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Clinical Protocol CA209010

A Randomized, Blinded, Phase 2 Dose-Ranging Study of BMS-936558 (MDX-1106) in Subjects With Progressive Advanced/Metastatic Clear-Cell Renal Cell Carcinoma Who Have Received Prior Anti-Angiogenic Therapy

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

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 03	06-Mar-2013	Incorporate Amendment 04
Amendment 04	06-Mar-2013	Update the Summary of Non-clinical results section to include new preliminary reproductive toxicology data. Updated the duration of contraception language and included a guidance on contraception.
Revised Protocol 02	13-Dec-2011	Incorporate Amendment 03
Amendment 03	13-Dec-2011	Added interim analysis and pulse oximetry monitoring.
Revised Protocol 01	25-Aug-2011	Incorporates Amendment 02 and Administrative Letter 01.
Amendment 02	25-Aug-2011	Add language required for study conduct in European Union, update clinical information in background section, update study discontinuation criteria.
Administrative Letter 01	05-May-2011	Add SAE contact information to the protocol.
Original Protocol	19-Jan-2011	Not applicable.

SYNOPSIS

Clinical Protocol CA209010

Title of Study: Protocol CA209010: A Randomized, Blinded, Phase 2 Dose-Ranging Study Of BMS-936558 (MDX-1106) In Subjects With Progressive, Advanced/Metastatic Clear-Cell Renal Cell Carcinoma Who Have Received Prior Anti-Angiogenic Therapy

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): BMS-936558 dosed intravenously over 60 minutes at either 0.3, 2, or 10 mg/kg every 3 weeks until disease progression, unacceptable toxicity or other reasons specified in the protocol.

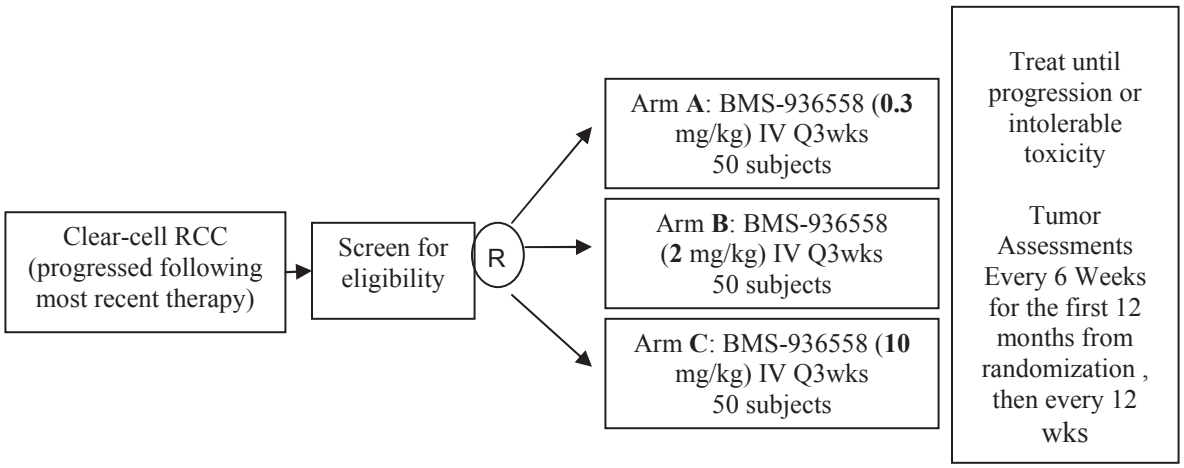
Study Phase: 2

Research Hypothesis: Efficacy of BMS-936558 as measured by progression free survival is dose dependent, when administered in subjects with progressive, advanced renal cell carcinoma who have received prior treatment with an anti-angiogenic agent.

Primary Objective: To evaluate the dose response relationship in the 0.3, 2, and 10 mg/kg BMS-936558 arms as measured by PFS.

