the contributing centers, as well as BMS personnel.

Please maintain a copy of this amendment with your protocol. Please provide a copy to your Investigational Review Board / Ethics Committee, unless agreed otherwise with BMS.

AMENDMENT ACKNOWLEDGMENT

I have read this Amendment and agree that it contains all necessary details for carrying out the changes described. I understand that it must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and approved or given favorable opinion before implementation unless to eliminate an immediate hazard to subjects.

If this Amendment substantially alters the study design or increases potential risk to subjects, the consent form will be revised and submitted to the Institutional Review Board/Independent Ethics Committee for approval/positive opinion. I will use the new consent form for any new subjects prior to enrollment, and for subjects currently enrolled in the study if they are affected by the Amendment.

Investigator's printed name and signature

Date

Medical Monitor/Study Director
(If required by applicable regulations and guidelines.)

*Date**Protocol Number:* CA209003 (MDX1106-03)*Site Number:**Amendment Number:* 03

MEDAREX

Page: 1 of 28
Protocol Number: MDX1106-03
Version: Amendment 2
Development Phase: Phase 1b
IND Number: 101,052
Document Status: Final
Date: 25 August 2009

Clinical Protocol MDX1106-03 Amendment 2

Summary of Change

A Phase 1b, Open-label, Multicenter, Multidose, Dose-escalation Study of MDX-1106 in Subjects with Selected Advanced or Recurrent Malignancies

Medical Monitor

Israel Lowy, MD, PhD
Senior Director, Clinical Science
Office Phone Number: +1-908-479-2447
Office Fax Number: +1-908-479-2410
Mobile Phone Number: +1-908-770-6477
Email: ILowy@medarex.com

Clinical Operations Contact

Daniel McDonald, MBA
Manager, Clinical Operations
Office Phone Number: +1-908-479-2529
Office Fax Number: +1-908-479-2415
Mobile Phone Number: +1-908-797-0122
Email: DMcDonald@medarex.com

SAE Reporting FAX Number

+1-908-479-2408

Central Emergency Phone Number

+1-800-246-2912

Property of Medarex, Inc.
519 Route 173 West
Bloomsbury, NJ 08804

Confidential

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be used, divulged, published, or otherwise disclosed without the written consent of Medarex, Inc. These restrictions on disclosure will apply equally to all future information supplied to you or generated by you in connection with the study.

PRIMARY SUBSTANTIVE CHANGES

The primary substantive changes are:

- Inclusion of subjects with colorectal adenocarcinoma (CRC) as another indication to be studied in the protocol.
- Addition of 2 additional expansion cohorts for melanoma at doses other than at the primary expansion dose, as well as addition of the colorectal expansion cohort and the separation of the melanoma/renal carcinoma cohorts into 2 cohorts of 16 each.
- Added requirement for permission to collect slides or tissue samples from pre-enrollment tumor biopsies, if available, for examination of tumor markers and inflammatory infiltrates.
- Expanded the text describing the statistical analysis and summarization of efficacy and safety parameters.

GLOBAL CHANGES

The following changes have been to the synopsis, Time and Events schedules, and the body of the protocol.

1. Added CRC as another indication to be studied in the protocol.
2. Clarified dose escalations or de-escalations as being required only if a 10% or greater change in weight (increase or decrease) occurred.
3. Added 2 additional expansion cohorts of subjects with melanoma (at doses other than at the primary expansion dose), a colorectal expansion cohort, and split the melanoma/renal carcinoma cohort into individual cohorts, resulting in an increase from 76 to 124 in the maximum number of subjects to be enrolled.
4. Length of the follow-up period changed from approximately 1 year to 46 weeks.
5. Added blood tests for CEA and CA-19-9 for subjects with CRC.

Reason for substantial and global changes:

1. Early positive trend in CRC in other studies of MDX-1106 supported adding CRC as additional indication.
2. Clarified conditions for dose escalations/de-escalations.
3. Two additional melanoma cohorts were added at dose levels other than the primary expansion dose, and the number of subjects in the renal expansion cohort was changed to 16 to gain additional safety and tolerability information as well as provide an initial estimate of efficacy.
4. Clarification of follow-up time period.

5. Analyses for CEA and CA-19-9 were added to test for these specific biomarkers in subjects with CRC.
6. Text added to allow for collection of pre-study slides/tissue samples for use in future research.
7. Description of statistical analyses expanded for clarity.

SECTION CHANGES

The following changes (indicated with a ~~strikeout~~ (deleted text) or **shaded areas** (new text) have been made as Amendment 2 to the Protocol for Study MDX1106-03. Changes resulting from minor typographical or grammatical errors, or defining acronyms for the first time, are not summarized within the section changes noted below as they are not expected to affect the understanding or conduct of the study, the safety of subjects, the scope of the investigation, or the scientific quality of the study.

SYNOPSIS, OVERVIEW OF STUDY DESIGN, Dose Escalation

Change sentence six in first paragraph to read:

If ≥ 2 of up to 6 subjects in the 1 mg/kg dose cohort experiences a DLT during the first cycle, that cohort will have exceeded the maximum tolerated dose (MTD, ~~which is~~), defined as the highest dose studied at which no more than 1 of 6 subjects has experienced a DLT in Cycle 1), and a lower dose level (0.3 mg/kg) will be tested.

Change sentence seven to read:

If 2 or more delayed DLTs are noted within a dose **escalation** cohort, further accrual will be held pending safety analysis of the event, and will be restarted only with Investigator and Sponsor (Medarex, Inc.) approval at all sites (with FDA and Institutional Review Board [IRB] notification)

Change sentence eight to read:

No dose escalations or de-escalations are permitted within each subject's treatment; dose adjustments are allowed only if there has been ~~a~~ **10% weight or greater change in weight (increase or decrease)** since the previous cycle. A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

Reason for change: Clarifications of text around dose escalations/de-escalations, minor editorial changes/clarifications.

SYNOPSIS, OVERVIEW OF STUDY DESIGN, Expansion Cohorts; Section 3.2; Section 3.2.1; Section 3.2.2 and Section 3.2.3

Add/delete section to read:

~~To further characterize safety and efficacy, additional subjects will be enrolled at the MTD (or the highest dose studied if the MTD is not identified) in 3 tumor-specific expansion cohorts: NSCLC, mCRPC, and MEL+RCC. Up to 16 subjects will be enrolled in each of the NSCLC and mCRPC cohorts. For the MEL+RCC expansion cohort, 16 subjects are required in 1 of the 2 indications; up to 16 subjects may be enrolled in the 'other' indication (enrollment may be stopped in the 'other' indication at the time that the other 3 expansion cohorts [NSCLC, mCRPC and either MEL or RCC] each accrue 16 subjects). A total of 6 subjects must be enrolled at the MTD (or the highest dose studied where ≤ 1 of 6 subjects experiences a DLT if the MTD is not identified) and evaluated through the end of Cycle 1 before any new subject is dosed in the expansion cohorts. If none of the first 5 subjects have a DLT by the end of Cycle 1, enrollment to the expansion cohorts can begin immediately following enrollment of the 6th subject.~~

~~Enrollment may be held in all expansion cohorts if the rate of DLTs is $\geq 33\%$ across all indications (including subjects from the dose escalation cohort at the expansion dose) or if the rate of DLTs is $\geq 33\%$ in a specific indication after enrollment of the first 6 subjects in that indication (including subjects from the dose escalation cohort at the expansion dose). After safety analysis by the Investigators and Medarex (with FDA and IRB notification), a decision will be made whether to resume enrollment at the current dose, or initiate a new expansion cohort of 16 subjects in 1 or more indications at a lower MDX-1106 dose (chosen according to the de-escalation rules above). For delayed DLTs, enrollment will be held using the same rules as that for DLTs. After safety review of delayed DLTs by the Investigators and Medarex (with FDA and IRB notification), a decision will be made whether to resume enrollment at the current dose (with or without a limitation in the total number of allowed cycles) or to initiate a new expansion cohort in 1 or more of the indications at a lower dose (using the same de-escalation schedules as that for DLTs).~~

To further characterize safety and efficacy, up to 7 expansion cohorts will be enrolled. A total of 6 subjects must be enrolled at the MTD (or the highest dose studied where ≤ 1 of 6 subjects experiences a DLT if the MTD is not identified) and evaluated through the end of Cycle 1 before any new subject is dosed in the expansion cohorts. If none of the first 5 subjects have a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following enrollment of the sixth subject.

Up to 7 expansion cohorts will be enrolled:

- a. 1 in each of the 5 disease indications at a tolerated dose chosen by the Sponsor that may be either the highest dose tested that does not exceed the MTD or a lower dose with evidence of study drug activity.
- b. an additional 2 cohorts in subjects with MEL will also be enrolled at doses other than the primary expansion dose (such as 1 and 3 mg/kg if the primary expansion occurs at the 10 mg/kg dose level).

In each cohort, a subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced (if they were withdrawn for early progression they will be counted in the per protocol estimate of overall efficacy).

Initiation of the Primary Expansion Cohorts

A total of 6 subjects must be enrolled at the MTD (or the highest dose studied where ≤ 1 of 6 subjects experiences a DLT if the MTD is not identified) and evaluated through the end of Cycle 1 before any new subject is dosed in the expansion cohorts. If none of the first 5 subjects have a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following enrollment of the sixth subject.

The primary expansion cohorts will enroll subjects from each of the 5 tumor-specific indications: NSCLC, mCRPC, RCC, CRC, and MEL. Approximately 16 subjects (dose escalation plus expansion) will be enrolled in each of the cohorts at the dose chosen for the expansion.

Initiation of the Additional Melanoma Expansion Cohorts

In order to gain additional safety and tolerability information at other doses, as well as provide an initial estimate of efficacy, 2 additional cohorts of subjects with MEL will be enrolled. Approximately 16 subjects per cohort (including any subjects with MEL who were treated in the dose-escalation cohort corresponding to that dose level) will be treated at a dose other than the primary expansion dose (such as at the 1 and 3 mg/kg dose levels if the primary expansion occurs at 10 mg/kg). Enrollment to the first additional expansion cohort (ie, 1 mg/kg dose level) can begin at the lowest planned dose immediately at the time that the primary expansion opens and will accrue separately beginning from the lowest to the highest dose planned. Accrual to the next higher dose will begin immediately on completion of enrollment to the prior additional cohort.

Stopping Rules for the Expansion Cohorts

Enrollment may be held in any expansion cohort if the rate of DLTs is $\geq 33\%$ across all 5 indications at the primary expansion dose level, or in a specific indication if the rate of DLTs is $\geq 33\%$ after enrollment of the first 6 subjects in that indication (including subjects from the dose-escalation cohort at the expansion dose). The DLT rate for a dose level will be based on the cumulative number of subjects at that dose level. Enrollment of additional subjects will be held

in a dose level where a $\geq 33\%$ DLT rate occurs and at any higher dose level enrolling at that point in time.

Subjects who are tolerating a study drug at a dose level that is being reviewed due to the occurrence of DLTs in another subject will not be automatically precluded from continued dosing during the safety review, and will be allowed to continue dosing for as long as tolerated unless directed otherwise as a result of the safety review. After safety analysis by the Investigators and Medarex (with FDA and IRB notification), a decision will be made whether to resume enrollment and continue dosing at the current dose or initiate a new expansion cohort of 16 subjects in 1 or more indications at a lower dose.

For delayed DLTs, enrollment will be held and/or restarted using the same rules as that for DLTs.

Reason for change: Increase the expansion cohorts with regard to number of cohorts tested (all 5 indications at the primary expansion dose level and two additional MEL expansions at other dose levels) with 16 subjects [dose-escalation plus expansion] within each cohort) in order to gain additional safety and tolerability information as well as provide an initial estimate of efficacy; provide guidance on the stopping rules for enrolling subjects into the expansion cohorts.

SYNOPSIS, OVERVIEW OF STUDY DESIGN, Administration of Additional Treatment Cycles and Section 3.3

Change second paragraph to read:

The maximum number of cycles to be administered to an individual subject in this study is 12. Following each treatment cycle, the decision to treat a subject with additional cycles of MDX-1106 will be based on tumor response assessment (evaluation performed between Days 52 and 56 and before the first dose in the next cycle). ~~Day 1 of each cycle occurs upon completion of the previous cycle, and should be 56 days following Day 1 of the previous cycle as outlined below).~~ If a subject is eligible to receive additional cycles, the first dose of the next cycle should be given no earlier than 14 ± 2 days and no later than 28 ± 2 days after the last dose of the prior treatment cycle ~~and no later than 21 days after the last dose~~ to maximize dose intensity. No subject will be permitted dose escalations or de-escalations; dose adjustments are allowed only if there has been ~~a~~ a 10% ~~weight~~ or greater change in weight (increase or decrease) since the previous cycle.

Delete number three in bulleted statement to read:

~~progressive disease (PD) that is confirmed and then worsens; 4)~~

Add first paragraph in Section 3.3 to read:

Tumor response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) with modifications. End of cycle tumor response assessments for all subjects will occur within Days 52 to 56 (results of assessments must be reviewed and documented before the first dose of the next cycle).

Change last 2 sentences of second paragraph in Section 3.3 to read:

Unless the subject develops a \geq Grade 3 (CTCAE) adverse event or other adverse event related to MDX-1106 that precludes further treatment, subjects will be treated until confirmed ~~clinical~~ complete response (CR) or progressive disease (PD) that is both confirmed and then further progresses as described below. If a subject is eligible to receive additional cycles, the first dose of the next cycle should be given 14 \pm 2 days after the last dose of the prior treatment cycle but no later than 28 \pm 2 days.

Reason for change: Clarify dosing time windows; clarification of text regarding cycles; global change regarding dose adjustments; expand and clarify criteria for tumor response; clarification and consistency across sections; minor editorial changes and clarifications.

SYNOPSIS, OVERVIEW OF STUDY DESIGN, Follow-Up Period and Section 3.4

Change section to read:

The maximum duration of follow-up will be ~~approximately 1 year~~ 46 weeks. All subjects should complete Follow-up Visit 1 ~~(1 to 7 days after the last visit of the last treatment cycle)~~. Completion of subsequent follow-up visits ~~(Follow-up Visits 2 to 6)~~ will depend on the status of the subject at the end of ~~treatment~~ the Treatment Period. Except for subjects who discontinue due to worsening PD, all subjects will be followed from the last visit ~~for approximately 1 year~~ until relapse, initiation of a new therapy, or a total of 1 year follow-up, whichever occurs first. Subjects whose PD is confirmed and who have further progression at a subsequent imaging evaluation will only complete Follow-up Visits 1 and 2; Follow-up Visit ~~1~~ 2 (for these subjects only) will only include pharmacokinetic and immunogenicity evaluations and adverse event collection.

Change Section 3.4 to read:

The maximum duration of follow-up will be ~~approximately 1 year~~ 46 weeks. All subjects should complete Follow-up Visit 1 (1 ~~to~~ 7 days after the last visit of the last treatment cycle). Completion of subsequent follow-up visits (Follow-up Visits 2 to 6) will depend on the status of the subject at the end of ~~treatment~~ the Treatment Period. Except for subjects who discontinue due to ~~worsening PD (as described above)~~, all subjects will be followed from the last visit ~~for approximately 1 year~~ until relapse, initiation of a new therapy, or a total of 1 year follow-up,

whichever occurs first. Subjects whose PD is confirmed and who have further progression at a subsequent imaging evaluation will only complete Follow-up Visits 1 and 2; Follow-up Visit ~~4=2~~ (for these subjects only) will only include pharmacokinetic and immunogenicity evaluations and adverse event collection.

Reason for change: Clarification of follow-up time period; clarification of Follow-up Visit 2 assessments to be performed for subjects with PD; minor editorial changes and clarifications.

SYNOPSIS, STUDY POPULATION AND STATISTICAL METHODS and SECTION 4

Change the first and second sentence for Study Population and Section 4 to read:

Up to ~~76~~¹²⁴ subjects will be enrolled if only the planned dose levels and expansions are used/enrolled. Subjects will be enrolled who have pathologically-verified mCRPC, RCC, CRC, MEL, or NSCLC that is clinically advanced or recurrent and progressing after prior treatment with other therapies, and for which no alternative curative option is available.

Change first sentence in Statistical Methods and Section 13.1 Sample Size Determination to read:

A sample size of up to ~~76~~¹²⁴ subjects is based on the study design for dose escalation, ~~4~~⁵ oncology indications, and the number of possible tumor-specific expansion cohorts for further safety and efficacy evaluation.

Change paragraph in section 13.1 Sample Size Determination to read:

To further characterize safety and efficacy, additional subjects will be enrolled at the MTD (or the highest dose studied if the MTD is not identified) or at a lower dose with evidence of study drug activity in ~~3~~⁵ tumor-specific expansion cohorts: NSCLC, mCRPC, ~~and MEL+RCC, CRC, and MEL~~. Up to 16 subjects will be enrolled in each of the ~~4~~⁵ oncology indications. In order to perform preliminary evaluation of BORR (anti-tumor activity), the sample size ~~at the MTD or highest dose level cohort~~ of an expansion cohort is determined by a power analysis. It is assumed that the subjects would have no response if they would not have received any therapy and that the BORR for subjects in the ~~MTD or highest dose level~~ expansion cohort would be 10%. Based on this assumption, a sample size of at least 16 subjects (in each tumor expansion cohort) ~~in the MTD or highest dose level cohort~~ is required to provide more than 80% power in a one-sample exact Binomial test at the significance level of 0.05.

Change first sentence of Section 13.2.2 Per-protocol Population to read:

The per-protocol population includes all subjects dosed ~~at the MTD (or the highest dose studied if the MTD is not identified)~~ in the expansion cohorts in the safety population who have the correct disease diagnosis, valid baseline tumor assessment, and at least 1 valid post-baseline tumor assessment.

Reason for change: Clarification of the terminology related to expansion cohorts with regard to the MTD; addition of the CRC cohort, change to the number of subjects because of the extra expansion cohorts; other minor editorial changes.

SYNOPSIS, EFFICACY EVALUATIONS

Change sentence one to read:

The primary efficacy ~~endpoint~~ **parameter** is the best overall response rate (BORR) during the first 3 cycles (proportion of subjects with confirmed responses of CR or PR) as determined by the results of Investigator evaluations for each indication.

Change sentence three to read:

Independent ~~confirmation~~ **review** of ~~responses~~ **tumor assessments** may be requested at the discretion of Medarex.

Change sentence four to read:

The secondary efficacy parameters include the following: BORR during the entire study for each indication and across all indications (regardless of time to response), response categories (CR, PR, SD, PD), disease control rate (sum of response rate for CR+PR+SD across subjects), **progression-free survival** and the time to response and duration of response for those subjects with confirmed responses.

Change sentence five and six to read:

Computed tomography/magnetic resonance imaging (CT/MRI [chest, abdomen, pelvis, and brain]) and bone scans will be performed at Screening and at the end of each cycle. Measurements of change in tumor burden must be reviewed and documented before initiating a new cycle of treatment with MDX-1106; ~~response assessment determinations must be confirmed and documented by the end of the next treatment cycle.~~ Tumor response status will be assessed using RECIST with modifications, as well as by ~~prostate~~ **tumor-specific antigen (PSA)** levels for mCRPC (**PSA**) and CRC (**CEA and CA19-9**).

Reason for change: Clarification of response assessments; inclusion of tumor-specific antigen levels for subjects with CRC; minor editorial changes.

SYNOPSIS, EXPLORATORY IMMUNE FUNCTION EVALUATIONS

Change the first sentence to read:

Samples will be collected and evaluated for lymphocyte phenotype, serum cytokines, and quantitative immunoglobulins, and additional optional research samples will be collected and stored for future research which may include **(but not limited to)** disease-related biomarkers (or

antibody responses to selected antigens), exploratory humoral and cellular immune responses to tumor antigens and a panel of recall non-tumor antigens.

Change third sentence to read:

Optional research-related tumor or other biopsies (e.g., inflamed tissue ~~at anatomical sites~~) that ~~are readily accessible without the need for~~ do not require general anesthesia) ~~requiring specific agreement by the subject in the informed consent~~ may be performed ~~obtained with the subject's explicit consent~~ to assess morphology and the presence or absence of inflammatory infiltrates, and their cellular characterization.

Reason for change: Clarification of the requirement of subject consent for optional biopsies; minor editorial changes/clarifications of text.

SYNOPSIS, SAFETY EVALUATIONS

Change last sentence to read:

Safety will also include evaluations of immune safety (as noted by irAEs, or laboratory tests for autoimmune sera) and immunogenicity.

Reason for change: Clarification of immune safety evaluations.

STATISTICAL METHODS

Change section to read:

In order to perform preliminary evaluation of BORR (anti-tumor activity), the sample size ~~at the MTD or highest dose level cohort~~ of an expansion cohort is determined by a power analysis. It is assumed that the subjects would have no response if they would not have received any therapy and that ~~the BORR for subjects in the MTD or highest dose~~ an expansion level cohort would be 10%. Based on this assumption, a sample size of 16 subjects (in each tumor expansion cohort) ~~in the MTD or highest dose level cohort~~ is required to provide more than 80% power in a one-sample exact Binomial test at the significance level of 0.05.

~~Descriptive statistics will include: mean, standard deviation, median, and minimum and maximum values for continuous variables; frequencies and percentages for categorical variables.~~

Efficacy and safety parameters will be summarized by dose and by indication using descriptive statistics. For ~~some efficacy parameters,~~ BORR in each expansion cohort, a one-sample exact Binomial test will be performed and the 95% confidence intervals will be determined. Time to response and duration of response will be summarized for those subjects with confirmed responses. For the expansion cohorts, efficacy ~~estimates~~ analyses will only be applicable to cohorts that enroll 16 subjects. The incidence, relationship to therapy, and severity of adverse events will be summarized using descriptive statistics. Changes in clinical laboratory tests,

immune safety assays, ECOG, physical examination, vital signs, ECGs, and immunogenicity results will be summarized using descriptive statistics.

Reason for change: Clarification of the terminology related to expansion cohorts with regard to the MTD; clarification of statistical analyses and presentations; other minor editorial changes.

SECTION 1.1, BACKGROUND

Change third sentence in second paragraph to read:

~~Four~~Five tumor types (metastatic castration-resistant prostate cancer [mCRPC], renal cell carcinoma [RCC], colorectal adenocarcinoma [CRC], malignant melanoma [MEL], and non-small cell lung cancer [NSCLC]) were selected for the current study, as they are representative of tumors for which a high medical need for new therapies exist; those for which there is a precedent for clinical responses to other immunotherapies; and those for which there is supportive correlative pathologic data suggesting that the PD-1/PD-L1/2 pathway is important for tumor progression.

Reason for change: Addition of the CRC cohort, change to the number of tumor types under study.

SECTION 1.5.1, SUMMARY OF SAFETY

Change section to read:

~~Initial safety experience of single~~Three Phase 1, dose-administration of MDX-1106 is available escalating clinical studies (at dose levels ranging from ~~ongoing Protocol MDX1106-01~~ Subjects 0.01 mg/kg to 10 mg/kg) have been initiated with advanced or refractory malignancies (~~prostate, colorectal, melanoma, renal cell,~~MDX-1106: 2 in oncology (MDX1106-01 and non-small cell lung cancer) received a single dose of MDX-1106 [this study, MDX1106-03 [Phase 1b)] and ~~were monitored for 12 weeks. Subjects without significant disease progression or toxicity during~~1 in hepatitis C (MDX1106-02). Data entered into the ~~12-week observation following the first dose could receive 2 additional~~MDX-1106 database as of 28 May 2009 show that 78 subjects have received 1 or more doses (of MDX-1106 (25 at the highest 10 mg/kg dose level). In these studies, there was no pattern in the ~~same~~ incidence, severity, or relationship of adverse events to MDX-1106 dose ~~initially given), administered 4 weeks apart, and followed by another 12-week observation before repeating the 2-dose cycle~~level. The dose levels, 0.3, 1.0, ~~3.0~~main toxicities noted include fatigue, anemia, increase in blood alkaline phosphatase, decrease in weight, and lymphopenia. No dose-limiting toxicities have been observed, and ~~40 mg/kg, were administered to cohorts~~only 1 subject (1 mg/kg) experienced a serious adverse event considered by the Investigator to be related to MDX-1106 (colitis, after receipt of 6

~~subjects, with a cohort expansion of an additional 15-5 doses over 9 months in Study MDX1106-01). There were no study drug-related deaths.~~

Preliminary efficacy results for the 2 cancer studies showed sustained objective responses to MDX-1106 in 3 subjects ~~at the 10 mg/kg dose level (, 1 each in the maximum dose studied). No dose-limiting toxicities (DLTs) have occurred in this study.~~

~~As of 15 April 2008, 17 subjects have experienced 40 serious adverse events: 1 mg/kg (renal carcinoma), 3 mg/kg (colorectal cancer), and 10 mg/kg (renal carcinoma) dose cohorts. The Investigators considered 1 event of diarrhea/colitis related to MDX-1106 treatment and considered 1 event of spinal cord compression possibly related to MDX-1106 treatment. Significant adverse events that are likely to be immune-related times to response (and that reflect on safety include polyarticular arthropathy (2 subjects, both low-grade adverse events) durations of response) were 56 days (57+ days), 57 days (530+ days), and diarrhea/colitis (1 subject).~~

~~There have been 2 cases of apparent flare of a syndrome of bilateral polyarticular arthropathy in subjects, both of whom had a prior history of similar type syndromes that was unknown to the Investigators at the time of enrollment (1 subject received MDX-1106 85 (295+ days) for the 1 mg/kg, 3 mg/kg, and 10 mg/kg dose subjects, respectively. A fourth subject with MEL has been stable for 14+ months, and is still receiving intermittent MDX-1106 10 mg/kg. Preliminary efficacy results from the single-dose hepatitis C study showed a response in 1 subject in the 0.1 mg/kg dose cohort (≥ 0.5 -log or greater decrease from the baseline viral load, repeated on ≥ 2 consecutive measures). Due to the limited clinical experience with MDX-1106, expected toxicities have not been fully defined. In this current study, MDX-1106 may be expected to have a toxicity profile similar to that of ipilimumab.~~

There have been 2 cases of apparent flare of a syndrome of bilateral polyarticular arthropathy in subjects, both of whom had a prior history of similar type syndromes that was unknown to the Investigators at the time of enrollment into MDX1106-01 (1 subject received MDX-1106 3 mg/kg and 1 received 10 mg/kg). These were not high-grade adverse events, and promptly responded to moderate corticosteroid treatment. These subjects are ineligible for re-treatment, despite 1 subject having had apparent shrinkage in pulmonary lung cancer lesions, and the other having had shrinkage in cutaneous melanoma lesions.

Change first sentence in paragraph five to read

A serious adverse event of diarrhea/colitis has been reported in a subject with ocular melanoma in MDX1106-01.

Change fifth sentence in paragraph five to read:

It is noteworthy in MDX1106-01 that 21 subjects have each received at least a single dose of MDX-1106 10 mg/kg, and 3-6 of these subjects have received 3-6 doses at least 1 additional dose of

10 mg/kg without such an adverse event, including 1 subject who has received 10 additional doses over 18 months. The potential for additional instances of colitis to emerge with repeated dosing will be closely monitored in this study.

Reason for change: Update section with more recent safety information; clarifications of text; minor editorial changes.

SECTION 3.1, DOSE ESCALATION:

Change last two paragraphs of Section 3.1 to read:

If 2 or more delayed DLTs are noted within a dose escalation cohort, further accrual will be held pending safety analysis of the event, and will be restarted only with Investigator and Sponsor (Medarex, Inc.) approval at all sites (with FDA and Institutional Review Board [IRB] notification).

~~A DLT is defined as~~ No dose escalations or de-escalations are permitted within each subject's treatment; dose adjustments are allowed only if there has been a study drug related \geq Grade 3 adverse event (using National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events Version 3.0 [CTCAE]) occurring during the first cycle (56 days) of dosing, excluding Grade 3 adverse event of tumor flare (defined as local pain, irritation, or rash localized at sites of known 10% or suspected tumor), Grade 3 rash, Grade 3 irAE (defined below) that resolves to a Grade 1 greater change in weight (increase or less within 28 days, or a transient (resolving within 6 hours of onset) Grade 3 infusion related adverse event. A Grade 3 irAE that resolves to a Grade 1 or less within 28 days, while not constituting a DLT for dose escalation/expansion purposes, may preclude further administration of MDX-1106 to the subject.

~~Delayed DLTs are adverse events that meet the criteria of DLTs that occur after Cycle 1. Delayed DLTs will not be used to estimate the MTD for dose escalation.~~

~~An irAE is defined as a clinically significant adverse event of any organ that is associated with study drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism. Serologic, immunologic, and histologic (biopsy) data should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.~~

~~No dose escalations or de-escalations are permitted within each subject's treatment; dose adjustments are allowed only if there has been \pm 10% weight change (decrease)~~ since the previous cycle. A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

Reason for change: Redundancy with regard to DLT information removed from this section; global change regarding dose adjustments.

SECTION 4.1, INCLUSION CRITERIA

Add text to number six to read:

6. At least 1 and up to 5 prior systemic therapies for advanced/recurrent and progressing disease (unlimited hormonal therapies allowed); Subjects with a diagnosis of mCRPC who have received hormonal therapy, but have not received any other form of systemic therapy (e.g., chemotherapy, immunotherapy) will be considered eligible.

Change second sentence and add third sentence to number eleven to read:

11. Surgery requiring ~~local~~ regional/epidural anesthesia must be completed at least 72 hours before study drug administration and subjects should be recovered. Cutaneous biopsies with only local anesthesia should be completed at least 1 hour prior to study drug administration;

Change first sentence of number thirteen to read:

Women must meet 1 of the following criteria: post-menopausal for at least 24 consecutive months; surgically incapable of bearing children (i.e., have had a hysterectomy or bilateral oophorectomy); or utilizing a reliable form of contraception (either medication [oral, implant, or injection] or a barrier method).

