Supplement 1: CA209-003 Study Protocol

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

MEDAREX

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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

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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).

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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 ≥ 33% across all indications (including subjects from the Dose-escalation Phase at the expansion dose) or if the rate of DLTs is ≥ 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 ≥ 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	Ribonuceic 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**	
		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]
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 ± 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 ± 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 ≤ 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 ≥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 ≥ 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 Period[1]					**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.

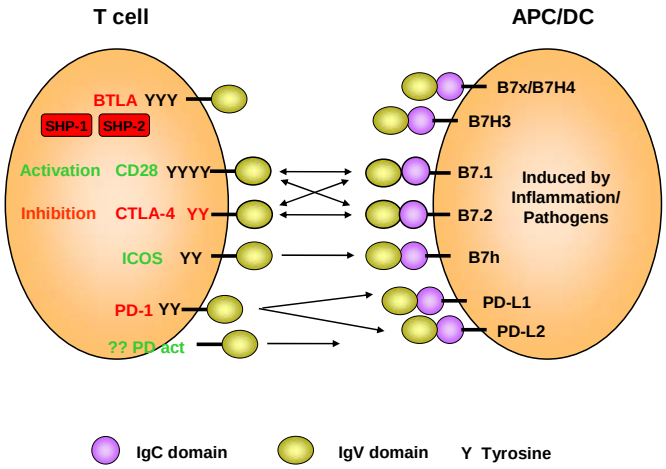
1.2. Programmed Death-1 and the Antitumor Immune Response

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 µg/mL and was not present at 1 µg/mL. This unexpected reactivity to endocrine cells is not expected to have physiological consequences due to the limited availability of cytoplasmic compartments in vivo. Similar staining patterns were observed in cynomolgus monkey tissues indicating that this is an appropriate animal

species to evaluate the potential toxicities of 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 hypocellurity were identified in the bone marrow. Myeloid and eosinophil hypercellularity were believed to be a secondary response to inflammation in the lung and not related to ipilimumab/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 $\leq$ 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 ≥ 33% across all indications (including subjects from the Dose-escalation Phase at the expansion dose) or if the rate of DLTs is ≥ 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 ≥ 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 ≥ 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 ≥ 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	≥ 2000/μL
Neutrophils	≥ 1500/μL
Platelets	≥ $100x10^3$/μL
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)

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 ≥ 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 ≥ 33% across all indications (including subjects from the Dose-escalation Phase at the expansion dose) **or** if the rate of DLTs is ≥ 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 ≥ 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 uretheral 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-immunosuppresive 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 ß-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 ≥ 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 ≤ 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
- ≥ 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 Immnol 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. BY-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	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). • **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	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. • **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	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.
Methods of measurements	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.
Clinical examination	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.
Chest X-ray	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.

continued

Definitions (continued)

Computed Tomography and Magnetic Resonance Imaging	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. 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. 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. 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.
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 Group[1] 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 ≥ 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 ≥ 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
IgA nephropathy
Addison's disease
Inflammatory bowel disease
Alopecia universalis
Interstitial cystitis
Ankylosing spondylitis
Lambert-Eaton myasthenia syndrome
Antiphospholipid antibody syndrome
Lupus erythematosus
Aplastic anemia
Lyme disease - chronic
Asthma
Meniere's syndrome
Autoimmune hemolytic anemia
Mooren's ulcer
Autoimmune hepatitis
Morphea
Autoimmune hypophysitis
Multiple sclerosis
Autoimmune hypoparathyroidism
Myasthenia gravis
Autoimmune myocarditis
Neuromyotonia
Autoimmune oophoritis
Opsoclonus myoclonus syndrome
Autoimmune orchitis
Optic neuritis
Autoimmune thrombocytopenic purpura
Ord's thyroiditis
Behcet's disease
Pemphigus
Bullous pemphigold
Pernicious anemia
Celiac disease
Polyarteritis nodusa
Chronic fatigue syndrome
Polyarthritis
Chronic inflammatory demyelinating polyneuropathy
Polygrandular autoimmune syndrome
Chung-Strauss syndrome
Primary biliary cirrhosis
Crohn's disease
Psoriasis
Dermatomyositis
Reiter's syndrome
Diabetes mellitus type 1
Rheumatoid arthritis
Dysautonomia
Sarcoidosis
Eczema
Scleroderma
Sjögren's syndrome
Epidermolysis bullosa acquista
Stiff-Person syndrome
Gestational pemphigoid
Takayasu's arteritis
Giant Cell arteritis
Ulcerative colitis
Goodpasture's syndrome
Vitiligo
Graves' disease
Vogt-Kovanagi-Harada disease
Guillain-Barré syndrome
Vulvodynia
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