StudyDesign:

Figure 1: Study Design



Study Population:

Key inclusion criteria include:

- Men and women ≥ 18 years of age.
- Subjects with histological confirmation of RCC with a clear cell component.
- Measurable disease as defined by RECIST 1.1 criteria.
- Subjects must have received treatment with at least one anti-angiogenic therapy (eg, sunitinib, sorafenib, pazopanib, axitinib, tivozanib, bevacizumab) in the advanced/metastatic setting. Previous treatment with immunotherapies (eg, IL-2, IFN-2α, vaccines), cytotoxic drugs, or other targeted agents (eg. mTOR inhibitors) is permitted.
- Subjects must have not received more than 3 prior treatment regimens in the advanced/metastatic setting and should have progressed from the most recent therapy within 6 months of study enrollment.
- Karnofsky Performance Score (KPS) ≥ 70%
- Tumor tissue (archival or recent acquisition) must be available (block or 5 - 15 FFPE unstained slides) for correlative studies.

Subjects must also meet other study criteria including exclusions for medical history, positive Hep B/C, HIV, and pregnancy tests, and other laboratory criteria.

Study Assessments and Primary Endpoint:

PFS is the primary endpoint of this trial. The final analyses of PFS and RR will be conducted after approximately 116 PFS events have been observed from all randomized subjects.

This study will consist of 3 phases: screening, treatment and follow-up.

Screening Phase:

1) Begins by establishing subject's initial eligibility and signing of the informed consent form (ICF)
2) Subject is enrolled using the Interactive Voice Response System (IVRS)
3) Tumor tissue (archival or recent acquisition) must be available for correlative studies
4) Subject is assessed for study eligibility within the required timeframe found in Table 5.1-1.

Treatment Phase:

- Begins with the randomization call to the IVRS by the unblinded pharmacist. The subject is randomly assigned to one of the treatment arms
- Within 3 working days from randomization the subject must receive the first dose of study medication (Day 1 of Cycle 1)
- On study labs should be drawn within 72 hours of re-dosing. Adverse event assessments should be documented at each clinic visit and WOCBP must have a pregnancy test every 6 weeks
- PK samples, immunogenicity samples and ECGs will be done according to the schedule in Table 5.1-4
- Subjects are re-dosed every 3 weeks with allowances for delay up to a maximum of 3 additional weeks
- This phase ends when the subject is discontinued from study therapy. Treated subjects will be evaluated for response according to the RECIST 1.1 guidelines every 6 weeks (± 1 week) for the first 12 months from randomization, then every 12 weeks (± 1 week) until disease progression is documented.

Follow-up Phase:

- Begins when the decision to discontinue a subject from study therapy is made (no further treatment with investigational product)
- The first 2 follow-up visits include PK/immunogenicity samples
- Subjects that discontinue treatment for reasons other than tumor progression will continue to have tumor assessments every 6 weeks (± 1 week) for the first 12 months from randomization and every 12 weeks (± 1 week) thereafter until tumor progression is documented
- Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline, or are deemed irreversible
- Subjects will be followed every 3 months for survival.

Statistical Methods:

PFS is the primary endpoint of this trial. The analysis of PFS will be conducted after approximately 116 events (progression or death) have been observed from 150 subjects. If the enrollment rate is assumed to be 15 subjects per month, it is expected that accrual will be completed after 10 months and the final analysis of PFS will be conducted after 19 months from start of study.

If the median PFS in the three treatment arms are 4, 5.7 and 8.1 months respectively, then with 116 PFS events, the study will have 90% power with a 1-sided 10% alpha to detect a dose response relationship using a log-rank trend

test. If the HR of any of the two high doses of BMS-936558 arms relative to the low dose BMS-936558 arm is 0.6, then the two-sided 80% CI will be (0.45, 0.79). If the HR is 0.75, then the 80% CI will be (0.57, 0.99).

Response rate (RR) is a secondary endpoint in this trial. If the RR in the three BMS-936558 arms are 5%, 12% and 20% respectively, the study will have 85% power using a Cochran-Armitage trend test with a 1-sided 10% alpha to detect a dose response relationship. If the observed RR in any of the higher dose of BMS-936558 arms (2 and 10 mg/kg) is 20% and is 5% in the low dose BMS-936558 arm then with 50 subjects per arm, the two-sided 80% CI for the difference in RR will be (6% - 24%). If the observed RRs are 12% and 5% respectively, then the two-sided 80% CI will be (0.01 - 14%).