Reason for change: Allowance of subjects with mCRPC who have received hormonal therapy; clarification of types of anesthesia allowed to biopsy and time period between biopsy and study drug administration; clarification of reliable forms of contraception.

SECTION 4.2, EXCLUSION CRITERIA

Change number two to read:

2. Prior malignancy active within the previous 2 years except for locally curable cancers that have been ~~adequately treated~~ apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix or breast;

Add last sentence to number three to read:

Subjects with asthma who require intermittent use of bronchodilators (such as albuterol) will not be excluded from this study

Reason for change: Allowance of subjects with asthma requiring intermittent bronchodilator treatment; clarification of text.

SECTION 7.4, STORAGE

Change last sentence of first paragraph to read:

~~Following dilution and transfer to the i.v. bag, After MDX-1106 can be stored~~ has been prepared for administration, the total storage time (combination of refrigeration and room temperature) is not to exceed 24 hours.

Change second paragraph to read:

Stability data for MDX-1106 following dilution and transfer to the i.v. bag supports either: 24 hours at 2°C to 8°C in the refrigerator, or 6 hours at room temperature/under room light and 18 hours at 2°C to 8°C in the refrigerator. 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 MDX-1106 and polyolefin bags have been observed.

Reason for change: Clarifications to procedures for preparation and storage of MDX-1106.

SECTION 7.7, DOSE ADJUSTMENTS, INFUSION DELAYS, AND MISSED DOSES

Change first and second sentence of first paragraph to read:

There will be no dose adjustments allowed for MDX-1106 except for weight changes ($\pm 10\%$) or greater [increase or decrease] at the beginning of each cycle. ~~There must be~~ If a ~~minimum~~ subject is eligible to receive additional cycles, the first dose of ~~14~~ the next cycle should be given no earlier than 14 ± 2 days ~~between study drug infusions~~ and no later than 28 ± 2 days after the last dose of the prior treatment cycle.

Reason for change: Clarify dosing time windows; clarification of text regarding cycles; global change regarding dose adjustments.

SECTION 8.4, STOPPING RULES FOR DOSE-LIMITING TOXICITIES IN THE EXPANSION COHORT

Change section to read:

Enrollment ~~will~~ may be held if either the rate of DLTs is $\geq 33\%$ across all indications (including subjects from the dose-escalation cohort at the expansion dose) **or** if the rate of DLTs is $\geq 33\%$ for a specific indication after enrollment of the first 6 subjects in that indication (including subjects from the dose-escalation cohort at the expansion dose). The DLT rate will be based on the total number of subjects in a cohort (dose-escalation plus expansion). New enrollment should be held in the dose level where a $\geq 33\%$ DLT rate occurs and at any higher dose level that might

also be enrolling at that point in time (lower dose level expansion may continue). Subjects who are tolerating a study drug dose level that is being reviewed due to DLTs that occurred in other subjects will not be automatically precluded from continued dosing during this safety review, and will be allowed to continue dosing for as long as it is tolerated unless the safety review mandates dose reduction. After safety analysis by the Investigators and Medarex (with FDA and IRB notification), a decision will be made whether to resume enrollment and continue dosing at the current dose, or initiate a new expansion cohort of 16 subjects in each of 1 or more of the indications at a lower MDX-1106 dose (chosen according to the de-escalation rules above). For delayed DLTs, enrollment will be held and/or restarted using the same rules as that for DLTs. ~~After which, the Investigators and the Medarex Medical Monitor (with FDA and IRB notification) will review the delayed DLTs, and a decision will be made whether to resume enrollment at the current dose (with or without a limitation in the total number of allowed cycles) or initiate a new expansion cohort in 1 or more of the indications at a lower dose (using the same de-escalation schedules as that for DLTs).~~

Reason for change: Provide guidance on the stopping rules for enrolling subjects into the expansion cohorts.

SECTION 8.7, STOPPING RULES FOR CLINICAL DETERIORATION

Change last sentence in first paragraph to read:

The decision to continue or stop treatment should be discussed with the Medarex Medical Monitor and will be documented in the study records.

Reason for change: Clarification of text.

SECTION 11.1.2 SCREENING PERIOD

Change the following bulleted items to read:

- Tumor-specific therapy history
- Serum β -HCG pregnancy test (~~before the first infusion;~~ for all women of childbearing potential; serum pregnancy test must be negative to continue).
- Tumor-specific antigens (PSA [for mCRPC only] including at least 3 PSA measurements over the preceding 6 months; CEA and CA19-9 [for CRC only]).

Reason for change: Correction/clarification of text regarding pregnancy test at Screening; inclusion of CRC tumor-specific testing.

SECTION 11.1.4 FOLLOW-UP PERIOD

Deleted text at end of section:

~~The following additional evaluation will also be performed as indicated in Table 1:~~

- ~~• Tumor specific therapy~~

Reason for change: Information on tumor-specific therapy not required at follow-up.

SECTION 12.1 DEFINITIONS, ACTION(S) TAKEN

Add to numerical scale:

7 Study drug dosage adjusted

Reason for change: Added for consistency with case report form.

SECTION 12.1.1 SAFETY REPORTING FOR ADVERSE EVENTS

Delete third bullet:

- ~~• Other clinically significant adverse events will be collected and should be followed to resolution/stabilization.~~

Change last sentence in section to read:

Only study drug-related serious ~~adverse events~~ or other clinically significant (e.g., late emerging irAEs that are not serious) adverse events will be collected for all subjects > 70 days after the administration of the last dose of study drug

Reason for change: Clarification of AE reporting rules.

SECTION 12.6 IMMUNE-RELATED ADVERSE EVENTS

Change third sentence of fourth paragraph to read:

All adverse events of colitis > Grade 2 are deemed to be Events of special interest (ESIs), and should be reported using the serious adverse event reporting procedures (Described in Section 12.3), even if the adverse event itself is not deemed as serious.

Reason for change: Minor editorial change.

SECTION 13.2.2 PER-PROTOCOL POPULATION

Add to last sentence of paragraph to read:

A subject who withdraws from the study during Cycle 1 for reasons other than a DLT will be replaced, hence will be excluded from per-protocol population, with the exception of those withdrawn for rapid progression after receiving only 2 or 3 doses.

Reason for change: Clarification of subjects eligible for the Per-protocol Population.

SECTION 13.3 STATISTICAL CONSIDERATION

Add last sentence to section to read:

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

Reason for change: Clarification of the p value to be used in determining statistical significance.

SECTION 13.3.4 EFFICACY

Add text after first sentence to read:

Tumor response status will be defined according to RECIST with modification (Appendix 1), PSA (for subjects with mCRPC; Appendix 2), or by tumor-specific antigen levels (CEA and CA 19-9) for subjects with CRC. In each expansion cohort, a one-sample exact Binomial test will be performed for the BORR and the 95% confidence intervals will be determined.

Change second paragraph to read:

The secondary efficacy parameters include BORR during the entire study for each indication and across all indications (regardless of time to response), response categories (CR, PR, SD, PD), disease control rate (sum of response rate for CR+PR+SD across subjects), progression-free survival, and the time to response and duration of response for those subjects with confirmed responses. All the secondary efficacy parameters will be summarized by dose and indication using descriptive statistics. Response will be defined according to RECIST with modification (Appendix 1) or PSA (Appendix 2) for each expansion cohort. Progression-free survival will be summarized using Kaplan-Meier survival methods. Time to response and duration of response will be summarized for those subjects with confirmed responses.

Reason for change: Clarification of secondary endpoints; clarification of assessments and inclusion of tumor-specific antigen levels; expanded description of statistical analyses for efficacy parameters; minor editorial changes.

SECTION 13.3.5

Delete Flow Cytometry section:

~~Flow Cytometry~~

~~Flow cytometry results will be summarized by dose level using descriptive statistics or as otherwise appropriate.~~

Reason for change: Assessment moved from safety as it should be considered as exploratory.

SECTION 13.3.7 EXPLORATORY IMMUNE FUNCTION STUDIES

Add text at the beginning of this section to read:

Flow Cytometry

Flow cytometry results will be summarized by dose level using descriptive statistics or as otherwise appropriate.

Change section title to read:

Exploratory Immune Function

Reason for change: Assessment moved from safety as it should be considered as exploratory; clarification of text.

SECTION 14.1 ETHICS AND GOOD CLINICAL PRACTICE

Add text at the end of the first paragraph to read:

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

Reason for change: Corrected to reference correct CFR guidance.

APPENDIX 2, PROSTATE RESPONSE EVALUATION CRITERIA

Add bullets to read:

- **PSA Response** will be defined as a PSA concentration < 50% of the PSA reference value occurring at any time after treatment is initiated. The PSA reference value will be the PSA concentration measured immediately prior to treatment.²
- PSA decrease of $\geq 30\%$ from baseline by Week 16 will also be assessed.

Change bullet four to read:

- **PSA Progression** is defined as follows:
 - In subjects where no decline in PSA from baseline is documented, PSA progression is a $\geq 25\%$ increase from the baseline value along with an increase in absolute value of

2 ng/mL or more after ~~12~~16 weeks of treatment. It should be confirmed by a second value obtained 3 or more weeks later.

Add Radiographic Assessment section to read:

Radiographic Assessment

- Bone lesions

- Progression is defined as the appearance of 2 or more new lesions.
- Progression should be confirmed by a repeat measurement at least 6 weeks later demonstrating additional new lesions.

- Soft tissue lesions

- Soft tissue lesions should be assessed according to the modified RECIST (Appendix 1).

Add footnote number 2 to read:

² Bubley GJ, Carducci M, Dahut W, Dawson N, Daliani D, Eisenberger M, et al. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the prostate-specific antigen working group. J Clin Oncol 1999;17:3461-7.

Delete text from the end of Appendix 2:

Radiographic Assessment

~~• Bone lesions~~

- ~~– Progression is defined as the appearance of 2 or more new lesions.~~
- ~~– Progression should be confirmed by a repeat measurement at least 6 weeks later demonstrating additional new lesions.~~

~~• Soft tissue lesions~~

- ~~– Soft tissue lesions should be assessed according to the modified RECIST (Appendix 1).~~

Reason for change: Addition of PSA response criteria; corrected length of time for PSA progression; moved radiographic assessment section, added reference.

APPENDIX 3: TUMOR-SPECIFIC INCLUSION/ EXCLUSION CRITERIA

Add text to the end of Appendix 3 to read:

COLORECTAL CANCER

Inclusion criteria:

1. Patients with histologically or cytologically confirmed recurrent or refractory colorectal carcinoma.
2. Tumor progression after prior therapy for colorectal cancer such as fluoroiprimidine (5 FU or capecitabine), irinotecan, oxaplatin, or cetuximab.
3. Progressive disease as defined by any 1 of the following:
 - The appearance of 1 or more new lesions.
 - At least a 20% increase in the sum of the longest diameters of the target lesions (taking as reference the smallest sum of the longest diameters recorded since the baseline measurements).
 - Increasing carcinoembryonic antigen (CEA). Two values above baseline that are obtained at least 2 weeks apart are adequate to document progressive disease even in the absence of corroborating radiographs, and can also be followed for minor response indications.
4. Must have measurable disease with at last 1 measurable lesion per RECIST with modification.

Reason for change: Section added due to addition of CRC indication to the study population.

TIME AND EVENTS SCHEDULE

Changes to the Time and Events Schedule, Tables 1 and 2 are on the following pages.

Table 1: Time and Events Schedule													
Period	Screening	Treatment										Follow-up ¹	
		Cycle 1					Cycles 2-12						
Visit Name	Screening	C1:1	C1:2	C1:3	C1:4	C1:5	Cn:1	Cn:2	Cn:3	Cn:4	Cn:5	Follow-up 1	Follow-up 2-6
Timepoint Per Cycle (Day)	-28 to -1	1 ⁴²	15 ⁴²	29 ⁴²	43 ⁴²	56 ²³	1 ³⁴	15 ⁴²	29 ⁴²	43 ⁴²	56 ²³	Last Cn:5 Visit + 1 to 7 Days	Previous Follow-up Visit + 56 Days ⁴⁵
Informed consent/HIPAA ⁵⁶	•												
Inclusion/exclusion criteria	•												
Demographics/medical history ^{67,8}	•												
Diagnosis confirmation and stage	•												
Baseline signs and symptoms	•												
Tumor-specific therapy information history	•												•
Hepatitis B and C testing ⁹	•												
Testosterone testing ⁹¹⁰	•												
MDX-1106 infusion		•	•	•	•		•	•	•	•			
Serum sample for pharmacokinetics ⁴⁰¹¹		•	•	•	•		•					•	• ¹⁴¹²
Serum sample for immunogenicity		•					• ¹³					•	• ¹⁴
Vital signs ¹⁵	•	•	•	•	•		•	•	•	•		•	•
Height	•												
Weight	•	•					• ¹⁶						
Complete physical exam ¹⁷	•						•					•	
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.													

continued

Table 1: Time and Events Schedule													
Period	Screening	Treatment										Follow-up ¹	
		Cycle 1					Cycles 2-12						
Visit Name	Screening	C1:1	C1:2	C1:3	C1:4	C1:5	Cn:1	Cn:2	Cn:3	Cn:4	Cn:5	Follow-up 1	Follow-up 2-6
Timepoint Per Cycle (Day)	-28 to -1	1 ⁴²	15 ⁴²	29 ⁴²	43 ⁴²	56 ²³	1 ³⁴	15 ⁴²	29 ⁴²	43 ⁴²	56 ²³	Last Cn:5 Visit + 1 to 7 Days	Previous Follow-up Visit + 56 Days ⁴⁵
Limited physical exam ¹⁸		•	•	•	•			•	•	•			•
ECOG performance	•	•	•	•	•		•	•	•	•		•	•
Hematology	•	• ¹⁹	• ¹⁹	• ¹⁹	• ¹⁹		• ¹⁹	• ¹⁹	• ¹⁹	• ¹⁹		•	•
Serum chemistry	•	• ¹⁹	• ¹⁹	• ¹⁹	• ¹⁹		• ¹⁹	• ¹⁹	• ¹⁹	• ¹⁹		•	•
Urinalysis	•	•					•					•	• ¹²
Immune safety assays		•					•					•	• ¹²
Pregnancy test ²⁰	•	•	•	•	•		•	•	•	•		•	• ¹²
Chest radiograph	•												
ECG (12-lead)	• ²¹						•					•	
CT/MRI (brain) ^{22,23}	• ²¹					• ^{23,24}					• ^{23,24}		• ²⁴
CT/MRI (chest, abdomen, pelvis) ²³	• ²¹					• ²³					• ²³		•
Bone scan ²⁵	• ²¹					• ²³					• ²³		•
PSA ²⁶ Tumor-specific blood tests ²⁶	•	•					•					•	•
Response assessment						• ^{23,27}					• ^{23,27}	•	•
Tumor or other biopsy ²⁸	•												
Flow cytometry ⁴²		•					• ¹³					•	

NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.

continued

Table 1: Time and Events Schedule													
Period	Screening	Treatment										Follow-up ¹	
		Cycle 1					Cycles 2-12						
Visit Name	Screening	C1:1	C1:2	C1:3	C1:4	C1:5	Cn:1	Cn:2	Cn:3	Cn:4	Cn:5	Follow-up 1	Follow-up 2-6
Timepoint Per Cycle (Day)	-28 to -1	1 ⁴²	15 ⁴²	29 ⁴²	43 ⁴²	56 ²³	1 ³⁴	15 ⁴²	29 ⁴²	43 ⁴²	56 ²³	Last Cn:5 Visit + 1 to 7 Days	Previous Follow-up Visit + 56 Days ⁴⁵
PBMC (cryopreserved) ⁴²		•					• ¹³					•	
Serum for cytokine panel ⁴²		•					• ¹³					•	
Serum for quantitative immunoglobulins ⁴²		•					• ¹³					•	
Concomitant medications ²⁹	•	•	•	•	•		•	•	•	•		•	• ³⁰
Adverse events ²⁹		•	•	•	•		•	•	•	•		•	• ³⁰
Off Study ²⁴													
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.													

¹ When a subject will discontinue study drug treatment, the date and reason for study drug discontinuation should be documented on the CRF, all remaining visits of that treatment cycle should be completed (without infusions and with only a single pharmacokinetic sample taken at applicable visits), and the subject should enter the Follow-up Period. When a subject will be withdrawn from the study (during the Treatment or Follow-up Period), all evaluations associated with that study visit should be performed and the date and reason for study discontinuation should be documented on the CRF.

² To be done ± 2 days of scheduled visit.

³ This visit is NOT a clinic visit. The purpose of this visit is for radiologic assessment and subsequent evaluation of results by the Investigator (response assessment). Radiologic procedures and response assessments should occur between Days 52 and 56 and BEFORE administering the first dose of study drug in the next cycle.

⁴ Day 1 of each cycle should occur 56 days following Day 1 of the previous cycle, but no sooner than 14 days after the last dose of the previous cycle.

continued

Table 1 Footnotes: *(continued)*

- ⁵ To be done \pm 7 days of scheduled visit.
- ⁶ Informed consent form and Health Information Portability and Accountability Act (HIPAA) authorization are to be provided before initiation of any Screening assessments and may be obtained before Day -28.
- ⁷ To include collection of prior medication and prior/concurrent medical conditions. For subjects with mCRPC, to include at least 3 PSA measurements over the preceding 6 months.
- ⁸ Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions CRF.
- ⁹ Hepatitis B surface antigen and Hepatitis C antibody (with reflex Hepatitis C RNA if antibody test is positive).
- ¹⁰ In subjects with mCRPC only. Testosterone level must be \leq 50 ng/dL.
- ¹¹ Pharmacokinetic sampling to be performed according to Table 2.
- ¹² Follow-up Visit 2 only.
- ¹³ Cycle 2 only.
- ¹⁴ Immunogenicity samples are to be collected at Follow-up Visit 2 and 34 only.
- ¹⁵ Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure. On the day of each infusion, vital signs will be obtained preinfusion, every 15 minutes during the infusion, at the end of the infusion, and 15, 30, and 60 minutes after completion of the infusion. When slowing or re-starting an infusion due to an infusion reaction/adverse event, vital signs should be monitored every 15 minutes or as directed by the Investigator until the infusion is completed, and 15, 30, and 60 minutes after completion of the infusion and/or until the subject is stabilized. Vital signs should be collected \pm 5 minutes from the scheduled times noted above.
- ¹⁶ Dose adjustments are required to be made if there has been \geq 10% weight or greater change in weight (increase or decrease) since the previous cycle. (Weights should be determined at the onset of each new treatment cycle as a minimum, but may be done more frequently at sites whose standard dose administration procedures require weight determination before each dose.)
- ¹⁷ Complete physical examination includes assessment of the skin, head, eyes, nose, throat, neck, joints, lungs, heart, abdomen (including liver and spleen), lymph nodes, and extremities. A brief neurological examination should also be performed. All abnormal findings noted at the Screening physical examination should be recorded on the Medical History CRF, and any new or worse signs or symptoms are to be recorded on the Adverse Event CRF.

continued

Table 1 Footnotes: (*continued*)

- ¹⁸ Limited physical examination includes assessment of the lungs, heart, abdomen, and skin. All abnormal findings noted at the Cycle 1/Day 1 evaluation should be recorded on the Medical History CRF. Abnormal findings of clinical significance that occur after the Cycle 1/Day 1 evaluation (or new adverse events) should be explicitly documented on the Adverse Event CRF.
- ¹⁹ During the study Treatment Period, hematology and serum chemistries will be evaluated by both local and central laboratories at these timepoints. The hematology and clinical chemistry laboratories **must be performed and reviewed before dosing.** (If practicable, central laboratory samples may be drawn up to 48 hours prior to infusions for preinfusion safety review in lieu of local laboratories.) These labs may be performed up to 48 hours prior to the planned dosing. Any new \geq Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the Medarex Medical Monitor should be contacted.
- ²⁰ Serum β -HCG pregnancy test ~~within 7 days before the first infusion~~ at Screening; urine pregnancy test at all other time points for women of childbearing potential. Urine pregnancy tests on days of study drug administration must be performed and negative before study drug administration.
- ²¹ Baseline imaging and 12-lead ECG done as part of the subject's previous routine care before signing the informed consent form and completed within 28 days before the administration of MDX-1106 need not be repeated. Whenever possible, baseline imaging should be done at the same institution/facility and with the same modality which will be used to measure response during the subject's participation in the study.
- ²² Brain scan (MRI preferred) required at Screening if not performed within the previous 2 months (and NOT required for subjects with mCRPC).
- ²³ The same technique (CT/MRI) used at baseline should be utilized throughout the study.
- ²⁴ Brain scans during Treatment and Follow-up Periods are required only if there is a prior history of lesions present at Screening, or as clinically indicated. If required, subsequent brain CT scans/MRI should be repeated every other cycle (end of Cycle 2, 4, 6, etc.) and at Follow-Up Visits 2, 4 and 6.
- ²⁵ Bone scans must be done at all visits indicated for subjects with mCRPC. For subjects with MEL, RCC, CRC, and NSLC, bone scans at baseline or subsequent visits will be performed only if clinically indicated. If required, subsequent bone scans should be repeated every other cycle (end of Cycle 2, 4, 6, etc.) and at Follow-Up Visits 2, 4, and 6.
- ²⁶ Blood tests are to be tumor specific (e.g., CEA and CA 19-9 for colorectal cancer; PSA for prostate cancer).
- ²⁷ Tumor response status will be assessed by the Investigators using RECIST with modification. Response assessments must be performed by the Investigators at the end of each cycle to document eligibility for entry into the next treatment cycle. Copies of scans may be requested by Medarex for independent review.

continued

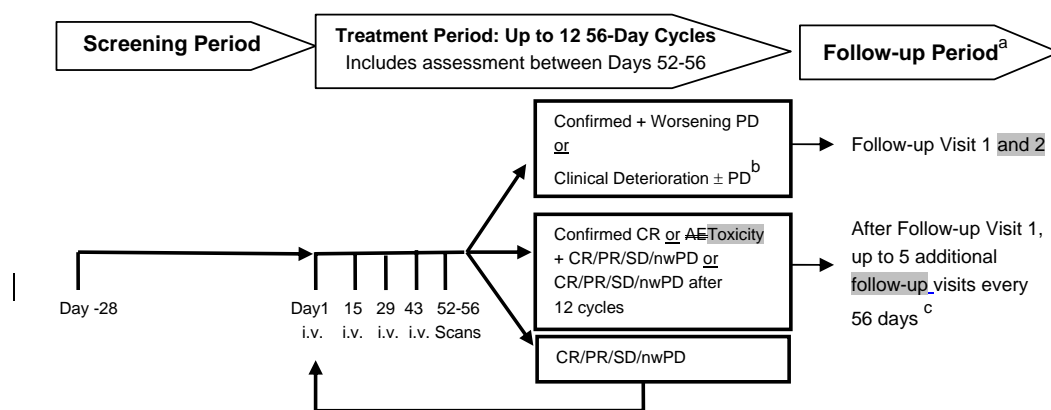
Table 1 Footnotes: *(continued)*

- ²⁸ A tumor biopsy is required at baseline if there is no other record of histological diagnosis of tumor. **Consent to request previous tumor biopsy specimens is required.** Optional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed at Screening and at other times during the protocol as clinically indicated. Optional tumor or other biopsy requires specific agreement by the subject in the informed consent.
- ²⁹ All subjects who ~~are withdrawn from~~ intend to discontinue the study within 70 days after the administration of the last dose of study drug should be followed until resolution and/or stabilization of any study drug-related adverse events and adverse events that lead to the discontinuation, and should be monitored for 70 days following the last dose of MDX-1106 for the occurrence of study drug-related adverse events. ~~Subjects should be contacted at least once within 70 days following the last dose of MDX-1106. Telephone contact is acceptable and should be within ±10 days of the 70 day time point. These subjects should complete Follow-up Visits 1 and 2.~~
- ³⁰ For all follow-up periods beyond 70 days from the last dose of study drug, only study drug-related serious adverse events or late-occurring immune-related adverse events should be reported.
- ²⁴ ~~When a subject discontinues study drug treatment, the date and reason for study drug discontinuation should be documented on the CRF, all remaining visits of that treatment cycle should be completed (without infusions and with only a single pharmacokinetic sample taken at applicable visits), and the subject should enter the Follow up Period. When a subject is withdrawn from the study (during the Treatment or Follow up Period), all evaluations associated with that study visit should be performed and the date and reason for study discontinuation should be documented on the CRF.~~

Table 2: Pharmacokinetic Blood Sampling Schedule							
Time point	Treatment Period¹					Follow-up Period	
	Cycle 1				Cycles 2-12	Visit 1	Visit 2
	Day 1	Day 15	Day 29	Day 43	Day 1		
Non-infusion day						•	•
Infusion day (pre-infusion [within 2 hours of start of infusion])	•	•	•	•	•		
Infusion day (60 minutes end of infusion) ²	•	•	•	•	•		

1. If a subject permanently discontinues study drug treatment, a single pharmacokinetic sample will be taken at each remaining visit for that cycle.
2. In the event of a delay during the infusion, the sample will be taken at the END of the infusion.

Figure 2: Individual Subject Flow (Up to 2 Years Treatment, Up to 1 Year Follow- up)



~~AE = adverse event~~; CR = complete response; PR = partial response; SD = stable disease;
nwPD = non-worsening progressive disease

MEDAREX

Page:	1 of 29
Protocol Number:	MDX1106-03
Version:	Amendment 1
IND Number:	101,850
Document Status:	Final
Date:	19 September 2008

Clinical Protocol MDX1106-03 Amendment 1

Summary of Change

A Phase 1b, Open-label, Multicenter, Multidose, Dose-escalation Study of MDX-1106 in Subjects with Selected Advanced or Recurrent Malignancies

Medarex Medical Monitor

Israel Lowy, MD, PhD
Senior Director, Clinical Science
Office Phone Number: +1-908-479-2447
Office Fax Number: +1-908-479-2410
Mobile Phone Number: +1-908-770-6477
Email: ILowy@medarex.com

Medarex Clinical Operations Contact

Daniel McDonald, MBA
Manager, Clinical Operations
Office Phone Number: +1-908-479-2529
Office Fax Number: +1-908-479-2415
Mobile Phone Number: +1-908-797-0122
Email: DMcDonald@medarex.com

SAE Reporting FAX Number

+1-908-479-2408

Central Emergency Phone Number

+1-800-246-2912

If any Medarex contact information is changed during the course of the study, this will be done by Medarex, with written notification to the Investigator(s), and will not require (a) protocol amendment(s).

Property of Medarex, Inc.
519 Route 173 West
Bloomsbury, NJ 08804

Confidential

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be used, divulged, published, or otherwise disclosed without the written consent of Medarex, Inc. These restrictions on disclosure will apply equally to all future information supplied to you or generated by you in connection with the study.

Primary Change

None

Global Changes

- Deleted references for DLT definitions (~~DLT, see definition under SAFETY EVALUATIONS~~).
- Deleted the word Phase, unless it referred the Phase of the study (i.e., 1b).
- Changed ‘Dose-escalation Phase’ to ‘dose-escalation cohort.’
- Changed ‘will’ to ‘may’ (in reference to continued enrollment).
- Changed ‘paused’ to ‘held’ (in reference to continued enrollment).
- Changed ‘Treatment Period phase of the study’ to ‘Treatment Period part of the study.’
- Changed ‘stopped’ to ‘held’ (in reference to continued enrollment).
- Changed ‘drug-related’ to ‘study drug-related.’
- Changed ‘prior to’ to ‘before.’
- The dosage range of paracetamol (325 to 1000 mg) that may be given as pretreatment after experiencing an infusion reaction has been specified.

The majority of changes reflect modifications to the Medarex protocol template. The changes to the protocol template do not affect the understanding or conduct of the study, the safety of subjects, the scope of the investigation, or the scientific quality of the study.

These changes, along with changes resulting from minor typographical errors or defining acronyms for the first time, are not summarized within the section changes, as they are not expected to affect the understanding or conduct of the study, the safety of subjects, the scope of the investigation, or the scientific quality of the study.

Section Changes

The following changes (indicated with a ~~strikeout~~ (delete text) or **shaded areas** (new text) have been made as Amendment 1 to the Protocol for Study MDX1106-03.

Page 5, Synopsis: OBJECTIVES

Changed first sentence of primary objective to read:

The primary objective is to ~~characterize~~ **assess** the safety and tolerability of multiple doses of MDX-1106 in subjects with selected advanced or recurrent malignancies.

Reason for change: Clarification of primary objective.

Page 5, Synopsis: OVERVIEW OF STUDY DESIGN, Dose Escalation

Revised last sentence in first paragraph to read:

If ≥ 2 of up to 6 subjects in the 1 mg/kg dose cohort experiences a DLT during the first cycle, that cohort will have exceeded the maximum tolerated dose (MTD, which is defined as the highest ~~tested~~ dose studied at which no more than 1 of 6 subjects has experienced a DLT in Cycle 1), and a lower dose level (0.3 mg/kg) will be tested.

Added new sentence to last paragraph to read:

No dose escalations or de-escalations are permitted within each subject's treatment; **dose adjustments are allowed only if there has been $\pm 10\%$ weight change since the previous cycle.** A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

Reason for change: Clarification of study design and dose adjustments.

Page 6, Synopsis: OVERVIEW OF STUDY DESIGN, Expansion Cohort

Revised second sentence in second paragraph to read:

Enrollment may be held in all expansion cohorts if the rate of DLTs is $\geq 33\%$ across all indications (including subjects from the dose-escalation cohort at the expansion dose) or if the rate of DLTs is $\geq 33\%$ in a specific indication after enrollment of the first 6 subjects in that indication (including subjects from the dose-escalation cohort at the expansion dose). After safety analysis by the Investigators and Medarex (with FDA and IRB notification), a decision will be made whether to **resume enrollment at the current dose, or** initiate a new expansion cohort of 16 subjects in 1 or more indications at a lower MDX-1106 dose (chosen according to the de-escalation rules above). For delayed DLTs, enrollment will be held using the same rules

as that for DLTs. After safety review of delayed DLTs by the Investigators and Medarex (with FDA and IRB notification), a decision will be made whether to resume enrollment at the current dose (with or without a limitation in the total number of allowed cycles) or to initiate a new expansion cohort in 1 or more of the indications at a lower dose (using the same de-escalation schedules as that for DLTs).

Reason for change: Clarification of stopping rules for delayed DLT, safety monitoring, and enrollment continuation in the Expansion Cohort.

Pages 6 and 7, Synopsis: OVERVIEW OF STUDY DESIGN, Administration of Additional Treatment Cycles

Revised Section to read:

Tumor response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) with modifications. End of cycle tumor response assessments for all subjects will occur within Days 52 to 56 (results of assessments must be reviewed and documented before the first dose of the next cycle).

The maximum number of cycles to be administered to an individual subject in this study is 12. Following each treatment cycle, the decision to treat a subject with additional cycles of MDX-1106 will be based on ongoing tumor response (evaluation performed between Days 52 and 56 and before the first dose in the next cycle). Day 1 of each cycle occurs upon completion of the previous cycle, and should be 56 days following Day 1 of the previous cycle. ~~Unless the subject develops a \geq Grade 3 Common Terminology Criteria for Adverse Events (CTCAE) adverse event or other adverse event related to MDX-1106 that precludes further treatment, subjects will be treated until confirmed complete response (CR) or progressive disease (PD) that is confirmed and worsens. If a subject is eligible to receive additional cycles, the first dose of the next cycle should be given 14 days after the last dose of the prior treatment cycle but should not be later than 28 days.~~ If a subject is eligible to receive additional cycles, the first dose of the next cycle should be given no earlier than 14 days after the last dose of the prior treatment cycle and no later than 21 days after the last dose to maximize dose intensity. No subject will be permitted dose escalations or de-escalations; dose adjustments are allowed only if there has been \pm 10% weight change since the previous cycle.

Subjects who meet the following conditions may be treated with additional cycles:

- Subjects with a complete response (CR), partial response (PR) or stable disease (SD) will continue to receive MDX-1106 treatment until the first occurrence of either: 1) achievement of a confirmed CR; 2) clinical deterioration suggesting that no further benefit from treatment is likely; 3) progressive disease (PD) that is confirmed and then

worsens; 4) development of a \geq Grade 3 study drug-related adverse event (Common Terminology Criteria for Adverse Events [CTCAE]); 5) other intolerability to therapy; or 6) receipt of the maximum number of cycles.

- Subjects with PD that has been confirmed but is not worsening and with otherwise stable or improved clinical status should continue to be treated with study drug until there is further progression or clinical deterioration.

Reason for change: The flow of text has been changed to improve clarity.

Added new subsection for the Follow-up Period to read:

Follow-up Period

The maximum duration of follow up will be approximately 1 year. All subjects should complete Follow-up Visit 1 (1 to 7 days after the last visit of the last treatment cycle). Completion of subsequent follow-up visits (Follow-up Visits 2 to 6) will depend on the status of the subject at the end of treatment. Except for subjects who discontinue due to worsening PD, all subjects will be followed from the last visit for approximately 1 year until relapse, initiation of a new therapy, or a total of 1 year follow-up, whichever occurs first. Subjects whose PD is confirmed and who have further progression at a subsequent imaging evaluation will only complete Follow-up Visit 1.

Reason for change: Completeness, as this section was previously not included within the synopsis.

Page 7, Synopsis: DURATION AND TREATMENT/STUDY PARTICIPATION

Revised second sentence to read:

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

Reason for change: Administrative changes to reflect consistency with Medarex revised protocol template.

Page 7, Synopsis: STUDY POPULATION

Revised section to read:

Up to 76 subjects will be enrolled if only the planned dose levels are used. Subjects will be enrolled who have pathologically-verified mCRPC, RCC, MEL, or NSCLC that is clinically advanced or recurrent **and progressing** after prior treatment with other therapies, and for which no alternative curative option is available.

Reason for change: Clarification of study population.

Page 8, Synopsis: EXPLORATORY IMMUNE FUNCTION EVALUATIONS

Revised first sentence to read:

Samples will be collected and evaluated for lymphocyte phenotype, serum cytokines, and quantitative immunoglobulins, and additional **optional** research samples will be collected and stored for future research which may include disease-related biomarkers (or antibody responses to selected antigens), exploratory humoral and cellular immune responses to tumor antigens and a panel of recall non-tumor antigens.

Reason for change: Clarification that collection and use of additional research samples is optional (for subjects).

Page 8, Synopsis: SAFETY EVALUATIONS

Revised last sentence of DLT to read:

A Grade 3 irAE that resolves to a Grade 1 or less within 28 days, while not constituting a DLT for dose escalation/expansion purposes, **may** ~~will~~ preclude further administration of MDX-1106 to the subject.

Reason for change: Clarification of discontinuation of study drug.

Revised Delayed DLT definition to read:

Delayed DLTs are adverse events that meet the criteria of DLTs that occur after Cycle 1. Delayed DLTs will not be used to ~~determine~~ **estimate** the MTD for dose escalation.

Reason for change: Clarification that the MTD can only be estimated for the doses evaluated.

Revised Immune-Related Adverse Event subsection to read:

~~Given the intended mechanism of action of MDX-1106, particular attention will be given to adverse events that may follow enhanced T-cell activation such as dermatitis and colitis, or other irAEs.~~ An irAE is defined as a clinically significant adverse event of any organ that is associated with **study** drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism. Serological ~~and~~, immunological, and histologic (biopsy) data should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

Given the intended mechanism of action of MDX-1106, particular attention will be given to adverse events that may follow enhanced T-cell activation such as dermatitis and colitis, or other irAEs.

Reason for change: Reorganized for clarity. Clarified data to be used to support irAE diagnosis.

Page 9, Synopsis: STATISTICAL METHODS

Revised first paragraph and added new second paragraph to read:

~~The sample size for this study is not determined from power analysis.~~ A sample size of up to 76 subjects is based on the study design for dose escalation, 4 oncology indications, and the number of possible tumor-specific expansion cohorts for further safety and efficacy evaluation.

In order to perform preliminary evaluation of BORR (anti-tumor activity), the sample size at the MTD or highest dose level cohort is determined by a power analysis. It is assumed that the subjects would have no response if they would not have received any therapy and that BORR for subjects in the MTD or highest dose level cohort would be 10%. Based on this assumption, a sample size of 16 subjects (in each tumor expansion cohort) in the MTD or highest dose level cohort is required to provide more than 80% power in a one-sample exact Binomial test at the significance level of 0.05.

Reason for change: Clarification of power analysis.

Page 10, ABBREVIATIONS

Added new abbreviation: GMP (Good Manufacturing Practices)

Reason for changes: Template consistency.

Pages 12 through 17, Time and Event Schedule: Table 1

Revised Table 1 to read as follows on next pages:

Reason for changes: To reflect changes in study design.

TIME AND EVENTS SCHEDULE

Table 1: Time and Events Schedule

Period	Screening	Treatment										Follow-up	
		Cycle 1					Cycles 2-12						
Visit Name	Screening	C1:1	C1:2	C1:3	C1:4	C1:5	Cn:1	Cn:2	Cn:3	Cn:4	Cn:5	Follow-up 1	Follow-up 2-6
Timepoint Per Cycle (Day)	-28 to -1	1 ¹	15 ¹	29 ¹	43 ¹	56 ²	1 ³	15 ¹	29 ¹	43 ¹	56 ²	Last Cn:5 Visit + 1 to 7 Days	Previous Follow-up Visit + 56 Days ⁴
Informed consent/HIPAA ⁵	•												
Inclusion/exclusion criteria	•												
Demographics/medical history ⁶	•												
Diagnosis confirmation and stage	•												
Baseline signs and symptoms	• ⁷												
Tumor-specific therapy information	•												•
Hepatitis B and C testing ⁸	•												
Testosterone testing ⁹	•												
MDX-1106 infusion		•	•	•	•		•	•	•	•			
Serum sample for pharmacokinetics ¹⁰		•	•	•	•		•					•	• ¹¹
Serum sample for immunogenicity ¹²		•					• ¹³					•	• ¹⁴
Vital signs ¹⁵	•	•	•	•	•		•	•	•	•		•	•
Height	•												
Weight	•	•					• ¹⁶						
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.													

continued

Table 1: Time and Events Schedule

Period	Screening	Treatment										Follow-up	
		Cycle 1					Cycles 2-12						
Visit Name	Screening	C1:1	C1:2	C1:3	C1:4	C1:5	Cn:1	Cn:2	Cn:3	Cn:4	Cn:5	Follow-up 1	Follow-up 2-6
Timepoint Per Cycle (Day)	-28 to -1	1 ¹	15 ¹	29 ¹	43 ¹	56 ²	1 ³	15 ¹	29 ¹	43 ¹	56 ²	Last Cn:5 Visit + 1 to 7 Days	Previous Follow-up Visit + 56 Days ⁴
Complete physical exam ¹⁷	•						•					•	
Limited physical exam ¹⁸		•	•	•	•			•	•	•			•
ECOG performance	•	•	•	•	•		•	•	•	•		•	•
Hematology	•	• ¹⁹	• ¹⁹	• ¹⁹	• ¹⁹		• ¹⁹	• ¹⁹	• ¹⁹	• ¹⁹		•	•
Serum chemistry	•	• ¹⁹	• ¹⁹	• ¹⁹	• ¹⁹		• ¹⁹	• ¹⁹	• ¹⁹	• ¹⁹		•	•
Urinalysis	•	•					•					•	• ¹¹
Immune safety assays ¹²		•					•					•	• ¹¹
Pregnancy test ²⁰	•	•	•	•	•		•	•	•	•		•	• ¹¹
Chest radiograph	•												
ECG (12-lead)	• ²¹						•					•	
CT/MRI (brain) ^{22, 24}	• ²¹					• ^{2,23}					• ^{2,23}		• ²³
CT/MRI (chest, abdomen, pelvis) ²⁴	• ²¹					• ²					• ²		•
Bone scan ²⁵	• ²¹					• ²					• ²		•
PSA ²⁶	•	•					•					•	•
Response assessment						• ^{2,27}					• ^{2,27}	•	•
Tumor or other biopsy ²⁸	•												
Flow cytometry ¹²		•					• ¹³					•	
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.													

continued

Table 1: Time and Events Schedule

Period	Screening	Treatment										Follow-up	
Visit Name	Screening	Cycle 1					Cycles 2-12					Follow-up 1	Follow-up 2-6
Timepoint Per Cycle (Day)	-28 to -1	1 ¹	15 ¹	29 ¹	43 ¹	56 ²	1 ³	15 ¹	29 ¹	43 ¹	56 ²	Last Cn:5 Visit + 1 to 7 Days	Previous Follow-up Visit + 56 Days ⁴
PBMC (cryopreserved) ¹²		.					. ¹³					.	
Serum for cytokine panel ¹²		.					. ¹³					.	
Serum for quantitative immunoglobulins ¹²		.					. ¹³					.	
Concomitant medications ²⁹ ³⁰
Adverse events ²⁹	 ³⁰
Off-Study ³¹													
NOTE: Unless otherwise indicated, laboratory test collections are to be done before the start of study drug infusion on infusion days.													

¹ To be done \pm 2 days of scheduled visit.

² This visit is NOT a clinic visit. The purpose of this visit is for radiologic assessment and subsequent evaluation of results by the Investigator (response assessment). Radiologic procedures and response assessments should occur between Days 52 and 56 and BEFORE administering the first dose of study drug in the next cycle.

³ Day 1 of each cycle should occur 56 days following Day 1 of the previous cycle, but no sooner than 14 days after the last dose of the previous cycle.

⁴ To be done \pm 7 days of scheduled visit.

⁵ Informed consent form and Health Information Portability and Accountability Act (HIPAA) authorization are to be provided before initiation of any Screening assessments and may be obtained before Day -28.

⁶ To include collection of prior medication and prior/concurrent medical conditions. For subjects with mCRPC, to include at least 3 PSA measurements over the preceding 6 months.

Table 1 Footnotes: *(continued)*

- ⁷ Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions CRF.
- ⁸ Hepatitis B surface antigen and Hepatitis C antibody (with reflex Hepatitis C RNA if antibody test is positive).
- ⁹ In subjects with mCRPC only. Testosterone level must be ≤ 50 ng/dL.
- ¹⁰ Pharmacokinetic sampling to be performed according to Table 2.
- ¹¹ Follow-up Visit 2 only.
- ¹² To be collected pre-infusion.
- ¹³ Cycle 2 only.
- ¹⁴ Follow-up Visit 2 and 3 only.
- ¹⁵ Vital sign measurements to include temperature, pulse, and blood pressure. On the day of each infusion, vital signs will be obtained pre-infusion, every 15 minutes during the infusion, at the end of the infusion, and 15, 30, and 60 minutes after completion of the infusion. When slowing or re-starting an infusion due to an infusion reaction/adverse event, vital signs should be monitored every 15 minutes or as directed by the Investigator until the infusion is completed, and 15, 30, and 60 minutes after completion of the infusion and/or the subject is stabilized.
- ¹⁶ Dose adjustments are required to be made if there has been $\geq 10\%$ weight change since the previous cycle. [Weights should be determined at the onset of each new treatment cycle as a minimum, but may be done more frequently at sites whose standard dose administration procedures require weight determination before each dose.]
- ¹⁷ Complete physical examination includes assessment of the skin, head, eyes, nose, throat, neck, joints, lungs, heart, abdomen (including liver and spleen), lymph nodes, and extremities. A brief neurological examination should also be performed. All abnormal findings noted at the Screening physical examination should be recorded on the Medical History CRF, and any new or worse signs or symptoms are to be recorded on the Adverse Event CRF.
- ¹⁸ Limited physical examination includes assessment of the lungs, heart, abdomen, and skin. All abnormal findings noted at the Cycle 1/Day 1 evaluation should be recorded on the Medical History CRF. Abnormal findings of clinical significance that occur after the Cycle 1/Day 1 evaluation (or new adverse events) should be explicitly documented on the Adverse Event CRF.

Table 1 Footnotes: *(continued)*

- ¹⁹ During the study Treatment Period, hematology and serum chemistries will be evaluated by both local and central laboratories. The hematology and clinical chemistry laboratories **must be performed and reviewed before dosing**. Any new \geq Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the Medarex Medical Monitor should be contacted.
- ²⁰ Serum β -HCG pregnancy test within 7 days before the first infusion; urine pregnancy test at all other time points for women of childbearing potential. Urine pregnancy tests on days of study drug administration must be performed and negative before study drug administration.
- ²¹ Baseline imaging and 12-lead ECG done as part of the subject's previous routine care before signing the informed consent form and completed within 28 days before the administration of MDX-1106 need not be repeated. Whenever possible, baseline imaging should be done at the same institution/facility and with the same modality which will be used to measure response during the subject's participation in the study.
- ²² Brain scan (MRI preferred) required at Screening if not performed within the previous 2 months (and NOT required for subjects with mCRPC).
- ²³ Brain scans during Treatment and Follow-up Periods are required only if there is a prior history of lesions present at Screening, or as clinically indicated. If required, subsequent brain CT scans/MRI should be repeated every other cycle (end of Cycle 2, 4, 6, etc.) and at Follow-Up Visits 2, 4 and 6.
- ²⁴ The same technique (CT/MRI) used at baseline should be utilized throughout the study.
- ²⁵ Bone scans must be done at all visits indicated for subjects with mCRPC. For subjects with MEL, RCC, and NSLC, bone scans at baseline or subsequent visits will be performed only if clinically indicated. If required, subsequent bone scans should be repeated every other cycle (end of Cycle 2, 4, 6, etc.) and at Follow-Up Visits 2, 4, and 6.
- ²⁶ To be performed only in subjects with mCRPC.
- ²⁷ Tumor response status will be assessed by the Investigators using RECIST with modification. Response assessments must be performed by the Investigators at the end of each cycle to document eligibility for entry into the next treatment cycle. Copies of scans may be requested by Medarex for independent review.
- ²⁸ A tumor biopsy is required at baseline if there is no other record of histological diagnosis of tumor. Optional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed at Screening and at other times during the protocol as clinically indicated. Optional tumor or other biopsy requires specific agreement by the subject in the informed consent.

Table 1 Footnotes: *(continued)*

- ²⁹ All subjects who are withdrawn from the study within 70 days after the administration of the last dose of study drug should be followed until resolution and/or stabilization of any study drug-related adverse events and adverse events that lead to the discontinuation, and should be monitored for 70 days following the last dose of MDX-1106 for the occurrence of study drug-related adverse events. Subjects should be contacted at least once within 70 days following the last dose of MDX-1106. Telephone contact is acceptable and should be within ± 10 days of the 70-day time point.
- ³⁰ For all follow-up periods beyond 70 days from the last dose of study drug, only study drug-related serious adverse events should be reported.
- ³¹ When a subject discontinues study drug treatment, the date and reason for study drug discontinuation should be documented on the CRF, all remaining visits of that treatment cycle should be completed (without infusions and with only a single pharmacokinetic sample taken at applicable visits), and the subject should enter the Follow-up Period. When a subject is withdrawn from the study (during the Treatment or Follow-up Period), all evaluations associated with that study visit should be performed and the date and reason for study discontinuation should be documented on the CRF.

Pages 26 and 27, Section 1.5: Summary of Safety

Revised second paragraph to read:

As of 15 April 2008, 17 subjects have experienced 40 serious adverse events; ~~only 2 of these serious adverse event (diarrhea/colitis, spinal cord compression) were considered related to MDX-1106 treatment by the Investigator.~~ The Investigators considered 1 event of diarrhea/colitis related to MDX-1106 treatment and considered 1 event of spinal cord compression possibly related to MDX-1106 treatment. Significant adverse events that are likely to be immune-related and that reflect on safety include polyarticular arthropathy (2 subjects, both low-grade adverse events) and diarrhea/colitis (1 subject).

Reason for change: Information clarified.

Revised fourth paragraph to read:

A serious adverse event of diarrhea/colitis has been reported in a subject with ocular melanoma. The subject developed colitis more than 5 weeks after receiving his 5th dose of MDX-1106 1 mg/kg over almost 8 months. ~~This is the first instance of colitis in the MDX-1106 clinical program, and it is notable that the colitis did not occur until approximately 9 months after the subject's 1st dose of MDX-1106.~~ The colitis has been managed with steroids and infliximab, administered according to treatment guidelines developed for the management of irAEs observed in the ipilimumab development program. The colitis did not occur until approximately 9 months after the subject's 1st dose of MDX-1106. It is ~~also~~ noteworthy that 21 subjects have each received at least a single dose of MDX-1106 10 mg/kg, and 3 of these subjects have received 3 doses of 10 mg/kg without such an adverse event. The potential for additional instances of colitis to emerge with repeated dosing will be closely monitored in this study.

Reason for change: Information clarified.

Page 27, Section 2.1 Primary Objectives

Revised as per Synopsis changes.

Reason for changes: Consistency within document.

Pages 28 through 30, Section 3, Overview of Study Design

Revised as per Synopsis changes.

Reason for changes: Consistency within document.

Pages 31 and 32, Section 3.2: Administration of Additional Treatment Cycles

Revised PD bullet point to read:

- PD: Accumulating evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological (or PSA – for mCRPC) progression, or the appearance of new lesions or some enlarging lesions while certain target lesions are regressing (“mixed response”). It is thus reasonable, in the absence of clinical deterioration, to continue to treat these subjects until radiologic progression is **both confirmed and found to have worsened** at a subsequent imaging evaluation ~~is found to have progressed further~~. Evidence of PD will be based on a comparison with baseline (or nadir) scans, in which there is either an increase of 20% or more in the sum of the longest diameters (SLD) of target lesions taking as reference the smallest sum of the longest diameters (nadir) recorded since Screening, ~~and/or~~ unequivocal progression of non-target lesions, with or without the development of 1 or more new lesions (at least 2 new bone lesions for mCRPC). ~~The appearance of 1 or more new lesions will not in itself (in the absence of increased size of target/non-target lesions) constitute PD for this study.~~ PD should be confirmed by repeat scans at the next scheduled imaging evaluation 8 weeks later (but no sooner than 4 weeks).

Subjects with PD should be managed in the study as follows:

- ~~PD seen at the end of Cycle 1:~~ In the absence of clinical deterioration, ~~subjects may continue treatment. In the presence of clinical deterioration, the decision whether will NOT count as one of these PD findings to determine further progression stop treatment should be discussed with the Medarex Medical Monitor as described in Section 8.7.~~
- ~~PD at the end of Cycle 2 or later:~~ ~~determine further progression.~~ Subjects with stable or improved clinical status, ~~but evaluation at the end of Cycle 2 or later demonstrates evidence of PD,~~ will continue to be treated with study drug until their next scheduled imaging evaluation.
 - If, at each subsequent imaging evaluation (Cycle 3 or later), **there is no further increase** in the SLD, **no unequivocal increase in non-target lesions**, and no additional new lesions develop (non-worsening PD), and the subject’s clinical status remains stable or has improved, treatment should be continued, ~~even if PD is confirmed.~~

~~If after confirmation of PD~~ **At any subsequent imaging evaluation (Cycle 3 or later), there is further increase** in the SLD, **unequivocal increase in non-target lesions**, or development of additional new lesions (**worsening PD**) ~~at a subsequent imaging evaluation, then~~ the subject should stop treatment and return for Follow-up Visit 1.

For mCRPC, isolated PSA progression in the absence of radiologic or clinical deterioration will not be used to determine PD. Stopping treatment for clinical deterioration should be guided by clinical observations outlined in Section 8.7 and Investigator judgment.

Reason for change: Clarification of when to discontinue treatment due to progressive disease (PD).

Revised CTCAE bullet point to read:

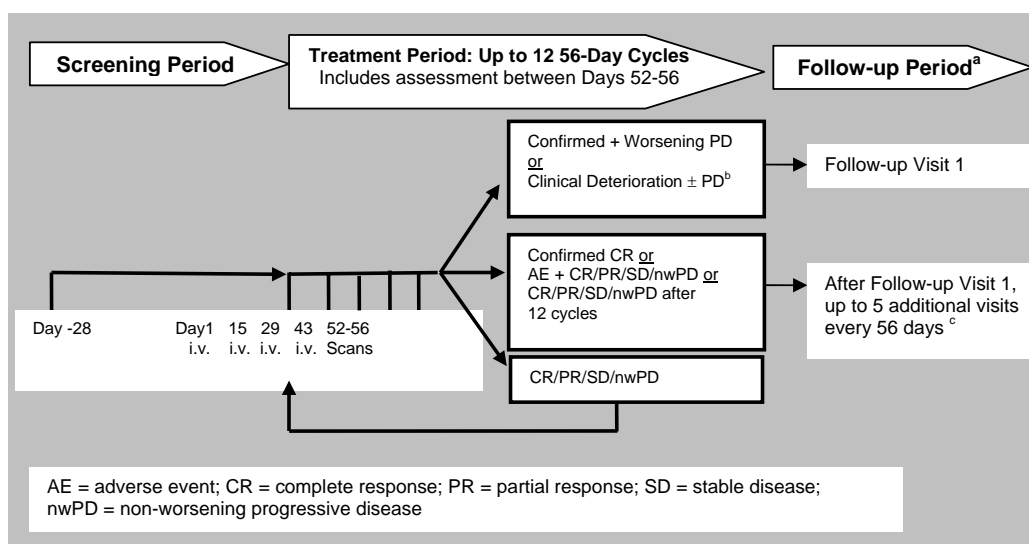
Development of a \geq Grade 3 (CTCAE) intolerability or adverse event related to MDX-1106 that precludes further treatment with the study drug, but subject does not have **worsening confirmed progression**: Subjects will complete the remaining visits of their current treatment cycle (without infusions) if possible. Subjects will then enter the Follow-Up Period until **worsening** progression or completion of all (6) Follow-up Visits.

Reason for change: Clarification of when to discontinue treatment due to confirmed and worsening PD.

Added the following text and figure:

The maximum duration of follow up will be approximately 1 year. All subjects should complete Follow-up Visit 1 (1-7 days after the last visit of the last treatment cycle). Completion of subsequent follow-up visits (Follow-up Visits 2 to 6) will depend on the status of the subject at the end of treatment. Except for subjects who discontinue due to PD (as described above), all subjects will be followed from the last visit for approximately 1 year until relapse, initiation of a new therapy, or a total of 1 year follow-up, whichever occurs first. Subjects whose PD is confirmed and who have further progression at a subsequent imaging evaluation will only complete Follow-up Visit 1. The flow of subjects through the study is diagrammed in Figure 2 below.

Figure 2: Individual Subject Flow (Up to 2 Years Treatment, Up to 1 Year Follow-up)



^a For subjects who discontinue from the study within 70 days after the administration of the last dose of study drug, the subject should be followed to resolution/stabilization of: 1) ongoing study drug-related adverse events; 2) new study drug related adverse that occur within the 70-day period; and 3) adverse events that led to the discontinuation. A telephone contact for the safety update would be acceptable if the subject cannot manage an office visit. Only study drug-related serious adverse events or other clinically significant adverse events will be collected >70 days after the last administration of study drug.

^b PD that has been confirmed and then worsens or there is clinical deterioration at a subsequent visit. Follow up Visit 1 should be done unless precluded by disease progression or clinical deterioration.

^c Follow-up should continue until relapse, initiation of a new therapy, or a total of 1 year follow-up (Follow-up Visit 1 only for worsening PD), whichever comes first.

Reason for change: Follow-up information previously missing from this section. Figure added for clarity of study design.

Page 33, Section 4: Study Population

Revised as per Synopsis changes.

Reason for changes: Consistency within document.

Pages 33 and 34, Section 4.1: Inclusion Criteria

Reordered Inclusion Criteria 1 through 4.

Reason for changes: Revised to flow in a logical decision-making order.

Revised inclusion criteria to read:

5. Must have at least 1 measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) with modification (see Appendix 1) progressing or new since last antitumor therapy. The measurable lesion(s) must be outside the field of radiation therapy (RT) if there was prior treatment with RT ~~if there was prior treatment with RT~~. Subjects with mCRPC and with only non-measurable bone lesions must have either progression with 2 or more new lesions or have PSA progression within the 6-week period before study drug administration;
6. At least 1 and up to 5 prior systemic therapies for advanced/recurrent **and progressing** disease (unlimited hormonal therapies allowed);
11. Prior surgery that required general anesthesia must be completed at least **2** ~~4~~ weeks before study drug administration. Surgery requiring local/epidural anesthesia must be completed at least 72 hours before study drug administration and subjects should be recovered;

Reason for changes: Criteria were deleted or modified to more specifically explain inclusions.

Page 36, Section 7.2: Packaging and Labeling

Revised section to read:

The study drug will be packaged and labeled according to current good **manufacturing clinical** practices (**GMPCCP**). Details of the packaging and labeling of clinical supplies may be found in the Pharmacy Manual.

Reason for changes: Text corrected.

Page 36, Section 7.4: Storage

Revised section to read:

MDX-1106 vials must be stored at a temperature of 2°C to 8°C and should be protected from light. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of MDX-1106 include laboratory coats and gloves. ~~Note: once MDX-1106 has been prepared for administration, the total storage time (combination of refrigeration and room temperature) is not to exceed 24 hours.~~ **Following dilution and transfer to the i.v. bag, MDX-1106 can be stored for 6 hours at room temperature/under room light and 18 hours at 2°C to 8°C in the refrigerator. Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent.**

~~Stability data for MDX-1106 supports 6 hours at room temperature/under room light and 18 hours at 2°C to 8°C in the refrigerator following dilution and transfer to the i.v. bag. Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent.~~

Reason for changes: Consistency with the Investigator's Brochure.

Page 38, Section 7.7: Dose Adjustments, Infusion Delays, and Missed Doses

Changed title to read:

Dose Adjustments, Infusion Delays, and Missed Doses

Added new first sentence to read:

There will be no dose adjustments allowed for MDX-1106 except for weight changes ($\pm 10\%$) at the beginning of each cycle.

Reason for change: Consistency within document regarding condition for dose adjustments.

Pages 38 through 40, Section 8: Toxicity and Management

Same changes made in Section 8.1, 8.2, 8.3 and 8.4 as in Synopsis.

Reason for Change: Consistency with change to synopsis.

Page 42, Section 8.6: Infusion Reactions

Changed the last sentence under Grade 2 symptoms and add a new sentence to read:

The following prophylactic pre-medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) and/or corticosteroids should be administered at least 30 minutes before additional MDX-1106 administrations. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

Reason for change: Clarification of premedications permitted and when to administer these medications.

Pages 43 and 44, Section 8.7: Stopping Rules for Clinical Deterioration

Revised end of second paragraph and added new third paragraph to read:

The decision to stop treatment should be discussed with the Medarex Medical Monitor.

~~For example:~~

Examples of events that may, in the Investigator's opinion, indicate a lack of clinical benefit include, but are not limited to, the following:

Reason for change: Administrative change to reflect consistency with Medarex revised protocol template.

Pages 44 and 45, Section 10: Concomitant Therapy

Revised item 1 to read:

1. Prophylactic premedication ~~with acetaminophen and diphenhydramine and steroids~~ may be given if indicated by previous experience with MDX-1106 in an individual subject as described in Section 8.6.

Reason for change: Redundancy with changes in Section 8.6.

Added new last paragraph to read:

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

Reason for change: Administrative change to reflect consistency with Medarex revised protocol template.

Pages 48 and 49, Section 1.1.3.1: Cycle 1

Revised bulleted item to read:

- Immune Safety Assays: Rheumatoid Factor (RF), Thyroid Stimulating Hormone (TSH), Free T4 Level, **adrenocorticotrophic hormone (ACTH)**, C-Reactive Protein (CRP), Antinuclear Antibody (ANA) titer and pattern.

The following tests, may also be performed on selected stored samples at a later date: anti-NA antibody, anti-phospholipid antibody, anti-SSA antibody (Ro), anti-islet cell antibody; anti-SSB antibody (La), anti-neutrophil cytoplasm antibody, antithyroglobulin antibody, C3 and C4, anti-LKM antibody, and CH50.