The analysis of PFS will be conducted on all randomized subjects. A two-sided, $\alpha = 0.2$ level, log-rank trend test, stratified by MSKCC prognostic score (0 vs 1 vs 2/3) and number of prior treatment regimens (1 or > 1) will be used to evaluate the dose response relationship. The PFS distribution of each randomized arm will be estimated using the Kaplan-Meier product-limit methods. A two-sided, 80% confidence interval for median PFS in each arm will be computed using the Brookmeyer and Crowley method.

The tumor response rate will be computed in each treatment arm for all randomized subjects. An exact two-sided 80% confidence interval for the response rate will be computed using the method of Clopper and Pearson. A dose response relationship will be evaluated using a two-sided $\alpha = 0.2$ Cochran-Armitage trend test.

Summary tables will be presented on safety parameters for each treatment arm. Toxicity rates (worst CTC grade per subject) of adverse events and laboratory tests, both of any occurrence or severe (Grade 3 - 4) events will be tabulated.

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1 INTRODUCTION AND STUDY RATIONALE

1.1 Study Rationale

CA209010 is a randomized, double-blinded, 3-arm dose-ranging Phase 2 study. Determining the optimal BMS-936558 dose (or doses) for evaluation in Phase 3 trials is critical for the BMS-936558 program. Unlike cytotoxic chemotherapy, the optimal dose for a biologic agent is often not the maximal tolerated dose (MTD). As such, a Phase 2 dose-ranging study provides an opportunity to obtain efficacy and safety information across a range of doses to identify a dose (or doses) to evaluate in Phase 3 studies.

1.2 Research Hypothesis

Efficacy of BMS-936558 as measured by progression free survival is dose dependent, when administered in subjects with progressive, advanced renal cell carcinoma who have received prior treatment with an anti-angiogenic agent.

1.3 Objectives

1.3.1 Primary Objective:

- To evaluate the dose response relationship in the 0.3, 2, and 10 mg/kg BMS-936558 arms as measured by PFS.

1.3.2 Secondary Objectives:

- To estimate PFS in the BMS-936558 arms
- To estimate the response rate in the BMS-936558 arms
- To estimate the OS in the BMS-936558 arms
- To estimate the rate of adverse events in the BMS-936558 arms

1.3.3 Exploratory Objectives:

- To evaluate changes in QTc in each treatment arm
- To estimate the immune-related response rate (irRR) and irPFS in the 2 and 10 mg/kg BMS-936558 arms relative to the 0.3 mg/kg arm
- To explore associations between PD-L1 expression in tumors and other immune response biomarkers on clinical outcome
- To characterize the pharmacokinetics of BMS-936558 and to explore exposure-safety and exposure-efficacy relationships.

1.4 Product Development Background

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.[1] 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. 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.[2] Collectively, these signals govern the balance between T-cell activation and tolerance to antigens.

1.4.1 Renal Cell Carcinoma (RCC): Background and Standard Treatments

Renal cell carcinoma (RCC) accounts for ~3% of all cancers in the US. This translates to 58,000 new cases with 13,000 associated deaths.[3] Metastatic disease is found in 30% of subjects at diagnosis. Close to 90 - 95% of metastatic disease is of the clear-cell histology.[4]

Until recently, immunotherapy with the cytokines IL-2 and IFNα were the only active treatments for metastatic RCC. IL-2 was approved based on a 15% durable response rate. However, due to substantial toxicities including hypotension (71%), diarrhea (67%), dyspnea (43%), rash (42%), supraventricular tachycardia (12%), and a variety of metabolic and hematologic disturbances, IL-2 is only administered to relatively young and exceptionally medically fit subjects.[5,6] In addition, due to the severe acute toxicities, its administration is limited to intensive care settings in tertiary care facilities. IFNα was not approved for the treatment of RCC. However, several clinical trials have documented an objective response rate of 6-20% and a modest improvement in overall survival (~2.5 months).[7] Though not as severe as IL-2, IFNα is also associated with significant adverse events including flu-like symptoms (92%), fatigue (88%), headache (44%), diarrhea (37%), and rash (18%).[8]

The recognition of the importance of Hypoxia Inducible Factor alpha (HIFα) signaling to the pathogenesis of clear-cell RCC led to the development of two new classes of therapeutics to manage this disease.[9] Constitutive HIFα activation leads to the upregulation or activation of several proteins including VEGF. VEGF contributes to the development and progression of RCC in several ways including stimulation of tumor proliferation and neovasculature formation. Constitutive HIFα activation or upregulation occurs by several means including mutation or deletion of the tumor suppressor gene, VHL, as well as activation of the upstream PI3K/Akt/mTOR signaling pathway.[9]

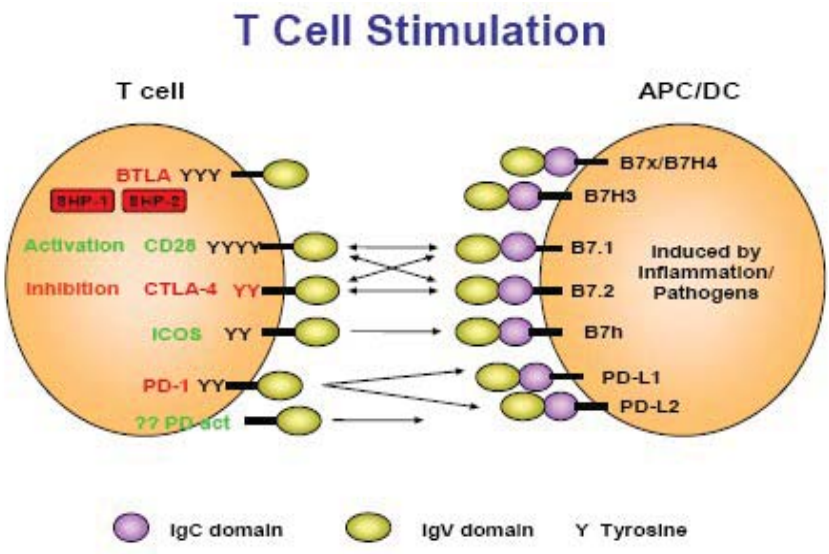
VEGF pathway inhibitors function to block VEGF signaling. Three VEGF pathway agents are currently recommended for 1st-line treatment of MSKCC good and intermediate prognostic

groups. Sunitinib (11 mo vs 5.9 mo), and the regimen bevacizumab/IFNα (10.2 mo vs 5.4 mo) showed improvement in mPFS over the active comparator IFNα, whereas pazopanib (11.1 mo vs 2.8 mo) showed superior mPFS over placebo.[10,11,12,13,14] For 2nd-line treatment, three VEGFR inhibitors are recommended: sunitinib, sorafenib, and pazopanib. In 2 single-arm studies, sunitinib demonstrated ORR of 34 - 40% and mPFS of 8.3 - 8.7 months.[15] Sorafenib (5.5 mo vs 2.8 mo) and pazopanib (7.4 mo vs 4.2 mo) showed improvements in mPFS over placebo.[14,16] As a class, the most common or clinically important toxicities elicited by VEGF pathway inhibitors are the following: fatigue (33 - 55%), diarrhea (20 - 53%), nausea (26 - 44%), hypertension (17 - 40%), LFT abnormalities (11 - 53%), hand-foot skin reaction (0 - 30%), Grade 3 - 4 neutropenia (1 - 11%), Grade 3 - 4 thrombocytopenia (1 - 8%) and low incidences of medically important events such as thrombosis, proteinuria, RPLS, bleeding, hypothyroidism, and drug-related cardiomyopathy.[10,11,12,13,14,15,16]

Two mTOR inhibitors have been approved for treatment of RCC. Temsirolimus was approved for treatment of 1st-line MSKCC poor risk patients based on the demonstration of improved mOS compared to IFNα (10.9 mo vs 7.3 mo).[17] Everolimus garnered approval based on the demonstration of improvement in mPFS as compared to placebo (4.9 mo vs 1.9 mo) in patients all of whom progressed on at least one prior VEGFR TKI therapy (sunitinib or sorafenib).[18] As a class, the most common or clinically important toxicities elicited by mTOR inhibitors are the following: fatigue (23 - 51%), nausea (15 - 37%), stomatitis (20 - 36%), diarrhea (21 - 27%), dyspnea (9 - 28%), pneumonitis (11%), infections (10 - 27%), Grade 3 - 4 anemia (10 - 20%).[17,18,19]