Abnormal endocrine results ~~should~~**will** be followed up with prolactin and a.m. cortisol tests, and may require an endocrine consult **and additional testing**.

Reason for change: Additional evaluation to increase subject safety. Clarification of how to follow-up abnormal endocrine results.

Moved collection of samples for flow cytometry, cytokine assays, and quantitative immunoglobulins. Revised collection of PBMCs:

- Flow cytometry: Fresh whole blood will be sent to the central laboratory. Phenotypic markers to be tested include: CD3, CD4, CD8, CD19, CD14, CD16+56, CD4+CD25, CD4+CD25+CD45RO, CD8+CD25, CD4+HLA-DR, CD8+HLA-DR, CD4+45RO, and CD8+45RO.
- Serum for subsequent cytokine panel assays: may include: IL-1, 4, 5, 6, 10, 13 and IFN gamma, TNF alpha, and TGF beta.
- Serum for quantitative immunoglobulins: Samples will be analyzed for IgM, IgG1, IgG2, IgG3, IgG4, IgA
- The following optional tests will be performed for research purposes:
 - ~~Flow cytometry: Fresh whole blood will be sent to the central laboratory. Phenotypic markers to be tested include: CD3, CD4, CD8, CD19, CD4+CD25, CD4+CD25+CD45RO, CD8+CD25, CD4+HLA-DR, CD8+HLA-DR, CD4+45RO, and CD8+45RO.~~
 - Cryopreserved peripheral blood mononuclear cells (PBMCs) and plasma: Samples may will be subsequently analyzed for immunoreactivity to a panel of peptide recall antigens (Cytomegalovirus, Epstein Barr Virus, and Influenza virus [CEF]). Tumor-specific antigen reactivity or other biomarker testing will be governed by type of tumor and availability of test antigens.
 - ~~Serum for subsequent cytokine panel assays: may include: IL-1, 4, 5, 6, 10, 13 and IFN gamma, TNF alpha, and TGF beta.~~
 - ~~Serum for quantitative immunoglobulins: Samples will be analyzed for IgM, IgG1, IgG2, IgG3, IgG4, IgA~~

Reason for change: To specify which samples were optional.

Page 50, Sections 11.1.4: Follow-up Period

Revised first paragraph to read:

Up to 6 follow-up visits will be conducted after completion of the Treatment Period or as indicated in Section 3.2. The maximum duration of follow up will be approximately 1 year. All subjects should complete Follow-up Visit 1 (1 to 7 days after the last visit of the last treatment cycle). Completion of subsequent follow-up visits (Follow-up Visits 2 to 6) will depend on the status of the subject at the end of treatment. Except for subjects who discontinue due to worsening PD, all subjects will be followed from the last visit for approximately 1 year until

relapse, initiation of a new therapy, or a total of 1 year follow-up, whichever occurs first. Subjects whose PD is confirmed and who have further progression at a subsequent imaging evaluation will only complete Follow-up Visit 1. The evaluations performed in Cycles 2 to 12 (with the exception of MDX infusions, weight, and urine pregnancy test) will be repeated during the Follow-up Visits as indicated in Table 1, and the results will be recorded on the CRF.

Reason for change: Clarification of duration of Follow-up Period.

Pages 50 and 51, Section 11.1.6 Study Participation

Changed section name and revised first paragraph to read:

Study Participation

Each subject will have their study participation documented, including the number of cycles completed, the duration of the Follow-up Period, and if discontinuing from the study, the reason for discontinuation. At the end of each cycle, the subject continuation status for each subject will be documented on the CRF.

~~Study Completion~~

~~Subjects who complete all 6 Follow-up Visits will be considered to have completed the study. Whether or not each subject completed the clinical study will be documented, including how long he/she was followed, and if withdrawn, the reason for withdrawal.~~

Reason for change: Administrative change to reflect consistency with Medarex revised protocol template.

Revised last paragraph to read:

Subjects who discontinue from the study should be followed until resolution and/or stabilization of any adverse event. All subjects who discontinue from the study should be monitored for 70 days following the last dose of MDX-1106 for the occurrence of study drug-related adverse events or other clinically significant adverse events considered by the Investigator to be related to MDX-1106 treatment. Subjects should be contacted at least once within 70 days following the last dose of MDX-1106. Telephone contact is acceptable and should be within ± 10 days of the 70-day time point.

Reason for change: Consistency within document.

Page 52, Section 11.2.3: Exploratory Evaluations of Immune Response

Moved sentence to read:

Additional efficacy evaluations may be performed to measure the impact of MDX-1106 upon the potency of the immune response that may ultimately be associated with beneficial clinical responses.

- Samples (including serum and PBMCs) for evaluation of cytokines, lymphocyte phenotype, quantitative immunoglobulins, disease-related biomarkers (or antibody responses to selected antigens), cellular immune responses to tumor antigens, and a panel of recall non-tumor antigens may be assessed.
- Available slides and tissue samples from tumor biopsies collected before enrollment in this study may also be examined for tumor markers and inflammatory infiltrates.
- Readily accessible tissue from the optional research-related biopsies may be collected at the time of apparent inflammatory infiltrate or clinical event of note at the tumor or other site. Tissue samples from these tumor biopsies, as well as from any other clinically indicated and consented biopsies conducted during the study will be collected, to assess morphology and the presence or absence of inflammatory infiltrates, and their cellular characterization. ~~Available slides and tissue samples from tumor biopsies collected before enrollment in this study may also be examined for tumor markers and inflammatory infiltrates.~~
- Additional sample collections and analyses may be performed at selected study sites with a site-specific amendment. All samples collected for these exploratory analyses will be stored, and may be used for subsequent research relevant to tumor immune response.

Reason for change: Clarification of procedures.

Page 55, Section 12.1.1 Safety Reporting for Adverse Events

Added new section to read:

All adverse events or other clinically significant adverse events occurring up to 70 days after administration of the last dose of study drug will be collected for subjects continuing in the study.

For subjects who discontinue from the study within 70 days after the administration of the last dose of study drug:

- Study drug-related adverse event information will be collected and should be followed to resolution/stabilization.
- Adverse events that lead to the discontinuation should be followed to resolution/stabilization.
- Other clinically significant adverse events will be collected and should be followed to resolution/stabilization
- A telephone contact for the safety update would be acceptable if the subject cannot manage an office visit.

Only study drug-related serious adverse events or other clinically significant adverse events will be collected > 70 days after the administration of the last dose of study drug.

Reason for change: Administrative change to reflect consistency with Medarex revised protocol template and coordination of follow up with visit schedule.

Page 56, Section 12.3.1: Reporting Responsibilities

Revised section to read:

Any serious adverse event occurring in a subject after he/she has provided informed consent and HIPAA authorization, and while receiving study treatment or during the 70 days following study drug administration must be reported. ~~All subjects who withdraw from the study should be monitored for 70 days following the last dose of MDX-1106 for the occurrence of serious adverse events considered by the Investigator to be related to MDX-1106 treatment. Subjects should be contacted at least once within 70 days following the last dose of MDX-1106. Telephone contact is acceptable and should be within ± 10 days of the 70-day time point. After 70 days following the last dose of MDX-1106, any serious adverse events considered by the Investigator to be related to MDX-1106 treatment must also be reported.~~ The timeframe for reporting after discontinuation of study drug may be extended if there is a strong suspicion that the study drug has not yet been eliminated or the pharmacodynamic effects of the study drug persist beyond 70 days. All serious adverse events must also be reported for the timeframe in which the study drug interferes with the standard medical treatment given to a subject.

Each serious adverse event must be reported by the Investigator to the Medarex Pharmacovigilance (PVG) Desk (SAE Reporting FAX Number), or designee, within 24 hours of learning of its occurrence, even if it is not felt be related to study drug. Serious adverse

events occurring after 70 days from the last dose of MDX-1106 must be reported if deemed related to study drug. The report must include the adverse event term, subject identifier, attribution, description, concomitant medication used to treat the adverse event, and any other relevant information. Follow-up information about a previously reported serious adverse event must also be reported to Medarex within 24 hours of receiving the information. Medarex, or its designee, may contact the Investigator to obtain further information about a reported serious adverse event. If warranted, an Investigator Alert may be issued to inform all Investigators involved in any study with the same study drug that a serious adverse event has been reported.

Reason for change: Administrative change to reflect consistency with Medarex revised protocol template.

Page 57, Section 12.5: Pregnancy

Revised last line in third paragraph to read:

When possible, **partner's** ~~such~~ pregnancies should be followed (to term) to determine the outcome.

Reason for change: Consistency with the revised study design.

Pages 58 and 59, Section 12.6 Immune-Related Adverse Events

Revised first paragraph to read:

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

Revised last paragraph to read:

Colitis is characterized by new onset of diarrhea, which may be accompanied by abdominal pain and or gastrointestinal bleeding. Events of Grade 3 or Grade 4 diarrhea as well as Grade 2 diarrhea with blood in stool should be evaluated for colitis. **All adverse events of colitis \geq Grade 2 are deemed to be of special interest, and should be reported using the serious adverse event reporting procedures (Described in Section 12.3), even if the adverse event itself is not deemed as serious.**

Reason for change: Consistency within document to reflect previous changes

Revised Management Algorithms for High Grade irAEs to read:

Management algorithms for high grade irAEs have been established for ipilimumab, where timely application of defined immunosuppressive regimens appear to be effective in limiting the morbidity and mortality from such events without compromising therapeutic efficacy. A **general** management algorithm with recommended guidelines for the treatment and monitoring of suspected irAEs, as well as algorithms for specific irAEs (i.e., diarrhea/colitis, endocrinopathy, and hepatotoxicity) are ~~is~~ provided in the Investigator Brochure. **All incidents of diarrhea should be managed according to this the diarrhea algorithm.** Additional clinical experience will be required to define the spectrum of irAE-like events that may emerge in the MDX-1106 program, and these algorithms are useful guides towards establishing an effective management approach as experience accumulates.

~~All adverse events of \geq Grade 2 are deemed to be of special interest, and should be reported using the serious adverse event reporting procedures, even if the adverse event itself is not deemed as serious.~~ In all cases, **study** drug-related \geq Grade 2 diarrhea/colitis will be managed with regular communication between the Investigator and the Medarex Medical Monitor, and with a minimum of at least 1 in-person visit per week until the diarrhea/colitis is $<$ Grade 2. Any Grade 2 adverse event of colitis (per CTCAE) that also results in additional medical requirements, such as more than 2 weeks of immunosuppressive doses of steroids ($>$ 10 mg/day of prednisone or equivalent), blood transfusion, or i.v. hyperalimentation, will be defined as a Grade 3 adverse event. Subjects are to be carefully monitored until recovery of the colitis to \leq Grade 1.

Reason for change: Consistency within document to reflect previous changes and to reflect changes in the Investigator's Brochure.

Page 59, Section 12.7: Rapid Notification of Adverse Events of Importance

Added new bullet point to read:

- \geq Grade 3 irAE other than diarrhea/colitis

Reason for change: FDA request.

Pages 59 and 60, Section 13: Statistical Methods

Added new second paragraph to read:

To further characterize safety and efficacy, additional subjects will be enrolled at the MTD (or the highest dose studied if the MTD is not identified) in 3 tumor-specific expansion cohorts: NSCLC, mCRPC, and MEL+RCC. Up to 16 subjects will be enrolled in each of the 4 ncology indications. In order to perform preliminary evaluation of BORR (anti-tumor activity), the sample size at the MTD or highest dose level cohort is determined by a power analysis. It is

assumed that the subjects would have no response if they would not have received any therapy and that the BORR for subjects in the MTD or highest dose level cohort would be 10%. Based on this assumption, a sample size of 16 subjects (in each tumor expansion cohort) in the MTD or highest dose level cohort is required to provide more than 80% power in a one-sample exact Binomial test at the significance level of 0.05.

Reason for change: Consistency within document to reflect previous changes in synopsis.

Page 60, Section 13.2.2, Per-protocol Population

Revised first sentence to read:

The per-protocol population includes all subjects dosed at the MTD (or the highest dose studied) ~~tested~~ if the MTD is not ~~identified~~ ~~determined~~ in the safety population who have the correct disease diagnosis, valid baseline tumor assessment, and at least 1 valid post-baseline tumor assessment.

Reason for change: Clarification that the MTD may not be identified at the doses studied.

Pages 62 and 63, Section 13.3.5: Safety

Revised physical examinations subsection to read:

Abnormal findings in physical examinations will be recorded as adverse events or baseline medical history ~~provided using descriptive statistics in the data listings~~ and will be included in the respective summaries ~~summarized by dose level using descriptive statistics.~~

Reason for change: Change in CRF design.

Added new subsections to read:

Flow Cytometry

Flow cytometry results will be summarized by dose level using descriptive statistics or as otherwise appropriate.

Immune Safety Evaluations

Immune safety tests results will be summarized by dose level using descriptive statistics.

Reason for change: Completeness.

Pages 65 and 66, Section 15.1: Protocol Amendments

Revised reasons for protocol amendments to read:

1. Increase in drug dosage or duration of exposure of subjects, or any significant increase in the number of subjects under study;
4. Addition or deletion of a test procedure intended to improve for safety monitoring.

Changed administrative amendment reason to read:

2. Minor changes (within regulatory guidelines) in the packaging or labeling of study drug.

Reason for changes: Administrative change to reflect consistency with Medarex revised protocol template.

Page 67, Section 15.3: Recording of Data and Retention of Documents

Added new third paragraph to read:

If Electronic Data Capture (EDC) system is deployed, the eCRF will be completed by the authorized study site personnel. Electronic queries will be used to communicate eligible discrepant data with the study sites.

Reason for change: Administrative change to reflect consistency with Medarex revised protocol template.

Pages 76 and 77, Appendix 1: RECIST with Modification

Revised definition of Target and Non Target Lesions/Progressive disease to read:

For Target Lesions:

- **Progressive disease** – At least a 20% increase in the sum of the longest diameters of target lesions (with addition of diameters of any newly emergent measurable lesions), taking as reference the smallest sum of the longest diameters (nadir) recorded since screening. ~~The appearance of 1 or more new lesions will not in itself constitute PD for this study. For this study PD must be confirmed by an additional scan at the next therapeutic assessment. After confirmation, if a subsequent therapeutic assessment shows further progression (i.e., further increase in SLD or additional new lesion[s]), the subject will stop study drug treatment. A subject with confirmed progression who does not have further progression on subsequent assessment will remain in the study and will be re-~~

~~evaluated at the completion of the next cycle unless the subject has rapid clinical deterioration (as defined in Section 8.7).~~

For Non-target Lesions:

- **Progressive disease** – Unequivocal progression of a nontarget lesion or appearance of 1 or more new lesions. ~~The appearance of 1 or more new lesions will not in itself constitute PD for this study. For this study PD must be confirmed by an additional scan at the next therapeutic assessment. After confirmation, if a subsequent therapeutic assessment shows further progression (i.e., further increase in SLD or additional new lesion[(s)], the subject will stop study drug treatment. A subject with confirmed progression who does not have further progression on subsequent assessment will remain in the study and will be re-evaluated at the completion of the next cycle unless the subject has rapid clinical deterioration (as defined in Section 8.7).~~

Reason for change: Consistency of definitions throughout document.

Page 84, Appendix 5: Pre-existing Autoimmune Disease

Alphabetized conditions

Reason for change: Administrative change to reflect consistency with Medarex revised protocol template.

***STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT***

**A Phase 1, Open-label, Multicenter, Multidose, Dose-escalation
Study of BMS-936558 in Subjects with Selected Advanced or
Recurrent Malignancies**

PROTOCOL CA209-003

VERSION 1.2

TABLE OF CONTENTS

TABLE OF CONTENTS	2
1 BACKGROUND AND RATIONALE.....	5
2 STUDY DESCRIPTION.....	6
2.1 Study Design	6
2.2 Treatment Assignment	8
2.3 Blinding and Unblinding	8
2.4 Protocol Amendments	8
3 OBJECTIVES	10
3.1 Primary.....	10
3.2 Secondary.....	10
3.3 Exploratory	11
4 ENDPOINTS	11
4.1 Primary: Safety Endpoints.....	11
4.2 Secondary.....	12
4.2.1 Immunogenicity Endpoints	12
4.2.2 Pharmacokinetic Endpoints	12
4.2.3 EFFICACY ENDPOINTS	13
4.2.3.1 Best Overall Response (BOR).....	13
4.2.3.2 Primary Efficacy Endpoints: ORR and DOR	13
4.2.3.3 Additional Efficacy Endpoints	13
4.2.4 Dose Response Assessment	14
4.2.5 Immune responses to tumor antigens.....	14
4.3 Key Exploratory Endpoints	15
4.3.1 PD-L1 expression by IHC (positive or negative)	15
4.3.2 PD1 Receptor Occupancy (RO) in peripheral blood	15

4.3.3	Overall Survival	15
4.4	Other Exploratory Endpoints	16
4.4.1	Exploratory Efficacy by irRECIST	16
4.4.2	Exploratory Efficacy Endpoints by Tumor Specific Antigens.....	16
4.4.3	Other exploratory biomarkers	16
5	SAMPLE SIZE AND POWER	17
6	STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES.....	17
6.1	Study Periods	17
6.2	Treatment Regimens.....	18
6.3	Populations for Analyses	19
7	STATISTICAL ANALYSES.....	19
7.1	General Methods	19
7.2	Study Conduct.....	20
7.3	Study Population.....	20
7.3.1	Subject Disposition.....	20
7.3.2	Demographics and Other Baseline Characteristics.....	21
7.3.3	Medical History.....	21
7.3.4	Disease Characteristics.....	21
7.3.5	Prior Therapy.....	22
7.4	Extent of Exposure.....	23
7.4.1	Study Medication	23
7.4.2	Dose Interruptions	23
7.4.3	Prior and Concomitant Therapy.....	23
7.5	Efficacy	24
7.5.1	Efficacy Analysis of OR, DOR, PFS and Related Endpoints	24
	Progression Free Survival (PFS) and Landmark PFSR.....	25
	Duration of Response (DOR).....	25
	Duration of Stable Disease (DSD).....	25

Time to Response (TTR).....	25
7.5.2 Exploratory Efficacy Analysis using Overall Survival (OS).....	26
7.5.3 Exploratory Efficacy Analysis using irRECIST.....	26
7.5.4 Other Exploratory Efficacy Analysis	26
7.6 Safety	27
7.6.1 Deaths	27
7.6.2 Serious Adverse Events	27
7.6.3 Adverse Events Leading to Discontinuation of Study Therapy ...	28
7.6.4 Adverse Events	28
7.6.5 Immune Safety Evaluations / Adverse Events of Special Interest	28
7.6.6 Clinical Laboratory Evaluations.....	29
7.6.7 Physical Examinations and Vital Signs.....	29
7.6.8 ECGs	30
7.7 Pharmacokinetic Analysis	30
7.8 Immunogenicity Analysis	30
7.9 Dose Response Analyses.....	30
7.10 Biomarkers Analyses.....	31
7.10.1 Key Biomarkers Analyses	31
7.10.2 Other Biomarker Analyses	31
8 CONVENTIONS.....	33
9 CONTENT OF REPORTS.....	33
10 REFERENCES.....	33
APPENDIX 1 33	
Listing of PD1 PT for Adverse Events of Special Interest (EOSI), as of February 20, 2012	33
APPENDIX 2 33	
Analysis of Safety Data - Reference to CT SOP 109.....	33

1 BACKGROUND AND RATIONALE

CA209003 is a Phase 1, open label, multicenter, multi-dose, dose-escalation study of BMS-936558 (MDX-1106), a fully human monoclonal IgG4 antibody, targeting the Programmed Death-1 (PD-1) membrane receptor on T lymphocytes and other cells of the immune system in Subjects with selected Advanced or Recurrent Malignancies. Three dose levels (1, 3, and 10 mg/kg) were tested in the dose escalation phase, with subjects enrolled using a 3+3 design, in order to determine the maximum tolerated dose (MTD), defined as the highest dose studied at which no more than 1 of 6 subjects has experienced a DLT in Cycle 1.

To further characterize safety and efficacy, sixteen subjects were enrolled in each of seven initial (primary) expansion cohorts of Melanoma (3 cohorts at each of 1mg/kg, 3mg/kg, and 10mg/kg), NSCLC (10mg/kg), RCC (10mg/kg), CRC (10mg/kg) and mCRPC (10mg/kg). Seven additional expansion cohorts were enrolled after Amendment 4, to study additional doses in subjects with Melanoma, NSCLC, and RCC.

Research Hypothesis:

The protocol was originally developed by Medarex Inc. and did not include a research hypothesis. Though there is no formal research hypothesis to be statistically tested in this study, based on the primary objective, it is expected that after multiple dosing of BMS-936558 at the 1mg/kg, 3mg/kg, or 10mg/kg dose in patients with selected malignancies, at least one of the studied doses demonstrates safety and tolerability. It is also expected, based on the study design, that the Maximum Tolerated Dose (MTD) or maximum administered dose will be determined following DLT evaluation.

Schedule of Analyses:

Administrative interim analyses including safety, efficacy, PK, or selected biomarkers may be performed at several times prior to completion of the study. The reasons include but are not limited to internal program decisions, such as dosing selection, meetings with regulatory authorities, and study presentations or publications.

In interim presentations, selected summaries may be provided separately for the pre-Amendment 4 population, due to the different amount of followup in subjects enrolled after Amendment 4.

2 STUDY DESCRIPTION

2.1 Study Design

This is a Phase 1, open-label, multicenter, multidose, dose-escalation study of BMS-936558. In the dose escalation procedure, a standard 3+3 design is used to find the maximum tolerability dose (MTD) based on observed number of dose limiting toxicities (DLTs). Three dose levels were originally planned: 1, 3, and 10 mg/kg. Subjects were assigned to a dose level in the order of study entry. Under Amendment 4, 0.1 and 0.3 mg/kg dose levels were included which did not impact the dose escalation plan that has been completed.

To further characterize safety and efficacy, subjects were enrolled in tumor specific expansion cohorts. Enrollment to 7 initial expansion cohorts (Table 1) with approximately 16 subjects (dose escalation plus expansion) for each cohort was completed prior to Amendment 4. In order to gain additional safety, tolerability and preliminary efficacy assessment in NSCLC, MEL and RCC, 7 additional expansion cohorts as described in Figure 1 are enrolled under Amendment 4. Subjects with MEL enrolled at 0.1 and 0.3 mg/kg dose levels are permitted to dose escalate to 1 mg/kg dose level upon confirmed and worsening PD within the first 2 treatment cycles and in consultation and agreement by BMS Medical Monitor.

Table 1: Expansion Cohorts Completed Prior to Amendment 4

Tumor Type	Dose Level
Melanoma	1 mg/kg
Melanoma	3 mg/kg
Melanoma	10 mg/kg
Renal Cell Carcinoma	10 mg/kg
Non-small Cell Lung Cancer	10 mg/kg
Colorectal Cancer	10 mg/kg
Prostate Cancer	10 mg/kg

The study consists of 3 periods: Screening (up to 28 days), Treatment (up to 3 years of active therapy [maximum 2 years initial treatment plus additional remaining period if re-initiation occurs]), and Follow-up (up to 46 weeks). Treatment continues until confirmed complete response (CR), progressive disease (PD) or the maximum number of cycles (initial 12 plus an additional maximum of 6, for a total of up to 18) has been administered. Subjects entering follow-up period with ongoing disease control (CR, PR, or SD) may be permitted to reinitiate study therapy upon confirmed disease progression after discussion and agreement with BMS Medical Monitor. The flow of subjects through the study is diagrammed in Figure 2.

Figure 1: Expansion Cohorts Added Under Protocol Amendment 4

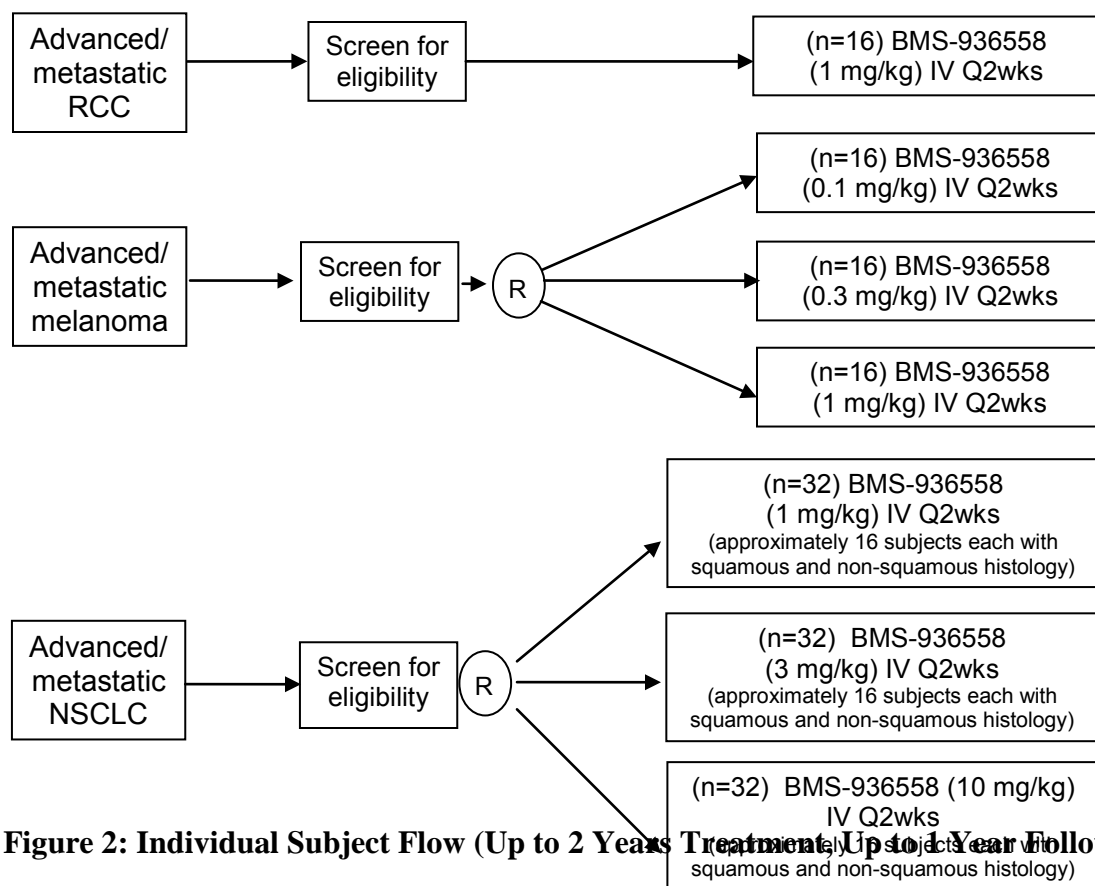
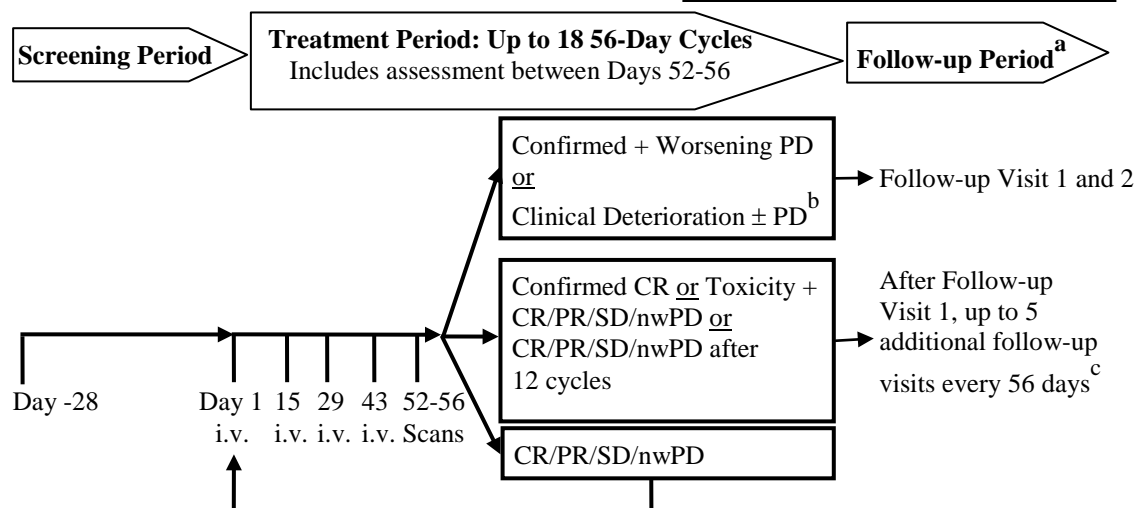


Figure 2: Individual Subject Flow (Up to 2 Years Treatment, Up to 1 Year Follow-up)



CR = complete response; PR = partial response; SD = stable disease;
nwPD = non-worsening progressive disease

^a For all subjects, all adverse events occurring within 70 days of administration of the last dose of study drug will be collected for subjects continuing in the study. For subjects who will discontinue from the study within 70 days after the administration of the last dose of study drug: 1) study drug-related adverse event information will be collected and should be followed to resolution/stabilization, 2) a telephone contact for a safety update would be acceptable if the subject cannot manage an office visit, otherwise the subject should complete Follow-up Visit 2; and 3) only clinically significant or serious adverse events that become known and are considered related to study drug will be reported more than 70 days after administration of the last dose of study drug.

^b PD that has been confirmed and then worsens or there is clinical deterioration at a subsequent visit. Follow-up Visits 1 and 2 should be done unless precluded by disease progression or clinical deterioration.

^c Follow-up should continue until relapse, initiation of a new therapy, or a total of 46 weeks (Follow-up Visits 1 and 2 only for worsening PD), whichever occurs first.

2.2 Treatment Assignment

The investigative site contacted BMS for treatment assignment once a subject was determined to be eligible for enrollment. Subjects who met all eligibility requirements were assigned to a treatment group as determined by BMS. Once assigned, numbers for any screening failures, non-treated, non-evaluable, or discontinued subjects were not re-used.