1.4.2 Biology of PD-1

Figure 1.4.2-1: Biology of PD-1



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 (Figure 1.4.2-1). PD-1 is a 55 kD type I transmembrane protein that is part of the immunoglobulin gene superfamily.[20] 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 downregulate T-cell activation upon binding to PD-1 in both murine and human systems.[21,22,23] PD-1 delivers a negative signal by the recruitment of SHP-2 to the phosphorylated tyrosine residue in the ITSM in its cytoplasmic region.[24,25] PD-1 is primarily expressed on activated T cells, B cells, and myeloid cells.[2]

Further evidence for a negative regulatory role of PD-1 comes from studies of PD-1-deficient mice. PD-1-deficient mice develop various autoimmune phenotypes, including dilated cardiomyopathy, a lupus-like syndrome with arthritis and nephritis, and accelerated diabetes mellitus.[26,27,28,29] The emergence of these autoimmune phenotypes is dependent upon the genetic background of the mouse strain and many of these phenotypes emerge at different times and show variable penetrance. In addition to the phenotypes of null mutations, PD-1 inhibition by antibody-mediated blockade in several murine models has been found to play a role in the development of autoimmune diseases such as encephalomyelitis,[30] graft-versus-host disease,[31] and Type I diabetes.[28] Taken together, these results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self antigens.

1.4.3 Summary of Results from BMS-936558 Investigational Program

For a complete review of non-clinical and clinical information, please refer to the BMS-936558 Investigator Brochure (IB).

1.4.3.1 Non-clinical

Preclinical animal models of tumors have shown that blockade of Programmed death-1 (PD-1) by monoclonal antibodies (mAbs) can enhance the anti-tumor immune response and result in tumor rejection. Antitumor activity by PD-1 blockade functions in PD-L1+ tumors as well as for tumors that are negative for the expression of PD-L1.[32,33,34,35,36,37] This suggests that host mechanisms (ie, expression of PD-L1 in antigen-presenting cells) limit the antitumor response. Consequently, both PD-L1 positive and negative tumors may be targeted using this approach. In humans, constitutive PD-L1 expression is normally limited to macrophage-lineage cells, although expression of PD-L1 can be induced on other hematologic cells as well, including activated T cells. However, aberrant expression of PD-L1 by tumor cells has been reported in a number of human malignancies.[33,38,39,40,41,42,43,44] PD-L1 expressed by tumor cells has been shown to enhance apoptosis of activated tumor-specific T cells in vitro.[20] Moreover, the expression of PD-L1 may protect the tumor cells from the induction of apoptosis by effector

T cells.[45] Retrospective analyses of several human tumor types suggest that tumor overexpression (as measured by IHC) of PD-L1 may permit immune evasion by tumors. In renal cell carcinoma, high surface expression levels of PD-L1 on tumor cells are related to tumor aggressiveness.[39,43] 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.

Reproductive and Developmental Toxicity

Preliminary new non-clinical safety findings of adverse pregnancy outcomes and infant losses in the absence of overt maternal toxicity have been reported.[46] The findings of increased late stage pregnancy loss and early infant deaths/euthanasia in BMS-936558 (nivolumab) exposed pregnant monkeys suggest a potential risk to human pregnancy if there is continued treatment with BMS-936558 during pregnancy.

1.4.3.2 Pharmacology

BMS-936558 (MDX-1106) is a fully human, IgG4 (kappa) isotype, mAb that binds PD-1. Blockade of the PD-1 pathway by BMS-936558 was studied using the mixed lymphocyte reaction (MLR). PD-1 blockade resulted in a reproducible enhancement of both proliferation and IFN-γ release in the MLR. The effect of BMS-936558 on antigen-specific recall response was investigated using a CMV-restimulation assay with human PBMC, and was evaluated by ELISA. These data indicated that BMS-936558, versus an isotype-matched control antibody, augmented IFN-γ secretion from CMV-specific memory T cells in a dose-dependent manner. PD-1 blockade by BMS-936558 has therefore been pursued as a promising avenue for immunotherapy of tumors.