The dose escalation part of the study and the primary MTD expansion cohorts and additional non-MTD melanoma expansion cohorts were not randomized. Under Amendment 4, subjects with NSCLC enrolled under the additional NSCLC expansion cohorts were randomly assigned to one of the 3 dose levels (1, 3, or 10 mg/kg) in the order of enrollment in order to avoid allocation bias in subject dose assignment. Randomization in these cohorts was stratified by histology cell type (squamous vs. non-squamous). Similarly, subjects with MEL enrolled under the additional MEL expansion cohorts were randomly assigned to one of 3 dose levels (0.1, 0.3, or 1mg/kg). The random assignment was according to a computer-generated randomization schema prepared by a Randomization Coordinator with the Drug Supply Management Department of BMS Research and Development. Subjects in these cohorts who needed to be replaced were randomized to receive the same dose as the original subject.

2.3 Blinding and Unblinding

Blinding is not applicable as this is an open-label study.

2.4 Protocol Amendments

The protocol has incorporated amendments 1 to 5 and administrative letter 1.

Amendment 1 (dated Sep 19, 2008 with up to 76 subjects in 4 malignancies):

- Changes to the protocol template, minor typographical errors and defining acronyms.

Amendment 2 (dated Aug 25, 2009 with up to 124 subjects enrolled in 5 malignancies):

- Inclusion of subjects with colorectal adenocarcinoma (CRC) as another indication.
- Addition of 2 additional expansion cohorts for melanoma at doses other than 10mg/kg
- Addition of the colorectal expansion cohort and separation of the melanoma/renal carcinoma cohorts into 2 cohorts of 16 each.
- Added requirement for permission to collect slides or tissue samples from pre-enrollment tumor biopsies, if available, for examination of tumor markers and inflammatory infiltrates.
- Expanded the text describing statistical analysis and summary of efficacy and safety parameters.

Amendment 3 (dated Feb 08, 2010):

- Incorporate information and processes resulting from the acquisition of Medarex, Inc. by Bristol-Myers Squibb Co (BMS).
- Incorporate new and revised protocol sections to provide more clarity to investigators and to provide new instructions where applicable.

Amendment 4 (dated Oct 08, 2010 with up to 290 subjects to be enrolled in 5 malignancies):

- Evaluation of three new expansion cohorts in subjects with NSCLC (squamous and non-squamous histology) administered BMS-936558 every 14 days at 1, 3, and 10 mg/kg respectively
- Evaluation of an expansion cohort in subjects with MEL administered BMS-936558 every 42 days at 1 mg/kg
- Evaluation of three additional expansion cohorts in subjects with MEL administered BMS-936558 every 14 days at 0.1, 0.3, and 1 mg/kg respectively
- Evaluation of an expansion cohort in subjects with clear cell RCC

- Inclusion of an exploratory analysis using an immune-based response criteria based on modifications to the Response Evaluation Criteria In Solid Tumors (v 1.0)
- Allowance for reinitiating study therapy for subjects that progress during the follow-up phase either after having achieved a confirmed complete response to therapy or after completion of all 12 treatment cycles with an ongoing immune-related stable disease (irSD) or immune-related partial response (irPR).

Amendment 5 (dated January 23 2012) key objectives:

- Addition of an exploratory objective for collecting data for Overall Survival (OS)
- Addition of biomarker exploratory objectives on evaluation of PD-L1 expression in tumor as a potential predictive marker for BMS-936558, and evaluation of PD-1 receptor occupancy.
- Addition of language on interim administrative analyses on various endpoints to support program decisions
- Clarification of the Response Evaluable Population Definition
- Addition/Clarification of statistical analyses on the new exploratory objectives.

3 OBJECTIVES

3.1 Primary

- To assess the MTD of BMS-936558 based on DLT criteria.
- To assess the safety and tolerability of multiple doses of BMS-936558 in subjects with selected advanced or recurrent malignancies (mCRPC, RCC, CRC, MEL, and NSCLC)

3.2 Secondary

- To assess the host immune response to BMS-936558 (immunogenicity)
- To characterize the pharmacokinetic profile of multiple doses of BMS-936558

- To assess the preliminary efficacy of BMS-936558 monotherapy
- To characterize the dose response relationship in melanoma and NSCLC
- To explore effects of BMS-936558 on humoral and cellular immune responses to tumor antigens and recall responses to a panel of non-tumor antigens

Although the last objective was listed in the initial protocol as secondary, it is considered an exploratory objective. While data are being captured there are no plans for immediate analysis to address that objective; A listing of the data collected to support that objective will be provided at the time of the CSR.

3.3 Exploratory

- To explore potential predictive markers associated with BMS-936558 clinical activity based on levels of expression of PD-L1 in tumor specimens prior to treatment.
- To investigate the immunomodulatory activity of BMS-936558 on selected immune cell populations and soluble factors in blood.
- To characterize the levels of PD-1 receptor occupancy in peripheral blood
- To assess the overall survival (OS) in subjects receiving BMS-936558

In addition, though not specifically listed as exploratory objectives, the protocol planned for exploratory efficacy analysis using irRECIST criteria, and additional assessments based on tumor specific antigens (PSA for mCRPC, CEA and CA19-9 for CRC).

4 ENDPOINTS

The following section summarizes the link between study objectives (primary, secondary and key exploratory) and the different endpoints.

4.1 Primary: Safety Endpoints

Incidence of adverse events (AE), incidence of serious AEs, incidence of treatment related AEs, and incidence of discontinuations due to AE's, incidence of deaths, and laboratory abnormalities are the corresponding study level primary safety endpoints. Additional safety outcomes will include changes in vital signs, and ECG parameter measurements.

Incidence of AE of special interest such as AE related to a potential immune mechanism of study drug will also be reported. These are described in the protocol as immune related AE (irAE) or inflammatory events regardless of causality (IERC), based on early thinking around the type of these AE's, as those which may be triggered by a loss of tolerance to enteric or self antigens. Although specified in the protocol, anti-PD1 as a program is not using the nomenclature of irAE or IERC, moving forward; instead, these type of adverse events will be captured among the events of special interest (AEOSI). The complete list of qualifying primary terms associated with such toxicities, are defined in Appendix 1, as agreed to by the pharmacovigilance and clinical departments within BMS.

Secondary and key exploratory endpoints are outlined below.

4.2 Secondary

4.2.1 Immunogenicity Endpoints

The incidence of Human Anti-Human-Antibody (HAHA) during treatment and incidence of an increase in HAHA levels from baseline are endpoints for this analysis. This is based on samples collected pre-dose on Cycle 1 Day 1, predose on Cycle 2 Day 1 and all follow-up visits.

4.2.2 Pharmacokinetic Endpoints

The pharmacokinetic parameters derived from serum concentration versus time data in subjects with intensive PK sampling enrolled in expansion cohorts post Amendment 4 are.

- C_{max}: Maximum observed drug concentration in serum
- T_{max}: Time to reach C_{max} in serum
- T-HALF: Terminal-phase elimination half-life in serum
- AUC(0-T): Area under the plasma/serum drug concentration-time curve from time zero to last measurable sampling time
- AUC(INF): Area under the plasma/serum drug concentration-time curve from time zero extrapolated to infinity
- AUC(TAU): Area under the plasma/serum drug concentration-time curve during a dosing interval of tau

- AI: Accumulation Index
- CL: Total body clearance of drug from serum
- Vss: Volume of distribution at steady state

In addition for all subjects the following PK endpoints are calculated:

- Cmin: BMS-936558 Minimum observed drug concentration in serum
- Ceoi: BMS-936558 End of infusion drug concentration in serum

4.2.3 EFFICACY ENDPOINTS

The following endpoints will be used to assess preliminary efficacy, are derived based on the RECIST 1.0 (*see protocol Appendix 2*). The tumor assessments are scheduled at screening and between days 52 and 56 of each cycle.

4.2.3.1 Best Overall Response (BOR)

The BOR is the best response designation over the study based on RECIST 1.0 criteria for the individual subject in the study. BOR outcomes are: CR, PR, SD and PD.

4.2.3.2 Primary Efficacy Endpoints: ORR and DOR

- **Objective Response Rate (ORR):** proportion of subjects whose confirmed best overall response (BOR) is either complete response (CR) or partial response (PR), where the denominator is the number of treated subjects in the population of interest.

Though ORR was the primary efficacy parameter per protocol, the durability of the responses is as important for a better understanding of the ORR.

- **Duration of Response (DOR):** is calculated for subjects with an objective response as the time between the date of the first documented tumor response (PR or CR) and the subsequent date of the objectively documented disease progression or death, whichever occurs first, or the last tumor assessment in case of censoring.

4.2.3.3 Additional Efficacy Endpoints

- **Disease Control Rate (DCR):** proportion of subjects with a BOR of CR, PR or SD, where the denominator is the number of treated subjects in the population of interest.

- **Progression Free Survival (PFS):** the time from the first dose of study medication to the first objective documentation of tumor progression or death due to any cause. Subjects who did not progress or die will be censored on the date of last tumor assessment. Subjects who did not have any on-study tumor assessments and did not die, will be censored on the date of the first dose of study medication.
- **Progression Free Survival Rate** at (landmark) time t (PFSRt) is the probability of a subject remaining progression free and surviving to time t; times of week 24 (end of 3 cycles) and possibly weeks 8 and 16 will be used.
- **Duration of Stable Disease (DSD)** designated for subjects with a BOR of SD, is calculated as the time from the date of first dose of study therapy until the date of progression or death, whichever occurs first (or last tumor assessment if censored).
- **Stable Disease Rate of at least 24 weeks** (Prolonged Stable Disease) designated for subjects with stable disease is the proportion of subjects with DSD of at least 24 weeks, where the denominator is the number of treated subjects in the population of interest.
- **Time to Response (TTR):** designated for subjects with an OR is the time from the first dose of study treatment until the first documented objective response.

TTR though defined in the original protocol, is not considered key endpoints and will not be used for analyses presented prior to the CSR.

4.2.4 Dose Response Assessment

The endpoints used to assess this objective will be measures of preliminary efficacy such as occurrence of an OR, %Change on tumor burden, PFS and OS. In addition, potential safety measures such as occurrence of AE of special interest may be used. The totality of the analyses will be evaluated to qualitatively assess dose response.

4.2.5 Immune responses to tumor antigens

Analyses to support this objective will only be provided if the corresponding assessment is performed by the CSR time. The endpoints would be measurements of immune responses to tumor antigens and of recall responses to non-tumor antigens.

4.3 Key Exploratory Endpoints

Endpoints related to key exploratory biomarkers and other key exploratory objectives will be described. More details on these and endpoints supporting other biomarker objectives will be part of a separate SAP, available prior to the CSR, due to evolving understanding and exploratory nature of these endpoints analyses some of which are hypotheses generating.

4.3.1 PD-L1 expression by IHC (positive or negative)

The endpoint used to support the objective of exploring the PD-L1 expression as a potential predictive marker of BMS-936558 clinical activity is the PD-L1 expression status (+, -, or unknown) derived from percent of tumor cells exhibiting cell surface staining for PD-L1 prior to treatment, assessed by immunohistochemistry (IHC). In the case of multiple specimens a subject would be identified as PD-L1+ if any of the specimens prior to treatment initiation met the criteria for PD-L1 positivity. The definition of positivity including % expression in tumor cells will be explored in an ongoing manner. For the April 2012 NEJM publication a 5% threshold for tumor cells will be applied.

The PD-L1 status may also be calculated based on staining with different antibodies, and or based on additional thresholds for positivity, which are deemed to be biologically sensible. Such evaluations will be explored once sufficient subjects' data is available. Moreover PD-L1 expression may be measured on the surface of other cell types in addition to tumor cells, and positivity in any of those may ultimately be used to classify a subject as PD-L1 positive.

4.3.2 PD1 Receptor Occupancy (RO) in peripheral blood

The Receptor Occupancy endpoint is the percent of PD-1 receptor occupied by BMS-936558 on circulating CD3+ cells, measured by flow cytometry. This is measured on Cycle 2 Day 1 and at subsequent planned time points.

4.3.3 Overall Survival

Overall survival (OS) is defined as the time from the first date of dosing until date of death. For subjects without documentation of death, OS will be censored on the last date the subject was known to be alive.

4.4 Other Exploratory Endpoints

4.4.1 Exploratory Efficacy by irRECIST

Immune-Related Efficacy (by irRECIST, calculated from total tumor load)

- Immune-related best overall response (irBOR) with outcomes irCR, irPR, irSD, irPD
- Immune-related response rate (irORR) during the entire study
- Duration of ir responses (DOirR) for those subjects with ir-responses
- irORR based on the irBOR outcomes in the first 3 cycles may also be derived.

The calculation of immune related endpoints described above, require measurements of new lesions; As this data collection was implemented retrospectively some new lesion data may be incomplete or missing; Therefore derivation of these endpoints for analyses is contingent on ensuring accurate and consistent recording of new lesion measurements.

If calculation of the above endpoints is not feasible, subjects who appear to follow such patterns based on the target lesions tumor measurements will be identified. Patterns include persistent reduction in tumor load in presence of new lesions and these will not be counted for ORR calculation.

4.4.2 Exploratory Efficacy Endpoints by Tumor Specific Antigens

PSA measurements and changes from baseline for mCRPC, CEA and CA19-9 measurements and changes from baseline for CRC. These endpoints will only be presented in the CSR.

4.4.3 Other exploratory biomarkers

The immunomodulatory activity of BMS-936558 on selected immune cell populations and soluble factors will be assessed by:

Measures (percent and counts) in fresh whole blood phenotypic markers including: CD3, CD4, CD8, CD19, CD14, CD16+56, CD4+CD25, CD4+CD25+CD45RO, CD8+CD25, CD4+HLA-DR, CD8+HLA-DR, CD4+45RO, and CD8+45RO and changes from baseline, via flow cytometry.

Measures, including changes from baseline, in soluble factors based on cytokines panel assays including IL-1, 4, 5, 6, 10, 13 IFN gamma, and TNF alpha.

Measures of immune safety assays including Rheumatoid Factor (RF), Thyroid Stimulating Hormone (TSH), Free T4 Level, adrenocorticotrophic hormone (ACTH), C-reactive protein (CRP), Antinuclear Antibody (ANA) titer and pattern.

These and any additional biomarker endpoints will be described in a biomarker specific SAP.

5 SAMPLE SIZE AND POWER

The sample size during dose escalation depends on the observed toxicity and cannot be precisely determined. At expansion cohorts, up to 16 or 32 subjects are treated at fixed doses in a tumor type to provide additional safety information and preliminary assessment of tumor response, within a disease indication.

With 16 subjects treated in an expansion cohort, at a fixed dose and tumor type the 90% confidence interval for an objective response rate would be (5.3% to 42%) if 3 (19%) subjects had a response, (9.0% to 48%) if 4 (25%) subjects had a response and (13.2% to 54.8%) if 5 (31%) subjects had a response. Similarly, with 32 subjects in each NSCLC expansion cohort, the 90% confidence interval for an objective response rate would be (3% to 22%) if 3 (9.4%) subjects had a response, (4.4% to 26.4%) if 4 (12.5%) subjects had a response, and (6.4%, 30%) if 5 (16%) subjects had a response.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

This study consists of up to 5 periods: 3 primary periods: screening, treatment and follow-up. A potential re-treatment period is also allowed, and all subjects will be followed for survival.

Screening Period: up to 28 days before administration of study drug

Treatment Period: first iv infusion of BMS-936558 until up to 3 years of active therapy [maximum 2 years initial treatment plus additional remaining period if re-initiation occurs]

- Each treatment cycle is comprised of 4 doses of study drug administered on Days 1, 15, 29, and 43 with a response assessment between Days 52 and 56.
- Treatment continues until confirmed complete response (CR), progressive disease (PD) or the maximum number of (four dose) cycles (12) has been administered.

Follow-up Period:

- Except for subjects who discontinue due to worsening PD, all subjects are followed from the last visit until relapse, initiation of a new therapy, or the maximum 1 year.

Re-treatment Period:

- Subjects entering the follow-up period with ongoing disease control (CR, PR, or SD) may be permitted to reinitiate study therapy upon confirmed disease progression after discussion and agreement with the BMS Medical Monitor.

Survival Follow-up Period

- Following completion of the treatment and follow-up periods, all subjects will be followed for survival after completion of treatment phases and through the follow up period of the protocol. At the time of implementation of Amendment 5 of the study protocol, all subjects will be assessed for their survival status and dates of death reported for any subjects that are deceased. After that initial assessment of all study subjects, any surviving subjects will have their survival status assessed approximately every 3 months by either a telephone or in-person contact until study completion or termination by the Sponsor.

6.2 Treatment Regimens

The treatment as assigned per protocol are indicated by tumor type in Table 2. For the cohorts in which dose escalation is allowed, all by treatment presentations will use the assigned dose at the time of study therapy initiation.

Table 2: Treatment Assignments by Dose Expansion Cohort			
Malignancy Cohort	BMS-936558 Dose (mg/kg)		Potential Dose Escalation (mg/kg)
	Pre Amendment 4	Post Amendment 4	
MEL		0.1	1
		0.3	1
	1	1	
	3		
	10		
NSCLC		1	
		3	
	10	10	
RCC		1	
	10		

CRC	10		
mCRPC	10		

6.3 Populations for Analyses

- All Enrolled Population: All subjects who signed informed consent form.
- All Treated Population: All subjects who received at least 1 or any partial dose of BMS-936558.
- Immunogenicity Population: All subjects who receive at least one dose of study medication and have available HAHA data.
- Pharmacokinetic Population: All treated subjects who have PK concentrations will be included in the listings. All available PK parameter values will be included in the PK data set and reported but only subjects with adequate PK profiles will be used in the summary statistics and statistical analyses.
- Response Evaluable Population: All treated subjects who have measurable disease at baseline and at least one of the following: 1) at least one on-treatment tumor evaluation, 2) clinical progression, or 3) death prior to the first on-treatment tumor evaluation.
- Biomarker Population: All treated subjects will be used and those subjects without baseline measurements for a specific marker will be included and categorized as unknown. In association analyses with other endpoints, such as efficacy, the analysis may be based on response evaluable population. In addition, for publications, subset analyses may be presented. For pharmacodynamic analyses of changes from baseline, treated subjects with baseline measurement and at least one biomarker on treatment measurement will be included.

7 STATISTICAL ANALYSES

7.1 General Methods

The software used for all summary statistics and statistical analyses will be SAS version 8.2 or higher. (SAS Institute, Inc., Cary, NC.).

Unless otherwise stated, the information will be firstly listed by dose group and overall. Moreover, the continuous data will be summarized using the following descriptive statistics: number of observations, mean, standard deviation (SD), median, minimum, and maximum. Categorical data will be summarized using frequencies and percentages. The percentages will be rounded and thus may not always sum up to 100%.

Time to event distribution will be estimated using Kaplan Meier techniques. When appropriate, the median along with confidence interval (CI) will be provided using Brookmeyer and Crowley methodology. PFS Rate at fixed time point (e.g. PFS rate at week 24) will be derived from the Kaplan Meier estimate and the corresponding CI will be derived based on Greenwood formula. Since not all subjects adhere to the scheduled tumor measurement date, a window of 1 week prior to the PFS rate time points will be applied. The same window will be applied to the calculation of stable disease duration of ≥ 24 weeks.

The time to event endpoints of PFS, DOR, DSD, and OS will be censored as indicated in the endpoint definitions.

If there is knowledge of subjects receiving additional therapy for their disease while on study (e.g. when they are off study treatment) subjects will be identified following adjudication by clinical, and maybe used in sensitivity analyses for efficacy.

7.2 Study Conduct

All potential serious breaches of the conditions and principles of Good Clinical Practice (GCP) in connection with the study or protocol will be reported. Additionally, relevant protocol deviations, defined as any significant protocol deviation that could potentially affect the interpretability of the study results, will be reported.

7.3 Study Population

Summaries of study population will be based on all treated subjects except that of subject disposition which will be based on all enrolled subjects.

7.3.1 Subject Disposition

The subjects status will be listed including disease and dose, enrollment date, first and last dosing date, the off-study date (or date of last conduct) and the off study reasons. For purposes of interim analyses while the study is ongoing, subjects without recorded off-study documentation will be assumed to be off-study 1 year after their last dosing date with 'Unknown' reason.

The subject disposition will be tabulated by dose and overall for each tumor type and across tumors and will present the following: 1) numbers and proportions of the never treated and treated subjects out of the all enrolled subjects; 2) numbers and proportions of subjects off-treatment (study drug discontinuation) with reasons for drug discontinuation (AE, CR, Completion of maximum cycles, death, disease progression, withdrew consent, or other); 3) numbers and proportions of subjects off-study (permanent study discontinuation) with reasons for study discontinuation (AE, Completion of 6 follow-up visits, death, disease progression, lost to follow up, withdrew consent, or other).

7.3.2 Demographics and Other Baseline Characteristics

Summary of Demographic Characteristics for All Treated Subjects by dose and overall across tumor types as well as by tumor type for:

- Age (summary statistics; <65 yrs, ≥ 65yrs)
- Gender (male, female)
- Race (white, black, asian, other)
- Ethnicity (hispanic/latino, not hispanic/latino)

Summary of Physical Measurements for All Treated Subjects by dose and overall across tumor types as well as by tumor type for:

- Weight (summary statistics)
- Height (summary statistics)
- ECOG performance status (0, 1, 2, 3)

Listing of Demographic Characteristics and Physical Measurements for All Treated Subjects

7.3.3 Medical History

Listing of General Medical History for All Treated Subjects

7.3.4 Disease Characteristics

Summary of Disease Diagnosis for All Treated Subjects by dose and overall [Including histology types for NSCLC]

Summary of Baseline Lesion Type for All Treated Subject by dose and tumor type [adjudicated by clinical; n (%) subjects with at least one lesion in categories: Bone, Liver, Lung, Lymph Node, Other]

Listing of Disease Diagnosis for All Treated Subjects [including NSCLC histology]

Listing of Baseline lesion types, by tumor

7.3.5 Prior Therapy

Summary of Prior Therapy is tabulated for all tumor types by dose and overall [Surgery, Immunological or Biologic, Hormonal Radiotherapy, Chemotherapy, Alternative/Herbal, Prior Medications - Other]. In addition the number of prior regimens (1, 2, 3, 4+) is tabulated by tumor type and overall.

Disease specific prior therapies are presented by dose and overall for all treated subjects, based on adjudication by clinical:

RCC: Summary of Prior Anti-Angiogenic and Immunotherapy

MELANOMA: Summary of Prior RAF Inhibitor and Immunotherapy

NSCLC: Summary of Prior Platinum Based Therapy and TKI Therapy by treatment

RCC: Summary of Prior Surgery: Nephrectomy (%)

NSCLC Summary of Prior Therapeutic Surgery

NSCLC Summary of Prior Therapeutic Radiotherapy

Listing of Prior Surgery for All Treated Subjects

Listing of Prior Radiotherapy for All Treated Subjects

Listing of Prior Medication Related to Study Indication for All Treated Subjects and by Tumor type within each category

7.4 Extent of Exposure

7.4.1 Study Medication

Dose administration of BMS-936558 will be listed for all treated subjects by disease, dose, visit date and cycle, presenting total dosing duration (weeks) and reasons for dose prolongation or interruption.

The duration of therapy is defined at the time between the date of first dose and the date of last dose of study drug plus 14 days (the intended duration of last dose).

Duration of therapy of BMS-936558 will be tabulated by dose and across doses for each tumor type and across tumor types presented in 8 week intervals by the frequency (%) of subjects with duration ≤ 8 weeks, 8-16 weeks, etc and by median and range.

In addition exposure will be presented across tumor types and within each tumor by dose and across doses by tabulating the cumulative dose, dose intensity (Mean, Median, SD and Range), as well as the Relative dose intensity ($<60\%$, $60\%-80\%$, $80\%-90\%$, $\geq 90\%-100\%$ and $>100\%$).

Cumulative dose (mg/kg) is defined as the sum of all doses received by the subject. Dose intensity (mg/kg/2 weeks) is defined as the cumulative dose divided by the duration of therapy, in 2 weeks. Relative dose intensity was defined as the dose intensity divided by 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg and 10 mg/kg respectively, the planned dose in two weeks.

7.4.2 Dose Interruptions

A summary of infusion interruptions and delays will be presented by dose, for all treated subjects as follows: Frequency (%) of subjects not interrupted/prolonged and those with interruptions and prolongations is presented with frequency (%) for each reason for interruption/prolongation.

The drug delays will be similarly summarized, by frequency (%) of subjects with drug not delayed and those with drug delayed with reasons.

7.4.3 Prior and Concomitant Therapy

A listing of Concomitant Medications will be presented for All Treated Subjects

7.5 Efficacy

Efficacy populations used prior to the final study clinical report may differ from pre-specified populations depending on the purpose and timing of the analysis. For example, due to the study being conducted in two parts (pre-Amendment 4 and post-Amendment 4, to ensure sufficient follow-up for observing and confirming a response, the efficacy population may be restricted to subjects with a minimum follow-up (e.g. at least 6 months) and or at least one on study tumor assessment. All efficacy populations would have a minimum requirement of measurable disease at baseline and having received at least one dose of study medication. The final study report will utilize only the pre-specified populations (e.g. all treated, response-evaluable).

7.5.1 Efficacy Analysis of OR, DOR, PFS and Related Endpoints

By subject listings will be provided for:

- Tumor measurements by visit and individual lesion.
- Tumor burden from target lesions by visit for each tumor dose, including percentage change from baseline and increase from the smallest tumor load, and the tumor response at each visit.
- Efficacy variables including BOR and PFS derived from the tumor burden changes for each tumor type and dose by subject.
- Duration of response for subjects with objective response.
- Duration of stable disease for subjects with objective response.

The individual subject percentage change from baseline in tumor burden from target lesions will be displayed graphically, versus weeks from initiation of treatment for each tumor and dose. In addition, for NSCLC subjects with squamous and non-squamous histology will be separately identified in summaries and plots.

Subjects' maximum percent reduction from baseline in the tumor burden from target lesions may be presented graphically by waterfall plots for each tumor.

Individual subjects listings will be provided for all tumors. Additional analyses of efficacy endpoints (e.g. frequencies and plots) will focus on tumors for which at least one objective response was demonstrated after treatment with BMS-936558 in this study.

For analyses conducted while the study is ongoing, results of some analyses may only be presented in a subgroup of longer follow-up, e.g. when time to event endpoints are non-estimable due to heavy censoring.

BOR, ORR, DCR and SD24weeks

The rates for the BOR outcomes, ORR, DCR and SD of at least 24 weeks Rate will be presented by for each tumor type by dose, with the exact CI, based on Clopper-Pearson.

In addition for NSCLC tumor the ORR and DCR will be tabulated by histology and dose within a histology.

Progression Free Survival (PFS) and Landmark PFSR

PFS will be described by Kaplan-Meier plots for each tumor by dose. The median and the corresponding 95% confidence interval will be reported. In addition the landmark PFS rates and the corresponding 95% CI at week 8, 16 and 24 will be calculated.

For NSCLC tumor, the analysis will be presented also by histology within each dose.

Duration of Response (DOR)

In addition to the listing, DOR will be estimated within each tumor by Kaplan-Meier method (if estimable) by medians and CI. A K-M plot may also be provided for DOR.

Duration of Stable Disease (DSD)

In addition to the listing, DSD will be estimated within each tumor by Kaplan-Meier method (if estimable) by medians and CI.

If results from time to event analysis, e.g. for DOR are non-estimable by K-M method due to heavy censoring while the study is ongoing (interim presentations) these endpoints may be described by simple summary statistics, .e.g. frequencies of subjects exceeding a specified duration e.g. 1 year or 6 months, among those on-study for at least that long.

Time to Response (TTR)

TTR will be estimated by summary statistics within each tumor.

7.5.2 Exploratory Efficacy Analysis using Overall Survival (OS)

Overall survival will be estimated using Kaplan-Meier method by dose within each tumor, for Melanoma, NSCLC and RCC, and presented by plots, as well as by median and 95% confidence intervals if estimable. For NSCLC, OS will also be presented by histology. OS may be presented by additional prognostic factors such as prior therapy for NSCLC (≤ 2 or > 2 prior therapies) if there is sufficient number of subjects (at least 10) in each subgroup. Other prognostic factors (such as ECOG or other tumor-specific prior therapy) may be explored if relevant.

The above OS analysis may be repeated for landmark OS at 6 and 12 months.

7.5.3 Exploratory Efficacy Analysis using irRECIST

As the study conduct is based on immune-related efficacy criteria, i.e. subjects including those with non-worsening PD are allowed to stay on study, some ‘immune related’ patterns of clinical outcome are expected and may be observed.

Analyses using the irRECIST criteria will be based on irBOR, immune-related response rate irORR, duration of immune related responses irDOR, and irPFS. This analysis will be performed if new lesion data is available and consistently and accurately collected, to allow for calculation of the total tumor burden.

If the new lesions data collection do not provide reliable measurements due to the retrospective implementation while the study was ongoing, immune-related patterns of tumor response will be identified based on the target lesions only; such patterns include ongoing progression (PD) due to new lesions with persistent reduction or stability in tumor burden based on target lesions. Subjects with such patterns of response will be identified within the target lesions listings.

Additional considerations for presenting DOR and PFS based on the immune related pattern may be implemented for subjects with such patterns of response, for the CSR.

7.5.4 Other Exploratory Efficacy Analysis

Summary statistics and plots of measures of tumor specific antigen levels: PSA (for subjects with mCRPC; or CEA and CA 19-9 for subjects with CRC, will be provided for these tumor types, based on data availability.

7.6 Safety

On-Treatment events/evaluations are defined to be those observed between the date of first dose of study drug and 70 days after last dose. Post-Treatment events/evaluations are those occurring more than 70 days after last dose date. Summaries of safety will be based on all treated subjects except that of serious adverse events and deaths which will be based on all enrolled subjects.

Identification of adverse events of special interest (AEOSI) with potential immune-related etiologies (e.g. irAEs) is based on ongoing review of safety data. Summaries of AEOSI will be programmatically generated upon availability of a pre-defined and comprehensive list of AEOSI MedDRA preferred terms.

Adverse events will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of database lock. Adverse events and laboratory tests results will be graded for severity using NCI CTCAE Version 3.0.

Drug related AEs are those events with relationship to study drug “Related” as recorded on the CRF.

Adverse events leading to discontinuation are AEs with action taken = “Drug was discontinued”.

In the AE summary tables, subjects will be counted only once (worst grade) at the Preferred Term (PT) and System Organ Class (SOC) levels. The AE tables will list the SOC (ordered by descending frequency) and the PTs (ordered by descending frequency within each SOC).

7.6.1 Deaths

Deaths will be summarized as follows:

- Frequency of deaths will be tabulated by reasons off study

- By-subject listings of deaths with reason for death for all enrolled subjects

7.6.2 Serious Adverse Events

The following summaries will be tabulated by treatment and overall for SAE’s for all treated:

Number (Percent) of Subjects with Serious Adverse Events

Number (Percent) of Subjects with Treatment Related Serious Adverse Events

Number (Percent) of Subjects with Serious Adverse Events, Grades 3-4

Number (Percent) of Subjects with Treatment-related Serious Adverse Events, Grades 3-4

Listings of All SAE and on-treatment Treatment related SAE will be provided.

7.6.3 Adverse Events Leading to Discontinuation of Study Therapy

Number (%) of Subjects with On-Treatment Adverse Events Leading to Discontinuation by treatment and across treatments for All Treated Subjects

Number (%) of Subjects with On-Treatment Treatment-Related Adverse Events Leading to Discontinuation by treatment and across treatments for All Treated Subjects

Listing of all On-Treatment Adverse Events Leading to Discontinuation for All Treated Subjects

7.6.4 Adverse Events

The AEs and treatment-Related AE will be listed by subject for all treated subjects.

Number (Percent) of Subjects with Adverse Events, by Grade and overall

Number (Percent) of Subjects with Adverse Events of Grades 3-4

Number (Percent) of Subjects with Treatment Related Adverse Events by Grade and overall

Number (Percent) of Subjects with Treatment Related Adverse Events of Grades 3-4

While the study is ongoing, the above tables may be presented separately for pre-and post-Amendment 4, due to difference in the follow-up time in these two populations.

Selected AE summaries including the number (%) of Subjects with Adverse Events will be presented for each tumor type. In addition, treatment related AE will also be presented by grade and overall for subsets of Melanoma, NSCLC, and RCC tumors.

7.6.5 Immune Safety Evaluations / Adverse Events of Special Interest

A separate listing and summary of all AEOSI including pre-specified AE of immune related nature will be provided.

Summaries of treatment related AEOSI by grade and Grade 3-4 treatment related AEOSI will be tabulated for each category of special interest and across categories, by dose and overall.

7.6.6 Clinical Laboratory Evaluations

The analysis population for each test is restricted to all treated subjects who underwent that test.

Summary of Toxicity Changes from Baseline for Hematology for All Treated Subjects by treatment and across treatments [shift table of worst On-Treatment CTC grade compared to baseline CTC grade]

Summary of Toxicity Changes from Baseline for Serum Chemistry for All Treated Subjects by treatment and across treatments [shift table of worst On-Treatment CTC grade compared to baseline CTC grade]

Summary Statistics and Change from Baseline for Scheduled Laboratory Results for All Treated Subjects by treatment and across treatments

The clinical laboratory test values and especially those outside normal range will be listed.

Listing of Laboratory Values for Subjects Meeting Abnormality Criteria will be provided: The laboratory values which are outside normal range will be flagged as + (above upper normal limit) and - (below lower normal limit). The NCI CTCAE grade and grade toxicity abnormalities will also be flagged in the data listings.

Laboratory Abnormality Criteria based on CTC will be provided.

For laboratory tests without CTC criteria, including TSH, RF or other immune safety assays summaries, results may be summarized by frequencies of subjects with lab values outside pre-specified multiples of the normal range, as agreed with clinical.

7.6.7 Physical Examinations and Vital Signs

Physical measurement (height, weight) and vital sign measurements will be listed.

Summary statistics will be tabulated for scheduled vital sign measurements and changes from baseline for all treated subjects.

7.6.8 ECGs

Summary of Scheduled ECG Intervals and Heart Rates will be tabulated by dose for All Treated Subjects.

Listing of all Electrocardiogram Abnormalities for All Treated Subjects.

Listing of all Electrocardiogram Intervals and Heart Rates.

7.7 Pharmacokinetic Analysis

The pharmacokinetic parameters (including C_{max}, T_{max}, AUC[0-T] and AUC[TAU]) and concentration parameters (including C_{min} and C_{eof}) of BMS-936558 will be listed and summarized by dose and study cycle/day.

To describe the dependency on dose, scatter plots of C_{max} and AUC(TAU) versus dose will be provided for each cycle/day measured. The dose proportionality analysis will be performed based on a power model, by fitting linear regression models to log(C_{max}) and log(AUC(TAU)) versus log(dose) separately. The point estimates and 90% confidence intervals of the dose proportionality parameter (slope of the linear regression model) will be presented, based on the methods of Gough et al.

To evaluate the steady state of BMS-936558 concentration in the body, the geometric means of C_{min} and C_{eof} vs. cycle by dose will be estimated and plotted with individual subject measurements superimposed in the Figures.

7.8 Immunogenicity Analysis

A listing will be provided of all available immunogenicity data. Additionally, a listing of immunogenicity data from those subjects with at least one positive Human Anti-Human Antibody (HAHA) at any time point will be provided by dose regimen. The frequency of subjects with at least one positive HAHA assessment, and frequency of subjects who develop HAHA after a negative baseline assessment will be provided by dose. To examine the potential relationship between immunogenicity and safety, the frequency and type of AEs of special interest may be examined by overall immunogenicity status.

7.9 Dose Response Analyses

Initial assessment of dose response will be based on a review of results of the pre-specified efficacy or safety analyses. If any apparent dose-response associations are observed,

additional methods will be implemented to better characterize the dose response in melanoma or NSCLC cohorts. These will include modeling of efficacy endpoints such as tumor response as a function of dose based on parametric models, non-parametric, or possibly Bayesian approach.

7.10 Biomarkers Analyses

The analyses specified below will be described only for key biomarker endpoints. Additional analyses on biomarkers will be presented in a separate SAP for biomarker analyses.

7.10.1 Key Biomarkers Analyses

PD-L1 expression by IHC analysis.

The PD-L1 expression status (+, -, or unknown) will be tabulated by tumor and overall for all treated subjects.

Associations of PD-L1 expression and clinical outcome will be primarily based on tabulations of ORR by PD-L1 status and Kaplan Meier plots and by estimates of PFS by PD-L1 status within each tumor. The above may also be presented by dose within a tumor, and by histology for NSCLC based on subject availability. In addition, Overall Survival plots and OS estimates will be presented by PD-L1 expression status. In association analyses with other endpoints such as efficacy, the analysis may be based on response evaluable population. In addition, for publications, subset analyses may be presented.

The definition of positivity including %expression in tumor cells will be explored in an ongoing manner, e.g. different cutoffs if there is sufficient biological justification; therefore some analyses may be repeated. For the April 2012 NEJM publication a 5% threshold for tumor cells will be applied.

Details of such analyses will be provided in the biomarker SAP.

Receptor Occupancy: summary statistics will be tabulated for receptor occupancy (%) by dose; these may also be presented graphically by distribution plots of median and or quartiles and individual subject values at each dose.

7.10.2 Other Biomarker Analyses

The pharmacodynamic effects based on the immunomodulatory activity of BMS-936558 (MDX-1106) on selected immune cell populations (flow cytometry) and soluble factors in

blood and those based on the level of PD-1 receptor occupancy by BMS-936558 in peripheral blood, exploratory immune function markers including flow cytometry markers, humoral and cellular immune responses to tumor antigens (if available) will be assessed by summary statistics for outcomes from these markers and their changes (or percent changes) from baseline tabulated by cycle/visit (or weeks since treatment initiation) and dose. In addition, the time course of biomarker measures will be investigated graphically, by summary plots (i.e. box plots) or individual subject plots over time.

Possible associations between changes in biomarker measures of interest and exposure (e.g. dose or PK exposure) will be explored. Potential associations of various biomarker measures (baseline value or change from baseline) with clinical outcome (e.g., tumor response, disease control, or PFS) will be explored. Some markers baseline values (e.g. expression levels of PD-L1 protein in tumor) may be explored to assess potential predictive effects of clinical outcome by these markers. Methods such as, but not limited to, logistic regression may be used to further assess such associations. Measures from markers based on optional samples, e.g. tumor-based markers may be similarly presented, depending on data availability.

Administrative interim analyses of biomarker data may be provided at various times during the study (e.g. for the initial and the additional study cohorts) in order to support program decisions or publications.

More details of the above analyses will be presented in the biomarker SAP.

8 CONVENTIONS

Safety data will be handled according to the BMS safety data conventions, described in “Analysis of Safety Data - Reference to CT SOP 109” (Appendix 2). This document includes descriptions on how to analyze AE data as well as how to handle partial dates, missing dates, and unknown end dates when analyzing safety data.

- The following conversion factors will be used to convert days to months or years: 1 month = 30.4375 days and 1 year = 365.25 days. Windowing use for PFS rate (or SD or at least 24 weeks) consists of a week prior to the planned meeting therefore a PFS rate at 24 weeks includes subjects with at least 23 weeks PFS.
- Duration (e.g. duration response, and time to response) will be calculated as follows:

$$\text{Duration} = (\text{Last date} - \text{first date} + 1)$$

Baseline is defined as the last scheduled measurement taken prior to the first dose of BMS-936558.

9 CONTENT OF REPORTS

Administrative interim analyses may be performed at several times prior to completion of the study in order to facilitate program decisions and to support presentations or publications. Populations utilized in these analyses may differ from pre-specified populations depending on the purpose and timing of the analyses.

10 REFERENCES

NA

APPENDIX 1

Listing of PD1 PT for Adverse Events of Special Interest (EOSI), as of February 20, 2012

APPENDIX 2

Analysis of Safety Data - Reference to CT SOP 109

Appendix 1: Listing of PD1 PT for Adverse Events of Special Interest (EOSI), as of February 20, 2012

PT	EOSI	MedDRA Version
17 ketosteroids urine	irEndocrine	14.1
17 ketosteroids urine abnormal	irEndocrine	
17 ketosteroids urine decreased	irEndocrine	Date Terms
17 ketosteroids urine increased	irEndocrine	Checked
17 ketosteroids urine normal	irEndocrine	2/16/2012 9:38
17-hydroxyprogesterone decreased	irEndocrine	
17-hydroxyprogesterone increased	irEndocrine	
18q minus syndrome	irEndocrine	
Acquired porphyria	irEndocrine	
Acromegaly	irEndocrine	
ACTH stimulation test	irEndocrine	
ACTH stimulation test abnormal	irEndocrine	
ACTH stimulation test normal	irEndocrine	
Addison's disease	irEndocrine	
Adiposogenital dystrophy	irEndocrine	
Adrenal atrophy	irEndocrine	
Adrenal cortex necrosis	irEndocrine	
Adrenal insufficiency	irEndocrine	
Adrenal insufficiency neonatal	irEndocrine	
Adrenal medulla hyperfunction	irEndocrine	
Adrenal suppression	irEndocrine	
Adrenocortical insufficiency acute	irEndocrine	
Adrenocortical insufficiency neonatal	irEndocrine	
Adrenogenital syndrome	irEndocrine	
Albright's disease	irEndocrine	
Alcoholic pseudo Cushing's syndrome	irEndocrine	
Aldosterone urine	irEndocrine	

Aldosterone urine abnormal	irEndocrine
Aldosterone urine decreased	irEndocrine
Aldosterone urine increased	irEndocrine
Aldosterone urine normal	irEndocrine
Amenorrhoea	irEndocrine
Androgen deficiency	irEndocrine
Androgen insensitivity syndrome	irEndocrine
Androgenetic alopecia	irEndocrine
Androgens	irEndocrine
Androgens abnormal	irEndocrine
Androgens decreased	irEndocrine
Androgens increased	irEndocrine
Androgens normal	irEndocrine
Anorchism	irEndocrine
Anovulatory cycle	irEndocrine
Antigonadotrophins present	irEndocrine
Anti-thyroid antibody	irEndocrine
Anti-thyroid antibody negative	irEndocrine
Anti-thyroid antibody positive	irEndocrine
Autoimmune thyroiditis	irEndocrine
Basedow's disease	irEndocrine
Biopsy adrenal gland	irEndocrine
Biopsy adrenal gland abnormal	irEndocrine
Biopsy adrenal gland normal	irEndocrine
Biopsy parathyroid gland	irEndocrine
Biopsy parathyroid gland abnormal	irEndocrine
Biopsy parathyroid gland normal	irEndocrine
Biopsy thyroid gland	irEndocrine
Biopsy thyroid gland abnormal	irEndocrine
Biopsy thyroid gland normal	irEndocrine
Bleeding anovulatory	irEndocrine
Blood aldosterone	irEndocrine
Blood aldosterone abnormal	irEndocrine

Blood aldosterone decreased	irEndocrine
Blood aldosterone increased	irEndocrine
Blood aldosterone normal	irEndocrine
Blood androstenedione	irEndocrine
Blood androstenedione decreased	irEndocrine
Blood androstenedione increased	irEndocrine
Blood antidiuretic hormone	irEndocrine
Blood antidiuretic hormone abnormal	irEndocrine
Blood antidiuretic hormone decreased	irEndocrine
Blood antidiuretic hormone increased	irEndocrine
Blood antidiuretic hormone normal	irEndocrine
Blood calcitonin	irEndocrine
Blood calcitonin abnormal	irEndocrine
Blood calcitonin decreased	irEndocrine
Blood calcitonin increased	irEndocrine
Blood calcitonin normal	irEndocrine
Blood catecholamines	irEndocrine
Blood catecholamines abnormal	irEndocrine
Blood catecholamines decreased	irEndocrine
Blood catecholamines increased	irEndocrine
Blood catecholamines normal	irEndocrine
Blood corticosterone	irEndocrine
Blood corticosterone abnormal	irEndocrine
Blood corticosterone decreased	irEndocrine
Blood corticosterone increased	irEndocrine
Blood corticosterone normal	irEndocrine
Blood corticotrophin	irEndocrine
Blood corticotrophin abnormal	irEndocrine
Blood corticotrophin decreased	irEndocrine
Blood corticotrophin increased	irEndocrine
Blood corticotrophin normal	irEndocrine
Blood cortisol	irEndocrine
Blood cortisol abnormal	irEndocrine

Blood cortisol decreased	irEndocrine
Blood cortisol increased	irEndocrine
Blood cortisol normal	irEndocrine
Blood follicle stimulating hormone	irEndocrine
Blood follicle stimulating hormone abnormal	irEndocrine
Blood follicle stimulating hormone decreased	irEndocrine
Blood follicle stimulating hormone increased	irEndocrine
Blood follicle stimulating hormone normal	irEndocrine
Blood gastrin	irEndocrine
Blood gastrin decreased	irEndocrine
Blood gastrin increased	irEndocrine
Blood gastrin normal	irEndocrine
Blood glucagon	irEndocrine
Blood glucagon abnormal	irEndocrine
Blood glucagon decreased	irEndocrine
Blood glucagon increased	irEndocrine
Blood glucagon normal	irEndocrine
Blood gonadotrophin	irEndocrine
Blood gonadotrophin abnormal	irEndocrine
Blood gonadotrophin decreased	irEndocrine
Blood gonadotrophin increased	irEndocrine
Blood gonadotrophin normal	irEndocrine
Blood gonadotrophin releasing hormone decreased	irEndocrine
Blood gonadotrophin releasing hormone increased	irEndocrine
Blood growth hormone	irEndocrine
Blood growth hormone abnormal	irEndocrine
Blood growth hormone decreased	irEndocrine
Blood growth hormone increased	irEndocrine
Blood growth hormone normal	irEndocrine
Blood growth hormone releasing hormone increased	irEndocrine
Blood insulin	irEndocrine
Blood insulin abnormal	irEndocrine
Blood insulin decreased	irEndocrine

Blood insulin increased	irEndocrine
Blood insulin normal	irEndocrine
Blood luteinising hormone	irEndocrine
Blood luteinising hormone abnormal	irEndocrine
Blood luteinising hormone decreased	irEndocrine
Blood luteinising hormone increased	irEndocrine
Blood luteinising hormone normal	irEndocrine
Blood oestrogen	irEndocrine
Blood oestrogen abnormal	irEndocrine
Blood oestrogen decreased	irEndocrine
Blood oestrogen increased	irEndocrine
Blood oestrogen normal	irEndocrine
Blood parathyroid hormone	irEndocrine
Blood parathyroid hormone abnormal	irEndocrine
Blood parathyroid hormone decreased	irEndocrine
Blood parathyroid hormone increased	irEndocrine
Blood parathyroid hormone normal	irEndocrine
Blood pregnenolone increased	irEndocrine
Blood proinsulin	irEndocrine
Blood proinsulin abnormal	irEndocrine
Blood proinsulin decreased	irEndocrine
Blood proinsulin increased	irEndocrine
Blood proinsulin normal	irEndocrine
Blood prolactin	irEndocrine
Blood prolactin abnormal	irEndocrine
Blood prolactin decreased	irEndocrine
Blood prolactin increased	irEndocrine
Blood prolactin normal	irEndocrine
Blood testosterone	irEndocrine
Blood testosterone abnormal	irEndocrine
Blood testosterone decreased	irEndocrine
Blood testosterone free	irEndocrine
Blood testosterone free abnormal	irEndocrine

Blood testosterone free decreased	irEndocrine
Blood testosterone free increased	irEndocrine
Blood testosterone free normal	irEndocrine
Blood testosterone increased	irEndocrine
Blood testosterone normal	irEndocrine
Blood thyroid stimulating hormone	irEndocrine
Blood thyroid stimulating hormone abnormal	irEndocrine
Blood thyroid stimulating hormone decreased	irEndocrine
Blood thyroid stimulating hormone increased	irEndocrine
Blood thyroid stimulating hormone normal	irEndocrine
Bulbospinal muscular atrophy congenital	irEndocrine
Butanol-extractable iodine	irEndocrine
Butanol-extractable iodine decreased	irEndocrine
Butanol-extractable iodine increased	irEndocrine
Catabolic state	irEndocrine
Catecholamines urine	irEndocrine
Catecholamines urine abnormal	irEndocrine
Catecholamines urine decreased	irEndocrine
Catecholamines urine increased	irEndocrine
Catecholamines urine normal	irEndocrine
Citrate toxicity	irEndocrine
Congenital androgen deficiency	irEndocrine
Congenital hyperthyroidism	irEndocrine
Congenital hypothyroidism	irEndocrine
Cortisol free urine	irEndocrine
Cortisol free urine abnormal	irEndocrine
Cortisol free urine decreased	irEndocrine
Cortisol free urine increased	irEndocrine
Cortisol free urine normal	irEndocrine
Cryptorchism	irEndocrine
Crystal arthropathy	irEndocrine
Cushingoid	irEndocrine
Cushing's syndrome	irEndocrine

Dehydroepiandrosterone decreased	irEndocrine
Dehydroepiandrosterone increased	irEndocrine
Dehydroepiandrosterone test	irEndocrine
Delayed menarche	irEndocrine
Delayed puberty	irEndocrine
Dexamethasone suppression test	irEndocrine
Dexamethasone suppression test negative	irEndocrine
Dexamethasone suppression test positive	irEndocrine
Dihydrotestosterone decreased	irEndocrine
Dihydrotestosterone increased	irEndocrine
Dihydrotestosterone level	irEndocrine
Disorder Of Sex Development	irEndocrine
Dwarfism	irEndocrine
Dysfunctional uterine bleeding	irEndocrine
Early menarche	irEndocrine
Ectopic hyperthyroidism	irEndocrine
Endocrine ophthalmopathy	irEndocrine
Endocrine test	irEndocrine
Endocrine test abnormal	irEndocrine
Endocrine test normal	irEndocrine
Enlarged clitoris	irEndocrine
Enzyme abnormality	irEndocrine
Enzyme induction	irEndocrine
Enzyme inhibition	irEndocrine
Epinephrine	irEndocrine
Epinephrine abnormal	irEndocrine
Epinephrine decreased	irEndocrine
Epinephrine increased	irEndocrine
Epinephrine normal	irEndocrine
Epiphyses delayed fusion	irEndocrine
Epiphyses premature fusion	irEndocrine
Eunuchoidism	irEndocrine
Exophthalmos	irEndocrine

False negative pregnancy test	irEndocrine
Female sex hormone level abnormal	irEndocrine
Feminisation acquired	irEndocrine
Fertility increased	irEndocrine
Free thyroxine index	irEndocrine
Free thyroxine index abnormal	irEndocrine
Free thyroxine index decreased	irEndocrine
Free thyroxine index increased	irEndocrine
Free thyroxine index normal	irEndocrine
Generalised resistance to thyroid hormone	irEndocrine
Glucagon tolerance test	irEndocrine
Glucocorticoids abnormal	irEndocrine
Glucocorticoids decreased	irEndocrine
Glucocorticoids increased	irEndocrine
Glucocorticoids normal	irEndocrine
Goitre	irEndocrine
Gonadotrophin deficiency	irEndocrine
Gonadotrophin releasing hormone stimulation test	irEndocrine
Growth hormone deficiency	irEndocrine
Gynaecomastia	irEndocrine
Hashimoto's encephalopathy	irEndocrine
Hashitoxicosis	irEndocrine
Hermaphroditism	irEndocrine
Hirsutism	irEndocrine
Hormone level abnormal	irEndocrine
Human Chorionic Gonadotropin	
	irEndocrine
Human Chorionic Gonadotropin Abnormal	
	irEndocrine

Human Chorionic Gonadotropin Decreased

Human Chorionic Gonadotropin Increased

Human Chorionic Gonadotropin Negative

Human Chorionic Gonadotropin Positive

Human placental lactogen decreased

Human placental lactogen increased

Hydroxycorticosteroids increased

Hydroxycorticosteroids urine

Hydroxycorticosteroids urine abnormal

Hydroxycorticosteroids urine decreased

Hydroxycorticosteroids urine increased

Hydroxycorticosteroids urine normal

Hyperadrenalism

Hyperadrenocorticism

Hyperamylasaemia

Hyperandrogenism

Hypercatabolism

Hypercorticism

Hypercreatininaemia

Hypercreatininaemia

irEndocrine

irEndocrine

irEndocrine

irEndocrine

irEndocrine

irEndocrine

irEndocrine

irEndocrine

irEndocrine

irEndocrine

irEndocrine

irEndocrine

irEndocrine

irEndocrine

irEndocrine

irEndocrine

irEndocrine

irEndocrine

irEndocrine

irEndocrine

Hypergonadism	irEndocrine
Hyperlipasaemia	irEndocrine
Hypermetabolism	irEndocrine
Hyperoxalaemia	irEndocrine
Hyperphosphatasaemia	irEndocrine
Hyperthecosis	irEndocrine
Hyperthyroidism	irEndocrine
Hypoaldosteronism	irEndocrine
Hypogonadism	irEndocrine
Hypogonadism female	irEndocrine
Hypogonadism male	irEndocrine
Hypomenorrhoea	irEndocrine
Hypometabolism	irEndocrine
Hypoparathyroidism	irEndocrine
Hypophysitis	irEndocrine
Hypopituitarism	irEndocrine
Hypopituitarism foetal	irEndocrine
Hypoprolactinaemia	irEndocrine
Hypothyroidic goitre	irEndocrine
Hypothyroidism	irEndocrine
Incomplete precocious puberty	irEndocrine
Increased steroid activity	irEndocrine
Insulin C-peptide	irEndocrine
Insulin C-peptide abnormal	irEndocrine
Insulin C-peptide decreased	irEndocrine
Insulin C-peptide increased	irEndocrine
Insulin C-peptide normal	irEndocrine
Insulin tolerance test	irEndocrine
Insulin tolerance test abnormal	irEndocrine
Insulin tolerance test normal	irEndocrine
Insulin-like growth factor	irEndocrine
Insulin-like growth factor decreased	irEndocrine
Insulin-like growth factor increased	irEndocrine

Iodine uptake	irEndocrine
Iodine uptake abnormal	irEndocrine
Iodine uptake decreased	irEndocrine
Iodine uptake increased	irEndocrine
Iodine uptake normal	irEndocrine
Isolated adrenocorticotrophic hormone deficiency	irEndocrine
Klinefelter's syndrome	irEndocrine
Luteal phase deficiency	irEndocrine
Lymphocytic hypophysitis	irEndocrine
Macroamylasaemia	irEndocrine
Marine Lenhart syndrome	irEndocrine
Menstruation delayed	irEndocrine
Menstruation irregular	irEndocrine
Metabolic disorder	irEndocrine
Metabolic encephalopathy	irEndocrine
Metabolic syndrome	irEndocrine
Metanephrine urine	irEndocrine
Metanephrine urine abnormal	irEndocrine
Metanephrine urine decreased	irEndocrine
Metanephrine urine increased	irEndocrine
Metanephrine urine normal	irEndocrine
Metyrapone challenge test	irEndocrine
Metyrapone challenge test abnormal	irEndocrine
Metyrapone challenge test normal	irEndocrine
Myotonic dystrophy	irEndocrine
Myxoedema	irEndocrine
Myxoedema coma	irEndocrine
Norepinephrine	irEndocrine
Norepinephrine abnormal	irEndocrine
Norepinephrine decreased	irEndocrine
Norepinephrine increased	irEndocrine
Norepinephrine normal	irEndocrine
Normetanephrine urine decreased	irEndocrine

Normetanephrine urine increased	irEndocrine
Oestradiol	irEndocrine
Oestradiol abnormal	irEndocrine
Oestradiol decreased	irEndocrine
Oestradiol increased	irEndocrine
Oestradiol normal	irEndocrine
Oestriol	irEndocrine
Oestriol abnormal	irEndocrine
Oestriol decreased	irEndocrine
Oestriol increased	irEndocrine
Oestriol normal	irEndocrine
Oestrogen deficiency	irEndocrine
Oestrogen receptor assay	irEndocrine
Oestrogen receptor assay negative	irEndocrine
Oestrogen receptor assay positive	irEndocrine
Oestrogenic effect	irEndocrine
Oestrogens total urine	irEndocrine
Oestrogens total urine abnormal	irEndocrine
Oestrogens total urine decreased	irEndocrine
Oestrogens total urine increased	irEndocrine
Oestrogens total urine normal	irEndocrine
Oestrone	irEndocrine
Oestrone decreased	irEndocrine
Oestrone increased	irEndocrine
Olfacto genital dysplasia	irEndocrine
Oligomenorrhoea	irEndocrine
Ovarian atrophy	irEndocrine
Ovarian failure	irEndocrine
Ovarian failure postoperative	irEndocrine
Ovarian hyperfunction	irEndocrine
Ovarian hyperstimulation syndrome	irEndocrine
Ovulation delayed	irEndocrine
Ovulation disorder	irEndocrine

Oxalosis	irEndocrine
Oxycorticosteroids increased	irEndocrine
Oxytocin	irEndocrine
Oxytocin abnormal	irEndocrine
Oxytocin decreased	irEndocrine
Oxytocin increased	irEndocrine
Oxytocin normal	irEndocrine
Parathyroid scan abnormal	irEndocrine
Parathyroid scan normal	irEndocrine
Polycystic ovaries	irEndocrine
Post procedural hypothyroidism	irEndocrine
Postpartum hypopituitarism	irEndocrine
Precocious puberty	irEndocrine
Pregnancy test	irEndocrine
Pregnancy test false positive	irEndocrine
Pregnancy test negative	irEndocrine
Pregnancy test positive	irEndocrine
Pregnancy test urine	irEndocrine
Pregnancy test urine negative	irEndocrine
Pregnancy test urine positive	irEndocrine
Premature menopause	irEndocrine
Primary adrenal insufficiency	irEndocrine
Primary hypogonadism	irEndocrine
Primary hypothyroidism	irEndocrine
Progesterone	irEndocrine
Progesterone abnormal	irEndocrine
Progesterone decreased	irEndocrine
Progesterone increased	irEndocrine
Progesterone normal	irEndocrine
Progesterone receptor assay	irEndocrine
Progesterone receptor assay negative	irEndocrine
Progesterone receptor assay positive	irEndocrine
Protein bound iodine	irEndocrine

Protein bound iodine decreased	irEndocrine
Protein bound iodine increased	irEndocrine
Pseudohermaphroditism	irEndocrine
Pseudohermaphroditism female	irEndocrine
Pseudohermaphroditism male	irEndocrine
Pseudophaeochromocytoma	irEndocrine
Pseudoprecocious puberty	irEndocrine
Radiation thyroiditis	irEndocrine
Reproductive hormone	irEndocrine
Reverse tri-iodothyronine	irEndocrine
Reverse tri-iodothyronine decreased	irEndocrine
Reverse tri-iodothyronine increased	irEndocrine
Salivary oestriol increased	irEndocrine
Scan adrenal gland	irEndocrine
Scan adrenal gland abnormal	irEndocrine
Scan adrenal gland normal	irEndocrine
Scan parathyroid	irEndocrine
Scan thyroid gland	irEndocrine
Secondary adrenocortical insufficiency	irEndocrine
Secondary hyperthyroidism	irEndocrine
Secondary hypogonadism	irEndocrine
Secondary hypothyroidism	irEndocrine
Secondary sexual characteristics absence	irEndocrine
Secretin test	irEndocrine
Secretin test increased	irEndocrine
Sertoli-cell-only syndrome	irEndocrine
Sex hormone binding globulin	irEndocrine
Sex hormone binding globulin decreased	irEndocrine
Sex hormone binding globulin increased	irEndocrine
Somatostatin receptor scan	irEndocrine
Somatostatin receptor scan abnormal	irEndocrine
Somatostatin receptor scan normal	irEndocrine
Somatotropin suppression test	irEndocrine

Somatotropin suppression test abnormal	irEndocrine
Somatotropin suppression test normal	irEndocrine
Steroid activity	irEndocrine
Steroid withdrawal syndrome	irEndocrine
Tertiary hypothyroidism	irEndocrine
Testicular atrophy	irEndocrine
Testicular failure	irEndocrine
Testicular failure primary	irEndocrine
Testicular hyperfunction	irEndocrine
Tetrahydrocortisol urine decreased	irEndocrine
Tetrahydrocortisol urine increased	irEndocrine
Tetrahydrocortisone urine decreased	irEndocrine
Tetrahydrocortisone urine increased	irEndocrine
Thyroglobulin	irEndocrine
Thyroglobulin absent	irEndocrine
Thyroglobulin decreased	irEndocrine
Thyroglobulin increased	irEndocrine
Thyroglobulin present	irEndocrine
Thyroid atrophy	irEndocrine
Thyroid function test	irEndocrine
Thyroid function test abnormal	irEndocrine
Thyroid function test normal	irEndocrine
Thyroid gland abscess	irEndocrine
Thyroid gland scan abnormal	irEndocrine
Thyroid gland scan normal	irEndocrine
Thyroid releasing hormone challenge test	irEndocrine
Thyroid releasing hormone challenge test abnormal	irEndocrine
Thyroid releasing hormone challenge test normal	irEndocrine
Thyroiditis	irEndocrine
Thyroiditis acute	irEndocrine
Thyroiditis chronic	irEndocrine
Thyroiditis fibrous chronic	irEndocrine
Thyroiditis subacute	irEndocrine

Thyrototoxic crisis	irEndocrine
Thyrototoxic periodic paralysis	irEndocrine
Thyroxin binding globulin	irEndocrine
Thyroxin binding globulin abnormal	irEndocrine
Thyroxin binding globulin decreased	irEndocrine
Thyroxin binding globulin increased	irEndocrine
Thyroxin binding globulin normal	irEndocrine
Thyroxine	irEndocrine
Thyroxine abnormal	irEndocrine
Thyroxine decreased	irEndocrine
Thyroxine free	irEndocrine
Thyroxine free abnormal	irEndocrine
Thyroxine free decreased	irEndocrine
Thyroxine free increased	irEndocrine
Thyroxine free normal	irEndocrine
Thyroxine increased	irEndocrine
Thyroxine normal	irEndocrine
Toxic nodular goitre	irEndocrine
Tri-iodothyronine	irEndocrine
Tri-iodothyronine abnormal	irEndocrine
Tri-iodothyronine decreased	irEndocrine
Tri-iodothyronine free	irEndocrine
Tri-iodothyronine free abnormal	irEndocrine
Tri-iodothyronine free decreased	irEndocrine
Tri-iodothyronine free increased	irEndocrine
Tri-iodothyronine free normal	irEndocrine
Tri-iodothyronine increased	irEndocrine
Tri-iodothyronine normal	irEndocrine
Tri-iodothyronine uptake	irEndocrine
Tri-iodothyronine uptake abnormal	irEndocrine
Tri-iodothyronine uptake decreased	irEndocrine
Tri-iodothyronine uptake increased	irEndocrine
Tri-iodothyronine uptake normal	irEndocrine

True precocious puberty	irEndocrine
Turner's syndrome	irEndocrine
Ultrasound thyroid	irEndocrine
Ultrasound thyroid abnormal	irEndocrine
Ultrasound thyroid normal	irEndocrine
Urine cortisol/creatinine ratio	irEndocrine
Urine cortisol/creatinine ratio abnormal	irEndocrine
Urine cortisol/creatinine ratio decreased	irEndocrine
Urine cortisol/creatinine ratio increased	irEndocrine
Urine cortisol/creatinine ratio normal	irEndocrine
Vanillyl mandelic acid urine	irEndocrine
Vanillyl mandelic acid urine decreased	irEndocrine
Vanillyl mandelic acid urine increased	irEndocrine
Vasoactive intestinal polypeptide test	irEndocrine
Virilism	irEndocrine
Virilism foetal	irEndocrine
XXXY syndrome	irEndocrine
XXYY syndrome	irEndocrine
Abdominal wall haematoma	irGI
Allergic colitis	irGI
Anal erosion	irGI
Anal haemorrhage	irGI
Anal ulcer	irGI
Anal ulcer haemorrhage	irGI
Anastomotic ulcer	irGI
Anastomotic ulcer haemorrhage	irGI
Anastomotic ulcer perforation	irGI
Anastomotic ulcer, obstructive	irGI
Anorectal ulcer	irGI
Aorto-oesophageal fistula	irGI
Aphthous stomatitis	irGI
Appendicitis noninfective	irGI
Appendicitis perforated	irGI

Arthritis enteropathic	irGI
Bloody peritoneal effluent	irGI
Caecitis	irGI
Chronic gastrointestinal bleeding	irGI
Colitis	irGI
Colitis erosive	irGI
Colitis ischaemic	irGI
Colitis microscopic	
	irGI
Colitis psychogenic	irGI
Colitis ulcerative	irGI
Colonic haematoma	irGI
Contact stomatitis	irGI
Crohn's disease	irGI
Cytomegalovirus mucocutaneous ulcer	irGI
Diarrhoea	irGI
Diarrhoea haemorrhagic	irGI
Diarrhoea neonatal	irGI
Diverticular perforation	irGI
Diverticulitis intestinal haemorrhagic	irGI
Diverticulum intestinal haemorrhagic	irGI
Duodenal perforation	irGI
Duodenal scarring	irGI
Duodenal ulcer	irGI
Duodenal ulcer haemorrhage	irGI
Duodenal ulcer perforation	irGI
Duodenal ulcer perforation, obstructive	irGI
Duodenal ulcer, obstructive	irGI
Duodenitis	irGI
Duodenitis haemorrhagic	irGI
Enteritis	irGI
Enteritis leukopenic	irGI
Enterocolitis	irGI

Enterocolitis haemorrhagic	irGI
Eosinophilic colitis	irGI
Eosinophilic oesophagitis	irGI
Epiploic appendagitis	irGI
Erosive duodenitis	irGI
Erosive oesophagitis	irGI
Gastric antral vascular ectasia	irGI
Gastric haemorrhage	irGI
Gastric perforation	irGI
Gastric ulcer	irGI
Gastric ulcer haemorrhage	irGI
Gastric ulcer haemorrhage, obstructive	irGI
Gastric ulcer helicobacter	irGI
Gastric ulcer perforation	irGI
Gastric ulcer perforation, obstructive	irGI
Gastric ulcer, obstructive	irGI
Gastric varices haemorrhage	irGI
Gastritis	irGI
Gastritis alcoholic	irGI
Gastritis alcoholic haemorrhagic	irGI
Gastritis atrophic	irGI
Gastritis erosive	irGI
Gastritis haemorrhagic	irGI
Gastritis hypertrophic	irGI
Gastroduodenal haemorrhage	irGI
Gastroduodenal ulcer	irGI
Gastroduodenitis	irGI
Gastroduodenitis haemorrhagic	irGI
Gastroenteritis eosinophilic	irGI
Gastroenteritis radiation	irGI
Gastrointestinal erosion	irGI
Gastrointestinal haemorrhage	irGI
Gastrointestinal inflammation	irGI

Gastrointestinal perforation	irGI
Gastrointestinal toxicity	irGI
Gastrointestinal ulcer	irGI
Gastrointestinal ulcer haemorrhage	irGI
Gastrointestinal ulcer perforation	irGI
Gastrooesophageal Reflux Disease	
	irGI
Gastrooesophagitis	irGI
Gingival bleeding	irGI
Haematemesis	irGI
Haematochezia	irGI
Haemorrhagic ascites	irGI
Haemorrhagic erosive gastritis	irGI
Ileal perforation	irGI
Ileal ulcer	irGI
Ileal ulcer perforation	irGI
Ileitis	irGI
Inflammatory bowel disease	irGI
Intestinal haemorrhage	irGI
Intestinal perforation	irGI
Intestinal ulcer	irGI
Intestinal ulcer perforation	irGI
Intra-abdominal haemorrhage	irGI
Jejunal perforation	irGI
Jejunal ulcer	irGI
Jejunal ulcer perforation	irGI
Jejunitis	irGI
Large intestinal haemorrhage	irGI
Large intestinal ulcer	irGI
Large intestinal ulcer haemorrhage	irGI
Large intestine perforation	irGI
Lip haematoma	irGI

Lip haemorrhage	irGI
Lower gastrointestinal haemorrhage	irGI
Lupus enteritis	irGI
Malacoplakia gastrointestinal	irGI
Mallory-Weiss syndrome	irGI
Melaena	irGI
Melaena neonatal	irGI
Mesenteric panniculitis	irGI
Mesenteritis	irGI
Mouth haemorrhage	irGI
Mouth ulceration	irGI
Necrotising colitis	irGI
Necrotising enterocolitis neonatal	irGI
Necrotising gastritis	irGI
Necrotising oesophagitis	irGI
Neutropenic colitis	irGI
Oesophageal haemorrhage	irGI
Oesophageal perforation	irGI
Oesophageal rupture	irGI
Oesophageal ulcer	irGI
Oesophageal ulcer haemorrhage	irGI
Oesophageal ulcer perforation	irGI
Oesophageal varices haemorrhage	irGI
Oesophagitis	irGI
Oesophagitis chemical	irGI
Oesophagitis haemorrhagic	irGI
Oesophagitis ulcerative	irGI
Oral mucosa erosion	irGI
Pancreatic haemorrhage	irGI
Parotid gland haemorrhage	irGI
Peptic ulcer	irGI
Peptic ulcer haemorrhage	irGI
Peptic ulcer perforation	irGI

Peptic ulcer perforation, obstructive	irGI
Peptic ulcer reactivated	irGI
Peptic ulcer, obstructive	irGI
Periproctitis	irGI
Peritoneal haematoma	irGI
Peritoneal haemorrhage	irGI
Pharyngeal haematoma	irGI
Pharyngeal haemorrhage	irGI
Portal hypertensive enteropathy	irGI
Portal hypertensive gastropathy	irGI
Post procedural diarrhoea	irGI
Pouchitis	irGI
Proctitis	irGI
Proctitis haemorrhagic	irGI
Proctitis ulcerative	irGI
Proctocolitis	irGI
Pseudopolyposis	irGI
Pyoderma gangrenosum	irGI
Radiation oesophagitis	irGI
Rectal haemorrhage	irGI
Rectal perforation	irGI
Rectal ulcer	irGI
Rectal ulcer haemorrhage	irGI
Reflux gastritis	irGI
Remnant gastritis	irGI
Sigmoiditis	irGI
Small bowel angioedema	irGI
Small intestinal haemorrhage	irGI
Small intestinal perforation	irGI
Small intestinal ulcer haemorrhage	irGI
Small intestine ulcer	irGI
Stomatitis	irGI
Stomatitis haemorrhagic	irGI

Stomatitis necrotising	irGI
Stomatitis radiation	irGI
Stress ulcer	irGI
Tongue haematoma	irGI
Tongue haemorrhage	irGI
Tooth socket haemorrhage	irGI
Toxic dilatation of intestine	irGI
Upper gastrointestinal haemorrhage	irGI
5'nucleotidase	irHepatic
5'nucleotidase decreased	irHepatic
5'nucleotidase increased	irHepatic
Acute fatty liver of pregnancy	irHepatic
Acute graft versus host disease in liver	irHepatic
Acute hepatic failure	irHepatic
Alanine aminotransferase	irHepatic
Alanine aminotransferase abnormal	irHepatic
Alanine aminotransferase decreased	irHepatic
Alanine aminotransferase increased	irHepatic
Alanine aminotransferase normal	irHepatic
Alcoholic liver disease	irHepatic
Ammonia	irHepatic
Ammonia abnormal	irHepatic
Ammonia decreased	irHepatic
Ammonia increased	irHepatic
Ammonia normal	irHepatic
Aspartate aminotransferase	irHepatic
Aspartate aminotransferase abnormal	irHepatic
Aspartate aminotransferase decreased	irHepatic
Aspartate aminotransferase increased	irHepatic
Aspartate aminotransferase normal	irHepatic
Asterixis	irHepatic
Autoimmune hepatitis	irHepatic
Bile duct pressure	irHepatic

16 February 2012: Autoimmune hepatitis added from ir Others

Bile duct pressure increased	irHepatic
Bile output	irHepatic
Bile output abnormal	irHepatic
Bile output decreased	irHepatic
Bile output increased	irHepatic
Bilirubin conjugated	irHepatic
Bilirubin conjugated abnormal	irHepatic
Bilirubin conjugated increased	irHepatic
Bilirubin conjugated normal	irHepatic
Bilirubin excretion disorder	irHepatic
Bilirubin urine	irHepatic
Blood bilirubin	irHepatic
Blood bilirubin abnormal	irHepatic
Blood bilirubin decreased	irHepatic
Blood bilirubin increased	irHepatic
Blood bilirubin normal	irHepatic
Blood bilirubin unconjugated	irHepatic
Blood bilirubin unconjugated increased	irHepatic
Blood bilirubin unconjugated normal	irHepatic
Blood cholinesterase	irHepatic
Blood cholinesterase abnormal	irHepatic
Blood cholinesterase decreased	irHepatic
Blood cholinesterase increased	irHepatic
Blood cholinesterase normal	irHepatic
Bromosulphthalein test	irHepatic
Bromosulphthalein test abnormal	irHepatic
Bromosulphthalein test normal	irHepatic
Child-Pugh-Turcotte score increased	irHepatic
Cholestasis	irHepatic
Cholestasis of pregnancy	irHepatic
Cholestatic liver injury	irHepatic
Chronic hepatic failure	irHepatic
Chronic hepatitis	irHepatic

Coma hepatic	irHepatic
Crigler-Najjar syndrome	irHepatic
Cystic fibrosis hepatic disease	irHepatic
Cytolytic hepatitis	irHepatic
Deficiency Of Bile Secretion	
	irHepatic
Fatty liver alcoholic	irHepatic
Fractionated bile acids	irHepatic
Galactose elimination capacity test	irHepatic
Galactose elimination capacity test abnormal	irHepatic
Galactose elimination capacity test decreased	irHepatic
Galactose elimination capacity test increased	irHepatic
Galactose elimination capacity test normal	irHepatic
Gamma-glutamyltransferase	irHepatic
Gamma-glutamyltransferase abnormal	irHepatic
Gamma-glutamyltransferase decreased	irHepatic
Gamma-glutamyltransferase increased	irHepatic
Gamma-glutamyltransferase normal	irHepatic
Glycogen storage disease type I	irHepatic
Glycogen storage disease type III	irHepatic
Glycogen storage disease type VI	irHepatic
Granulomatous liver disease	irHepatic
Guanase increased	irHepatic
HELLP syndrome	irHepatic
Hepaplastin abnormal	irHepatic
Hepaplastin decreased	irHepatic
Hepaplastin increased	irHepatic
Hepaplastin normal	irHepatic
Hepaplastin test	irHepatic
Hepatic artery flow decreased	irHepatic
Hepatic encephalopathy	irHepatic
Hepatic enzyme	irHepatic
Hepatic enzyme abnormal	irHepatic

Hepatic enzyme decreased	irHepatic
Hepatic enzyme increased	irHepatic
Hepatic failure	irHepatic
Hepatic function abnormal	irHepatic
Hepatic infiltration eosinophilic	irHepatic
Hepatic necrosis	irHepatic
Hepatic steatosis	irHepatic
Hepatic vascular resistance increased	irHepatic
Hepatitis	irHepatic
Hepatitis acute	irHepatic
Hepatitis alcoholic	irHepatic
Hepatitis cholestatic	irHepatic
Hepatitis chronic active	irHepatic
Hepatitis chronic persistent	irHepatic
Hepatitis fulminant	irHepatic
Hepatitis mumps	irHepatic
Hepatitis neonatal	irHepatic
Hepatitis toxic	irHepatic
Hepatocellular damage neonatal	irHepatic
Hepatocellular foamy cell syndrome	irHepatic
Hepatocellular injury	irHepatic
Hepatorenal failure	irHepatic
Hepatorenal syndrome	irHepatic
Hepatotoxicity	irHepatic
Hyperammonaemia	irHepatic
Hyperbilirubinaemia	irHepatic
Hyperbilirubinaemia neonatal	irHepatic
Hypertransaminasaemia	irHepatic
Hypoalbuminaemia	irHepatic
Hypoproteinaemia	irHepatic
Icterus index	irHepatic
Icterus index decreased	irHepatic
Icterus index increased	irHepatic

Ischaemic hepatitis	irHepatic
Jaundice	irHepatic
Jaundice acholuric	irHepatic
Jaundice cholestatic	irHepatic
Jaundice extrahepatic obstructive	irHepatic
Jaundice hepatocellular	irHepatic
Jaundice neonatal	irHepatic
Kernicterus	irHepatic
Leucine aminopeptidase	irHepatic
Leucine aminopeptidase decreased	irHepatic
Leucine aminopeptidase increased	irHepatic
Liver disorder	irHepatic
Liver function test	irHepatic
Liver function test abnormal	irHepatic
Liver function test normal	irHepatic
Liver sarcoidosis	irHepatic
Lupus hepatitis	irHepatic
Mitochondrial aspartate aminotransferase increased	irHepatic
Mixed liver injury	irHepatic
Molar ratio of total branched-chain amino acid to tyrosine	irHepatic
Neonatal cholestasis	irHepatic
Ocular icterus	irHepatic
Peliosis hepatis	irHepatic
Portal triaditis	irHepatic
Portal vein flow decreased	irHepatic
Portal vein pressure increased	irHepatic
Post cholecystectomy syndrome	irHepatic
Radiation hepatitis	irHepatic
Reye's syndrome	irHepatic
Stauffer's syndrome	irHepatic
Subacute hepatic failure	irHepatic
Total bile acids	irHepatic
Total bile acids increased	irHepatic

16 February 2012: Liver disorder added

Transaminases	irHepatic
Transaminases abnormal	irHepatic
Transaminases decreased	irHepatic
Transaminases increased	irHepatic
Urinary 6 beta hydroxycortisol/cortisol ratio	irHepatic
Urine bilirubin decreased	irHepatic
Urine bilirubin increased	irHepatic
Urobilinogen faeces	irHepatic
Urobilinogen faeces abnormal	irHepatic
Urobilinogen faeces decreased	irHepatic
Urobilinogen faeces increased	irHepatic
Urobilinogen faeces normal	irHepatic
Urobilinogen Urine	irHepatic
Urobilinogen Urine Decreased	irHepatic
Urobilinogen Urine Increased	irHepatic
Yellow skin	irHepatic
Zieve syndrome	irHepatic
ABO haemolytic disease of newborn	irOthers
ABO incompatibility	irOthers
Acute disseminated encephalomyelitis	irOthers
Acute graft versus host disease	irOthers
Acute graft versus host disease in intestine	irOthers
Acute graft versus host disease in skin	irOthers
Acute haemorrhagic leukoencephalitis	irOthers
Agranulocytosis	irOthers
Alcoholic pancreatitis	irOthers
Allergic bronchitis	irOthers
Allergic cough	irOthers
Allergic cystitis	irOthers
Allergic keratitis	irOthers
Allergic oedema	irOthers
Allergic otitis media	irOthers
Allergic pharyngitis	irOthers

16 February 2012: Acute interstitial pneumonitis moved to Ir Pulmonary

16 February 2012: Allergic granulomatous angiitis moved to Ir Pulmonary

Allergic respiratory disease	irOthers
Allergic respiratory symptom	irOthers
Allergic sinusitis	irOthers
Allergic transfusion reaction	irOthers
Allergy to animal	irOthers
Allergy to arthropod bite	irOthers
Allergy to arthropod sting	irOthers
Allergy to chemicals	irOthers
Allergy to fermented products	irOthers
Allergy to metals	irOthers
Allergy to sting	irOthers
Allergy to vaccine	irOthers
Allergy to venom	irOthers
Alloimmunisation	irOthers
Amyloid arthropathy	irOthers
Amyloidosis	irOthers
Amyloidosis senile	irOthers
Anaemia haemolytic autoimmune	irOthers
Analgesic asthma syndrome	irOthers
Anaphylactic reaction	irOthers
Anaphylactic shock	irOthers
Anaphylactic transfusion reaction	irOthers
Anaphylactoid reaction	irOthers
Anaphylactoid shock	irOthers
Anaphylactoid syndrome of pregnancy	irOthers
Angiolymphoid hyperplasia with eosinophilia	irOthers
Ankylosing spondylitis	irOthers
Anti-neutrophil cytoplasmic antibody positive vasculitis	irOthers
Antiphospholipid syndrome	irOthers
Antisynthetase syndrome	irOthers
Aplasia pure red cell	irOthers
Aplastic anaemia	irOthers
Application site hypersensitivity	irOthers

16 February 2012: Alveolitis, Alveolitis allergic, Alveolitis fibrosing, and Alveolitis

Arteritis	irOthers
Arteritis coronary	irOthers
Arteritis infective	irOthers
Arteritis obliterans	irOthers
Arthritis	irOthers
Arthritis allergic	irOthers
Asthma	irOthers
Asthma late onset	irOthers
Atopic cataract	irOthers
Atopic keratoconjunctivitis	irOthers
Atopy	irOthers
Autoimmune disorder	irOthers
Autoimmune inner ear disease	irOthers
Autoimmune lymphoproliferative syndrome	irOthers
Autoimmune myocarditis	irOthers
Autoimmune neutropenia	irOthers
Autoimmune pancreatitis	irOthers
Autoimmune pancytopenia	irOthers
Autoimmune thrombocytopenia	irOthers
Bacterial allergy	irOthers
Biliary cirrhosis primary	irOthers
Blepharitis allergic	irOthers
Blood amylase	irOthers
Blood amylase abnormal	irOthers
Blood amylase decreased	irOthers
Blood amylase increased	irOthers
Blood amylase normal	irOthers
Blood elastase	irOthers
Blood elastase decreased	irOthers
Blood elastase increased	irOthers
Blood trypsin decreased	irOthers
Blood trypsin increased	irOthers
Bone marrow transplant rejection	irOthers

16 February 2012: Autoimmune hepatitis moved to irHepatitis

Bronchopulmonary aspergillosis allergic	irOthers
Bronchospasm	irOthers
Caplan's syndrome	irOthers
Cardiac amyloidosis	irOthers
Cardiac sarcoidosis	irOthers
Cerebral amyloid angiopathy	irOthers
Cerebral arteritis	irOthers
Cerebral sarcoidosis	irOthers
Cholangitis sclerosing	irOthers
Chronic allograft nephropathy	irOthers
Chronic graft versus host disease	irOthers
Chronic inflammatory demyelinating polyradiculoneuropathy	irOthers
Coeliac disease	irOthers
Cold type haemolytic anaemia	irOthers
Conjunctivitis allergic	irOthers
Contrast media allergy	irOthers
Contrast media reaction	irOthers
Coombs Negative Haemolytic Anaemia	irOthers
Coombs positive haemolytic anaemia	irOthers
Corneal graft rejection	irOthers
CREST syndrome	irOthers
Cryofibrinogenaemia	irOthers
Cryoglobulinaemia	irOthers
Cutaneous amyloidosis	irOthers
Cutaneous lupus erythematosus	irOthers
Cyclic Neutropenia	irOthers
Cytokine release syndrome	irOthers
Cytokine storm	irOthers
Cytomegalovirus pancreatitis	irOthers
Decreased immune responsiveness	irOthers
Dermatomyositis	irOthers
Diabetic mastopathy	irOthers
Dialysis amyloidosis	irOthers

Diffuse vasculitis	irOthers
Drug hypersensitivity	irOthers
Dry Eye	irOthers
Encephalitis allergic	irOthers
Encephalitis post measles	irOthers
Encephalitis post varicella	irOthers
Encephalopathy allergic	irOthers
Engraftment syndrome	irOthers
Eosinophilia	irOthers
Eosinophilia myalgia syndrome	irOthers
Eosinophilic bronchitis	irOthers
Eosinophilic cellulitis	irOthers
Eosinophilic cystitis	irOthers
Eosinophilic fasciitis	irOthers
Eosinophilic myocarditis	irOthers
Eosinophilic pustular folliculitis	irOthers
Eosinophilic pustulosis	irOthers
Eosinophilic rhinitis	irOthers
Episcleritis	irOthers
Erythema induratum	irOthers
Erythema nodosum	irOthers
Evans syndrome	irOthers
Exocrine pancreatic function test	irOthers
Exocrine pancreatic function test abnormal	irOthers
Exocrine pancreatic function test normal	irOthers
Eye allergy	irOthers
Familial amyloidosis	irOthers
Familial mediterranean fever	irOthers
Febrile Neutropenia	irOthers
Felty's syndrome	irOthers
Fibrillary glomerulonephritis	irOthers
First use syndrome	irOthers

16 February 2012: Eosinophilic pneumonia, Eosinophilic pneumonia acute and chronic, Eosinophilic pneumonia
Pulmonary

Flour sensitivity	irOthers
Focal segmental glomerulosclerosis	irOthers
Food allergy	irOthers
Gastrointestinal amyloidosis	irOthers
Giant papillary conjunctivitis	irOthers
Glomerulonephritis	irOthers
Glomerulonephritis acute	irOthers
Glomerulonephritis chronic	irOthers
Glomerulonephritis membranoproliferative	irOthers
Glomerulonephritis membranous	irOthers
Glomerulonephritis minimal lesion	irOthers
Glomerulonephritis proliferative	irOthers
Glomerulonephritis rapidly progressive	irOthers
Goodpasture's syndrome	irOthers
Graft versus host disease	irOthers
Graft versus host disease in lung	irOthers
Granulocytopenia	irOthers
Guillain-Barre syndrome	irOthers
Haemolytic anaemia	irOthers
Haemolytic transfusion reaction	irOthers
Heart transplant rejection	irOthers
Heart-lung transplant rejection	irOthers
Henoch-Schonlein purpura	irOthers
Henoch-Schonlein purpura nephritis	irOthers
Heparin-induced thrombocytopenia	irOthers
Hepatitis virus-associated nephropathy	irOthers
Hereditary neuropathic amyloidosis	irOthers
Hereditary pancreatitis	irOthers
Histiocytosis haematophagic	irOthers
House dust allergy	irOthers
Human seminal plasma hypersensitivity	irOthers
Hypereosinophilic syndrome	irOthers
Hypergammaglobulinaemia	irOthers

16 February 2012: Granulomatous pneumonitis moved to Ir Pulmonary

Hypersensitivity	irOthers
Idiopathic Neutropenia	irOthers
Idiopathic thrombocytopenic purpura	irOthers
IgA nephropathy	irOthers
Immediate post-injection reaction	irOthers
Immune system disorder	irOthers
Immunisation reaction	irOthers
Immunotactoid glomerulonephritis	irOthers
Implant site hypersensitivity	irOthers
Infection masked	irOthers
Infusion related reaction	irOthers
Infusion site hypersensitivity	irOthers
Infusion site oedema	irOthers
Infusion site reaction	irOthers
Injection related reaction	irOthers
Injection site hypersensitivity	irOthers
Injection site oedema	irOthers
Injection site reaction	irOthers
Injection site vasculitis	irOthers
Insulin autoimmune syndrome	irOthers
Intermediate uveitis	irOthers
Intestine transplant rejection	irOthers
Iodine allergy	irOthers
Iris hyperpigmentation	irOthers
Iris hypopigmentation	irOthers
Iritis	irOthers
Ischaemic pancreatitis	irOthers
Isoimmune haemolytic disease	irOthers
Jarisch-Herxheimer reaction	irOthers
Juvenile arthritis	irOthers
Kaposi's varicelliform eruption	irOthers
Kawasaki's disease	irOthers
Keratoderma blenorrhagica	irOthers

16 February 2012: Infusion related reaction added

16 February 2012: Infusion site oedema added

16 February 2012: Infusion site reaction added

16 February 2012: Injection related reaction added

16 February 2012: Injection site oedema added

16 February 2012: Injection site reaction added

16 February 2012: Interstitial lung disease moved to Ir Pulmonary

Kidney transplant rejection	irOthers
Kounis syndrome	irOthers
Langerhans' Cell Histiocytosis	irOthers
Laryngeal rheumatoid arthritis	irOthers
Laryngitis allergic	irOthers
Latent autoimmune diabetes in adults	irOthers
Leukoencephalomyelitis	irOthers
Lewis-Sumner syndrome	irOthers
Lipase	irOthers
Lipase abnormal	irOthers
Lipase decreased	irOthers
Lipase increased	irOthers
Lipase normal	irOthers
Lipase urine	irOthers
Lipase urine decreased	irOthers
Lipase urine increased	irOthers
Liver and pancreas transplant rejection	irOthers
Liver transplant rejection	irOthers
Lung transplant rejection	irOthers
Lupoid hepatic cirrhosis	irOthers
Lupus encephalitis	irOthers
Lupus endocarditis	irOthers
Lupus myocarditis	irOthers
Lupus nephritis	irOthers
Lupus pancreatitis	irOthers
Lupus vasculitis	irOthers
Lupus-like syndrome	irOthers
Mendelson's syndrome	irOthers
Meningism	irOthers
Meningitis	irOthers
Meningitis aseptic	irOthers
Meningitis eosinophilic	irOthers
Meningitis noninfective	irOthers

16 February 2012: Loeffler's syndrome, Lower respiratory tract inflammation

16 February 2012: Lupus pneumonitis moved to IrPulmonary

Mesangioproliferative glomerulonephritis	irOthers
Microscopic polyangiitis	irOthers
Milk allergy	irOthers
Mixed connective tissue disease	irOthers
Morphoea	irOthers
Multifocal motor neuropathy	irOthers
Multi-organ failure	irOthers
Multiple allergies	irOthers
Multiple chemical sensitivity	irOthers
Multiple organ transplant rejection	irOthers
Muscular sarcoidosis	irOthers
Myasthenia gravis	irOthers
Myasthenia gravis crisis	irOthers
Myasthenia gravis neonatal	irOthers
Mycotic allergy	irOthers
Myocarditis	irOthers
Myocarditis post infection	irOthers
Necrotising Bronchiolitis	irOthers
Necrotising panniculitis	irOthers
Neonatal lupus erythematosus	irOthers
Nephritic syndrome	irOthers
Nephritis	irOthers
Nephritis allergic	irOthers
Nephritis autoimmune	irOthers
Nephritis haemorrhagic	irOthers
Nephritis radiation	irOthers
Nephrogenic systemic fibrosis	irOthers
Nephrotic syndrome	irOthers
Neuropsychiatric lupus	irOthers
Neutropenia	irOthers
Ocular myasthenia	irOthers
Ocular sarcoidosis	irOthers
Ocular vasculitis	irOthers

Oedematous pancreatitis	irOthers
Oral allergy syndrome	irOthers
Overlap syndrome	irOthers
Pancreas infection	irOthers
Pancreas transplant rejection	irOthers
Pancreatic abscess	irOthers
Pancreatic enzymes	irOthers
Pancreatic enzymes abnormal	irOthers
Pancreatic enzymes decreased	irOthers
Pancreatic enzymes increased	irOthers
Pancreatic enzymes normal	irOthers
Pancreatic phlegmon	irOthers
Pancreatitis	irOthers
Pancreatitis acute	irOthers
Pancreatitis bacterial	irOthers
Pancreatitis chronic	irOthers
Pancreatitis fungal	irOthers
Pancreatitis haemorrhagic	irOthers
Pancreatitis helminthic	irOthers
Pancreatitis mumps	irOthers
Pancreatitis necrotising	irOthers
Pancreatitis relapsing	irOthers
Pancreatitis viral	irOthers
Pancreatorenal syndrome	irOthers
Panniculitis	irOthers
Paraneoplastic dermatomyositis	irOthers
Paraneoplastic retinopathy	irOthers
Parasite allergy	irOthers
Pepsinogen I decreased	irOthers
Pepsinogen I increased	irOthers
Perennial allergy	irOthers
Perfume sensitivity	irOthers
Pericarditis lupus	irOthers

Peritonitis lupus	irOthers
Pernicious anaemia	irOthers
Photosensitivity allergic reaction	irOthers
Pneumonia aspiration	irOthers
Pneumonia lipoid	irOthers
Polyarteritis nodosa	irOthers
Polyarthritis	irOthers
Polychondritis	irOthers
Polyglandular autoimmune syndrome type I	irOthers
Polyglandular autoimmune syndrome type II	irOthers
Polyglandular autoimmune syndrome type III	irOthers
Polymyalgia rheumatica	irOthers
Polymyositis	irOthers
Polyneuropathy in malignant disease	irOthers
Post streptococcal glomerulonephritis	irOthers
Primary amyloidosis	irOthers
Pseudomononucleosis	irOthers
Pseudovasculitis	irOthers
Pulmonary amyloidosis	irOthers
Pulmonary mycotoxicosis	irOthers
Pulmonary renal syndrome	irOthers
Reaction to azo-dyes	irOthers
Reaction to colouring	irOthers
Reaction to drug excipients	irOthers
Reaction to food additive	irOthers
Reaction to preservatives	irOthers
Refractoriness to platelet transfusion	irOthers
Reiter's syndrome	irOthers
Renal amyloidosis	irOthers
Renal and pancreas transplant rejection	irOthers
Renal arteritis	irOthers
Renal vasculitis	irOthers
Retinal depigmentation	irOthers

16 February 2012: Pneumonitis moved to IrPulmonary

16 February 2012: Pulmonary eosinophilia and Pulmonary granuloma moved to IrPulmonary

16 February 2012: Pulmonary sarcoidosis and Pulmonary vasculitis moved to IrPulmonary

Retinal vasculitis	irOthers
Rhesus haemolytic disease of newborn	irOthers
Rhesus incompatibility	irOthers
Rheumatic fever	irOthers
Rheumatoid arthritis	irOthers
Rheumatoid lung	irOthers
Rheumatoid nodule	irOthers
Rheumatoid scleritis	irOthers
Rheumatoid vasculitis	irOthers
Rhinitis allergic	irOthers
Rhinitis perennial	irOthers
Rhinitis seasonal	irOthers
Scleritis	irOthers
Scleritis allergic	irOthers
Scleroderma	irOthers
Scleroderma renal crisis	irOthers
Seasonal Allergy	irOthers
Secondary amyloidosis	irOthers
Sepsis syndrome	irOthers
Septal panniculitis	irOthers
Serum sickness	irOthers
Serum sickness-like reaction	irOthers
Shrinking lung syndrome	irOthers
Sjogren's Syndrome	irOthers
Skin graft rejection	irOthers
Skin reaction	irOthers
SLE arthritis	irOthers
Smoke sensitivity	irOthers
Solvent sensitivity	irOthers
Still's disease adult onset	irOthers
Stool chymotrypsin decreased	irOthers
Sympathetic ophthalmia	irOthers

16 February 2012: Sarcoidosis moved to IrPulmonary

Systemic inflammatory response syndrome	irOthers
Systemic lupus erythematosus	irOthers
Systemic sclerosis	irOthers
Tachyphylaxis	irOthers
Takayasu's arteritis	irOthers
Temporal arteritis	irOthers
Thromboangiitis obliterans	irOthers
Thymus enlargement	irOthers
Tongue amyloidosis	irOthers
Toxic oil syndrome	irOthers
Transfusion microchimerism	irOthers
Transfusion reaction	irOthers
Transplant rejection	irOthers
Tropical eosinophilia	irOthers
Tubulointerstitial nephritis	irOthers
Tubulointerstitial nephritis and uveitis syndrome	irOthers
Tumour necrosis factor receptor-associated periodic syndrome	irOthers
Type 2 Lepa Reaction	irOthers
Type I hypersensitivity	irOthers
Type II hypersensitivity	irOthers
Type III immune complex mediated reaction	irOthers
Type IV hypersensitivity reaction	irOthers
Urine amylase	irOthers
Urine amylase abnormal	irOthers
Urine amylase decreased	irOthers
Urine amylase increased	irOthers
Urine amylase normal	irOthers
Uveitis	irOthers
Vaccination complication	irOthers
Vaccination site hypersensitivity	irOthers
Vasculitis	irOthers
Vasculitis cerebral	irOthers

16 February 2012: Systemic sclerosis pulmonary moved to IrPulmonary

Vasculitis gastrointestinal	irOthers
Vasculitis necrotising	irOthers
Viral vasculitis	irOthers
Warm type haemolytic anaemia	irOthers
White clot syndrome	irOthers
Acute interstitial pneumonitis	irPulmonary
Acute lung injury	irPulmonary
Acute respiratory distress syndrome	irPulmonary
Acute respiratory failure	irPulmonary
Allergic granulomatous angiitis	irPulmonary
Alveolar proteinosis	irPulmonary
Alveolitis	irPulmonary
Alveolitis allergic	irPulmonary
Alveolitis fibrosing	irPulmonary
Alveolitis necrotising	irPulmonary
Diffuse alveolar damage	irPulmonary
Diffuse panbronchiolitis	irPulmonary
Eosinophilic pneumonia	irPulmonary
Eosinophilic pneumonia acute	irPulmonary
Eosinophilic pneumonia chronic	irPulmonary
Granulomatous pneumonitis	irPulmonary
Idiopathic pneumonia syndrome	irPulmonary
Interstitial lung disease	irPulmonary
Loeffler's syndrome	irPulmonary
Lower respiratory tract inflammation	irPulmonary
Lung infiltration	irPulmonary
Lupus pneumonitis	irPulmonary
Organising pneumonia	irPulmonary
Pneumonitis	irPulmonary
Pulmonary eosinophilia	irPulmonary
Pulmonary granuloma	irPulmonary
Pulmonary sarcoidosis	irPulmonary
Pulmonary toxicity	irPulmonary

16 February 2012: Wegener's granulomatosis moved to IrPulmonary

16 February 2012: irPulmonary is created with the following PTs

Acute interstitial pneumonitis (moved from IrOthers)

Acute lung injury

Acute respiratory distress syndrome

Acute respiratory failure

Allergic granulomatous angiitis (moved from IrOthers)

Alveolar proteinosis

Alveolitis (moved from IrOthers)

Alveolitis allergic (moved from IrOthers)

Alveolitis fibrosing (moved from IrOthers)

Alveolitis necrotising (moved from IrOthers)

Diffuse alveolar damage (moved from IrOthers)

Diffuse panbronchiolitis (moved from IrOthers)

Eosinophilic pneumonia (moved from IrOthers)

Eosinophilic pneumonia acute (moved from IrOthers)

Eosinophilic pneumonia chronic (moved from IrOthers)

Granulomatous pneumonitis (moved from IrOthers)

Idiopathic pneumonia syndrome

Interstitial lung disease (moved from IrOthers)

Loeffler's syndrome (moved from IrOthers)

Lower respiratory tract inflammation (moved from IrOthers)

Lung infiltration (moved from IrOthers)

Lupus pneumonitis (moved from IrOthers)

Organising pneumonia

Pneumonitis (moved from IrOthers)

Pulmonary eosinophilia (moved from IrOthers)

Pulmonary granuloma (moved from IrOthers)

Pulmonary sarcoidosis (moved from IrOthers)

Pulmonary toxicity

Pulmonary vasculitis	irPulmonary
Sarcoidosis	irPulmonary
Systemic sclerosis pulmonary	irPulmonary
Wegener's granulomatosis	irPulmonary
Acarodermatitis	irSkin
Acquired epidermolysis bullosa	irSkin
Acrodynia	irSkin
Albinism	irSkin
Alopecia	irSkin
Alopecia areata	irSkin
Angioedema	irSkin
Application site dermatitis	irSkin
Application site eczema	irSkin
Application site erythema	irSkin
Application site exfoliation	irSkin
Application site pruritus	irSkin
Application site rash	irSkin
Application site urticaria	irSkin
Application site vesicles	irSkin
Aquagenic pruritus	irSkin
Behcet's syndrome	irSkin
Benign familial pemphigus	irSkin
Blepharitis	irSkin
Blister	irSkin
Blood blister	irSkin
Bromoderma	irSkin
Bullous impetigo	irSkin
Butterfly rash	irSkin
Capillaritis	irSkin
Catheter site pruritus	irSkin
Catheter site rash	irSkin
Catheter site urticaria	irSkin
Cervical bulla	irSkin

Pulmonary vasculitis (moved from IrOthers)
Sarcoidosis (moved from IrOthers)
Systemic sclerosis pulmonary (moved from IrOthers)
Wegener's granulomatosis (moved from IrOthers)

Chemical burn of skin	irSkin
Cholestatic pruritus	irSkin
Chronic infantile neurological cutaneous and articular syndrome	irSkin
Circumoral oedema	irSkin
Congenital pigmentation disorder	irSkin
Cutaneous sarcoidosis	irSkin
Cutaneous vasculitis	irSkin
Dapsone syndrome	irSkin
Dennie-Morgan fold	irSkin
Dermatitis	irSkin
Dermatitis allergic	irSkin
Dermatitis atopic	irSkin
Dermatitis bullous	irSkin
Dermatitis contact	irSkin
Dermatitis diaper	irSkin
Dermatitis exfoliative	irSkin
Dermatitis exfoliative generalised	irSkin
Dermatitis herpetiformis	irSkin
Dermatitis infected	irSkin
Diabetic bullosis	irSkin
Diffuse cutaneous mastocytosis	irSkin
Drug eruption	irSkin
Drug rash with eosinophilia and systemic symptoms	irSkin
Ear canal erythema	irSkin
Eczema	irSkin
Eczema asteatotic	irSkin
Eczema eyelids	irSkin
Eczema herpeticum	irSkin
Eczema impetiginous	irSkin
Eczema infantile	irSkin
Eczema infected	irSkin
Eczema nummular	irSkin

Eczema vaccinatum	irSkin
Eczema vesicular	irSkin
Eczema weeping	irSkin
Epidermolysis	irSkin
Epidermolysis bullosa	irSkin
Eruptive pseudoangiomatosis	irSkin
Erythema	irSkin
Erythema ab igne	irSkin
Erythema elevatum diutinum	irSkin
Erythema multiforme	irSkin
Erythema of eyelid	irSkin
Erythema toxicum neonatorum	irSkin
Exfoliative rash	irSkin
Eyelid exfoliation	irSkin
Eyelid oedema	irSkin
Eyelids pruritus	irSkin
Face oedema	irSkin
Familial cold autoinflammatory syndrome	irSkin
Fixed eruption	irSkin
Foreign body reaction	irSkin
Generalised erythema	irSkin
Genital erythema	irSkin
Gleich's syndrome	irSkin
Granuloma	irSkin
Granuloma annulare	irSkin
Granuloma skin	irSkin
Haemorrhagic urticaria	irSkin
Hereditary angioedema	irSkin
Herpes gestationis	irSkin
Idiopathic guttate hypomelanosis	irSkin
Idiopathic urticaria	irSkin
Implant site dermatitis	irSkin
Implant site exfoliation	irSkin

Implant site pruritus	irSkin
Implant site rash	irSkin
Implant site urticaria	irSkin
Implant site vesicles	irSkin
Incision site blister	irSkin
Incision site erythema	irSkin
Incision site pruritus	irSkin
Infusion site dermatitis	irSkin
Infusion site exfoliation	irSkin
Infusion site pruritus	irSkin
Infusion site rash	irSkin
Infusion site urticaria	irSkin
Infusion site vesicles	irSkin
Injection site dermatitis	irSkin
Injection site eczema	irSkin
Injection site exfoliation	irSkin
Injection site macule	irSkin
Injection site pruritus	irSkin
Injection site rash	irSkin
Injection site urticaria	irSkin
Injection site vesicles	irSkin
Instillation site erythema	irSkin
Instillation site pruritus	irSkin
Interstitial granulomatous dermatitis	irSkin
Intertrigo	irSkin
Itching scar	irSkin
Keratolysis exfoliativa acquired	irSkin
Keratolysis exfoliativa congenital	irSkin
Laryngeal oedema	irSkin
Laryngotracheal oedema	irSkin
Latex allergy	irSkin
Leukocytoclastic vasculitis	irSkin
Leukoderma	irSkin

Linear IgA disease	irSkin
Lip blister	irSkin
Lip oedema	irSkin
Lip swelling	irSkin
Lupus miliaris disseminatus faciei	irSkin
Mazzotti reaction	irSkin
Mechanical urticaria	irSkin
Muckle-Wells syndrome	irSkin
Mucocutaneous rash	irSkin
Necrobiosis lipoidica diabetorum	irSkin
Necrolytic migratory erythema	irSkin
Neurodermatitis	irSkin
Nicotinic acid deficiency	irSkin
Nikolsky's sign	irSkin
Nodular vasculitis	irSkin
Ocular pemphigoid	irSkin
Oculomucocutaneous syndrome	irSkin
Oculorespiratory syndrome	irSkin
Oedema mouth	irSkin
Palmar erythema	irSkin
Palpable purpura	irSkin
Paraneoplastic pemphigus	irSkin
Pemphigoid	irSkin
Pemphigus	irSkin
Penile blister	irSkin
Perianal erythema	irSkin
Periorbital oedema	irSkin
Perivascular dermatitis	irSkin
Pigmentation disorder	irSkin
Plantar erythema	irSkin
Pogosta disease	irSkin
Polymorphic eruption of pregnancy	irSkin
Porphyria non-acute	irSkin

Post inflammatory pigmentation change	irSkin
Prurigo	irSkin
Pruritus	irSkin
Pruritus allergic	irSkin
Pruritus generalised	irSkin
Pruritus genital	irSkin
Pseudoporphyria	irSkin
Rash	irSkin
Rash erythematous	irSkin
Rash generalised	irSkin
Rash macular	irSkin
Rash maculo-papular	irSkin
Rash maculovesicular	irSkin
Rash morbilliform	irSkin
Rash neonatal	irSkin
Rash pruritic	irSkin
Rash rubelliform	irSkin
Rash scarlatiniform	irSkin
Rash vesicular	irSkin
Recall phenomenon	irSkin
Red man syndrome	irSkin
Schamberg's disease	irSkin
Schnitzler's syndrome	irSkin
Scrotal erythema	irSkin
Seborrhoeic dermatitis	irSkin
Segmented hyalinising vasculitis	irSkin
Senile pruritus	irSkin
Skin depigmentation	irSkin
Skin exfoliation	irSkin
Skin hypopigmentation	irSkin
Skin irritation	irSkin
Solar urticaria	irSkin
Somatoform disorder skin	irSkin

Staphylococcal scalded skin syndrome	irSkin
Stasis dermatitis	irSkin
Stevens-Johnson syndrome	irSkin
Systemic lupus erythematosus rash	irSkin
Tongue oedema	irSkin
Toxic epidermal necrolysis	irSkin
Toxic skin eruption	irSkin
Umbilical erythema	irSkin
Umbilical granuloma	irSkin
Uraemic pruritus	irSkin
Urticaria	irSkin
Urticaria aquagenic	irSkin
Urticaria cholinergic	irSkin
Urticaria chronic	irSkin
Urticaria contact	irSkin
Urticaria papular	irSkin
Urticaria physical	irSkin
Urticaria pigmentosa	irSkin
Urticaria pressure	irSkin
Urticaria thermal	irSkin
Urticaria vesiculosa	irSkin
Urticaria vibratory	irSkin
Vaccination site dermatitis	irSkin
Vaccination site exfoliation	irSkin
Vaccination site pruritus	irSkin
Vaccination site rash	irSkin
Vaccination site urticaria	irSkin
Vaccination site vesicles	irSkin
Vasculitic rash	irSkin
Vessel puncture site pruritus	irSkin
Viral rash	irSkin
Vitiligo	irSkin
Vulvovaginal Erythema	irSkin

Vulvovaginal pruritus

irSkin

Waardenburg syndrome

irSkin

Wiskott-Aldrich syndrome

irSkin

Analysis of Safety Data

Reference to CT SOP 109

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

Table of Contents

Document Control.....	3
Document Revision History	3
Objective.....	3
Scope.....	3
Overview	3
Deviations.....	4
Definitions	4
Related Tools and Documentation	4
A. Subject Population	5
B. Inclusion of Events in Primary Analysis	6
C. Analysis Periods	7
D. Selection of Adverse Events for Counting	8
E. Rescue Medications	9
F. Separation of Signs and Symptoms Data from Adverse Events Data	9
G. Medical Dictionary	10
H. Partial or Missing Adverse Events Data	11
I. Laboratory Data Analysis.....	13
J. Programming for Death Events Reporting	13

Document Control

Created:	January 12, 2004
Version:	1.0
Last Revised:	January 12, 2004
Effective From:	January 19, 2004
Owner	Dominic Labriola, Interim Head, Biostatistics & Programming

Document Revision History

Date	Version	Detailed Description	Author
12-Jan-2004	1.0	Issued for approval	R. Perry
26-Apr-2005	1.1	Changed 'GD SOP 12:01' to 'GD SOP 12'	D. Thomas
01-Mar-2006	1.2	Allow for imputation of SAE start dates	L. Pacelli
25-Aug-2008	1.3	Updates in SOP identification and to match BMS transition to 2 classifications for AE causality	D. Thomas
16- Sep-2010	1.4	Added section J : Programming for Death Events Reporting	D. Thomas

Objective

The purpose of this reference document is to supplement CT SOP 109, Management and Reporting of Safety Data in Clinical Trials by providing further definition around BMS clinical safety data analysis guidelines.

Scope

The safety data processing and analysis guidelines set forth in this document apply to all Phase I through Phase IV clinical trials conducted, sponsored, and funded by BMS R&D.

Overview

This guideline document was created to provide greater definition around BMS clinical safety data processing and reporting guidelines. These guidelines constitute minimum standards and may be supplemented as necessary for individual clinical programs.

Deviations

Deviations to the defined guidelines that may be necessary to fulfill the clinical needs of a program must be pre-approved. Exceptions should be documented and approved through the Global Standards Request Process (CT SOP 002). Unless prior approval is granted from Global Standards, deviations are not permitted.

Definitions

Baseline Subtraction of Events: A secondary safety analysis whereby adverse events with an onset date during study therapy (on-therapy events) are compared, by preferred terminology, to events with an onset date prior to therapy (baseline events). For common events, only those 'on-therapy' events having a severity or relationship greater than a baseline event are included in the analysis.

Related Tools and Documentation

Documentation associated with these guidelines includes:

- CT SOP 109 – Management and Reporting of Safety Data in Clinical Trials
- Global Development Policies and Procedures, Glossary and Acronyms
- CT SOP 002 – Development, Maintenance and Implementation of Global Standards

A. Subject Population

Key Guidelines

1. All subjects that receive one or more doses of study treatment constitute the population included in the primary safety analysis.
2. The analysis and reporting of safety data will be performed on an **as assigned** (open label trials) or as randomized (randomized trials) basis.
 - I. Exception: If a subject received the incorrect medication for **the entire period** of treatment, the subject will be analyzed in the treatment group associated with the incorrect medication.
 - II. Important safety events that occur while the subject is on an incorrect treatment will be specifically discussed in the text of the Clinical Study Report.

B. Inclusion of Events in Primary Analysis

Key Guidelines

- 1 All adverse events with an onset date during the treatment phase of a study will be included in the primary safety analysis. This analysis strategy conforms to the "treatment -emergent" concept as described in ICH-E9.
 - I Adverse events with an onset date prior to the first day of the active treatment phase of a study are not included in the primary safety analysis. This is regardless of the possible continuance of the adverse event into the treatment phase of the study.
 - II Pre-existing conditions or adverse events with an onset date prior to the active treatment phase of a study that worsen with regard to intensity (e.g. mild to moderate) or change from unrelated to study medication to unknown relationship or at least possibly related during the treatment phase of a study are included in the primary safety analysis.
 - III At a minimum, non-serious adverse events with an onset date on or before the last date of dosing and serious adverse events with an onset date within 30 days of the last date of dosing are included in the primary safety analysis. Depending on the investigational product being researched (e.g. biologics with long half-life, oncology trials, etc.), an extended observational period may be defined for the primary safety analysis - provided the extended period is defined in the analysis section of the protocol.
- 2 For development programs where the use of a pre-study treatment observational phase is important in determining the baseline status of a subject, baseline subtraction of events should be undertaken as a supplemental analysis. In such cases, this supplemental analysis is to be specified in the analysis plan.

C. Analysis Periods

Key Guidelines

- 1 Analysis periods must be defined in the statistical analysis plan. Typical study periods include:
 - I. Pre-treatment period - from first visit until initiation of the next study phase.
 - II. Baseline period - an observational period before the initiation of active study treatment used to establish a baseline for subjects. This phase is optional as some studies progress from pre-treatment phase to treatment phase.
 - III. Treatment period - begins on the first day study treatment (BMS investigational compound or placebo/active comparator) is administered. The duration of the treatment phase is defined in the protocol and includes the length study treatment is administered
 - IV. Long-term extension period - defined by a protocol as a follow-on period of study treatment administration after a short-term study. This phase begins on the first day of long-term extension dosing.
 - V. Post-treatment period - begins the day after the last dose of study therapy.
- 2 Crossover studies have a layer of complexity due to the planned switching of treatment assignments. The various phases of a crossover study are defined during the set-up and initiation of a study. On the day the next study treatment starts, a new treatment phase of the study begins.

D. Selection of Adverse Events for Counting

Key Guidelines

- 1 Where a subject has the same adverse event, based on preferred terminology, reported multiple times in a single analysis period, the subject will only be counted once at the preferred terminology level in adverse event frequency tables.
- 2 Where a subject has multiple adverse events within the same system organ class in a single analysis period, the subject will only be counted once at the system organ class level in adverse event frequency tables.
- 3 When a subject has the same adverse event, based on preferred terminology, reported multiple times in a single analysis period, the following criteria, in order of precedence, will be used to select the event to be included in summary tables:
 - Relationship to study medication
 - Intensity of event
 - Onset date and time
 - I If relationship is not already reported as Not related versus Related by the investigator, the reported categories will be collapsed into these two categories – Not related and Related. Related events will include those reported as certainly, probably, or possibly related to study medication and those of unknown relationship. Related events will take precedence over Not related events in determining the event to include in summary tables.
 - II More intense events will take precedence over less intense events in determining the event to include in summary tables.
 - III Earlier onset date-time events will take precedence over later onset date-time events in determining the event to include in summary tables.
- 4 When reporting adverse events by intensity, in addition to providing a summary table based on the event selection criteria detailed in D.3 above, summary tables will also be provided based on the most intense event during the analysis period - independent of relationship to study medication. For these tables, the following criteria, in order of precedence, will be used to select the event to be included in summary tables:
 - Intensity of event
 - Onset date and time

E. Rescue Medications

Key Guidelines

- 1 Where the use of rescue medication is allowed for safety and/or efficacy reasons, the safety analyses will be based on the protocol specified treatment groups.
- 2 Where the use of rescue medication is allowed, additional analyses may be warranted. Any such additional analysis must be approved by the Development Team and specified in the Analysis plan.

F. Separation of Signs and Symptoms Data from Adverse Events Data

Key Guidelines

For the purpose of efficacy evaluation, some studies collect information on disease signs and symptoms (e.g., joint swelling in a rheumatoid arthritis trial) using a collection instrument different than that of adverse events. In these cases:

- 1 Signs and symptoms data will not be combined with adverse event data in the primary safety analysis.
- 2 If appropriate, the separate analysis of signs and symptoms data should be clearly specified in the protocol prior to initiation of the study.

G. Medical Dictionary

Key Guidelines

- 1 The Medical Dictionary for Regulatory Activities (MedDRA) will be used when reporting adverse events, medical history findings and/or physical examination findings in standard terminology.
- 2 Analysis and reporting of MedDRA data will always be performed using the latest version of the MedDRA dictionary in production at BMS.
- 3 Unless otherwise requested by a health authority, only the primary MedDRA hierarchy will be used for regulatory submission reports.
- 4 MedDRA is an industry standard terminology that is maintained by an external organization. Updates to this dictionary can have significant impact on the analysis and reporting of our clinical data.
 - I The impact of updates implemented during the course of a study must be assessed and documented (e.g. changes in verbatim coding between interim and final databases).
 - II To avoid the potential of multiple codes being assigned to a single verbatim term, whenever data is integrated across multiple versions of MedDRA the data will be recoded, analyzed and reported in the latest version of MedDRA in production at BMS.
 - When integrated data is recoded, an impact assessment must be performed to reconcile differences in coding between the individual studies and the integrated database.

H. Partial or Missing Adverse Events Data

Key Guidelines

Missing and incomplete data will be processed according to data processing guidelines detailed in the study data review plan. When an analysis must be performed with incomplete or missing data, the following guidelines can be used to derive data for use in the analysis.

Onset Dates

- 1 If the onset date for an adverse event is missing or incomplete, an imputed date will be derived to slot the event to an appropriate analysis period. This derived date will not be reported in summary tables or listings. Every effort will be made to determine the actual onset date for the event or to obtain a reliable estimate for the onset date from the investigator.
- 2 If an onset date is missing, the derived onset date will be calculated as the first non-missing valid date from the following list (in order of precedence):
 - First active study medication date
 - Consent date
 - Visit date corresponding to the visit at which the event was reported (for non-serious adverse events only)

a) If a valid non-missing date is not available for any of these dates, the derived onset date will be set to missing.
3. If an onset date is incomplete, the derived onset date will be calculated using the following algorithm
 - I Calculate a surrogate date as the first non-missing valid date from the following list (in order of precedence):
 - First active study medication date
 - Consent date
 - Visit date corresponding to the visit at which the event was reported (for non-serious adverse events only)

a) If a valid non-missing date is not available for any of these dates, the surrogate date will be set to missing.

- II Based on the information provided, set the derived date to the earliest possible date. If only a year is provided, set the derived date to January first of that year. If a year and month is provided, set the derived date to the first day of that month.

- III If the surrogate date is non-missing then:
 - a) If the derived date is equal to or after the surrogate date use the derived date as calculated
 - b) If the derived date is prior to the surrogate date and the surrogate date is consistent with the partial data provided for the onset date, use the surrogate date as the derived date
 - c) If the derived date is prior to the surrogate date and the surrogate date is not consistent with the partial data provided for the onset date then set the derived onset date to be the latest possible date based on the partial onset date information provided. If only a year is provided, set the derived date to December 31st of that year. If a year and month is provided, set the derived date to the last day of that month.

- IV. If the surrogate date is missing (i.e. all three dates used to determine the surrogate date are missing) then use the derived date as determined in section 3-II.

Resolution Dates

- 1 Dates will not be derived for missing or partial resolution dates

Intensity

- 1 If an adverse event is reported with an unknown intensity, a derived intensity of 0.5 will be used for the event.
 - I The derived intensity will only be used in determining the event to be counted in frequency tables it will not be displayed in listings or tabulations of the data.

I. Laboratory Data Analysis

Key Guidelines

- 1 Analyze laboratory safety data using either a Marked Abnormality or a standard toxicity grade approach.
 - I The data analysis plan should outline the approach used and specify the criteria.
 - II The criteria must be pre-defined and consistent for all studies within a program.
- 2 Additional laboratory safety analyses (e.g. mean change from baseline) may also be performed and should be consistent throughout a program.
- 3 Implausible and improbable laboratory results will be corrected, if appropriate, at the source (i.e. laboratory) of the data.
 - I If a laboratory confirms a result which has been identified as implausible or improbable, the result will be included in the analysis and its impact, if necessary, addressed in the text of the study report.

J. Programming for Death Events Reporting

Key Guidelines

1. Programming for death events reporting for annual safety reports, investigator brochure updates, etc ..., that is performed on a not reconciled clinical database, must include all death data being collected in the subject CRF.
 - I. SAE and subject status are examples of CRF modules to be taken into account for the programming. This list is of course not exhaustive.