1.4.3.3 Clinical Results

Two studies contributed to most of the clinical experience with BMS-936558 in subjects with malignancies. MDX1106-01 was a Phase 1 single-dose dose escalation study in subjects (N = 39) with previously treated advanced or metastatic cancer. Subjects received a single dose of BMS-936558 at 0.3, 1, 3, or 10 mg/kg with an option for re-treatment at 3 months. CA209003 (MDX1106-003) is an ongoing Phase 1 multi-dose dose escalation study in subjects with previously treated advanced or metastatic melanoma, RCC, non-small cell lung cancer (NSCLC), colorectal cancer (CRC), or hormone-refractory prostate cancer (HRPC). As of the clinical cut-off date (31-May-2011), 169 subjects have received at least one dose of BMS-936558 intravenously every 2 weeks at doses of 0.1, 0.3, 1, 3, or 10 mg/kg. During the dose escalation portion of the study, subjects were treated at three dose levels: 1, 3, and 10 mg/kg. Initial cohort expansions occurred in each tumor type at the highest tolerable dose evaluated (10 mg/kg) as well as in melanoma at 1 mg/kg and 3 mg/kg. The protocol was subsequently amended (Amendment 4), to include expansion cohorts in RCC at 1 mg/kg, melanoma at 0.1, 0.3, and 1 mg/kg, and NSCLC (squamous and non-squamous) at 1, 3, and 10 mg/kg.

Safety Summary:

No MTD was identified in CA209003. The maximum dose level evaluated was 10 mg/kg. The most frequent AEs were fatigue (49%), diarrhea (29%), decreased appetite (27%), nausea (26%),

vomiting (22%), and rash (21%). There was no pattern in the incidence, severity or relationship of adverse events to the BMS-936558 dose level. Any grade drug-related AEs were experienced by 57% of subjects. The most common drug related AEs were fatigue (22%), rash (15%), pruritus (11%), and diarrhea (9%). Most drug-related AEs were Grade 1 or Grade 2 in severity. Similar to the overall AE profile, there was no apparent relationship in the incidence or severity of drug-related AEs to BMS-936558 dose level. There were no apparent differences in the frequency of adverse events based on subjects' tumor type. As of the clinical cut-off date (31-May-2011), 18 deaths have been reported. Death was considered secondary to disease progression and unrelated to BMS-936558 in 16 subjects. One (1) death was considered secondary to sepsis (Grade 5)/pneumonitis (Grade 4). The fatal sepsis was considered unrelated to study drug; however the preceding pneumonitis was considered related to BMS-936558. One (1) death was considered secondary to ischemic cardiomyopathy and considered unrelated to BMS-936558. Subsequent to the clinical cut-off date, other cases of pneumonitis, including 2 fatal cases, have been reported. Additional details regarding these cases are provided in the Investigator Brochure, Section 5.

Anti-tumor Activity Summary:

BMS-936558 has single agent anti-tumor activity. Preliminary best response data from 91 subjects in CA209003 (MDX1106-003) treated at 1, 3, or 10 mg/kg intravenously every 2 weeks demonstrated an overall objective response rate of 26/91 (29%) (including a single CR). A response of CR or PR has been reported at all dose levels (1, 3, and 10 mg/kg) for subjects with melanoma, RCC, and NSCLC. No responses (CR or PR) have been reported in subjects with CRC or HRPC. The median duration of response was 29.1, 56.3, and 74.0 weeks for subjects with NSCLC, RCC, and melanoma, respectively. There was no apparent relationship between the frequency of objective responses and the BMS-936558 dose level. In melanoma subjects treated across 3 dose levels, the response rate was 4/19 (21%) at 1 mg/kg, 7/16 (44%) at 3 mg/kg, and 5/19 (26%) at 10 mg/kg.

A total of N = 18 subjects with clear-cell RCC made up a subset of the data. Most (N = 16) subjects were treated with 10 mg/kg while 2 subjects received 1 mg/kg. All RCC subjects had received prior treatment: 1 prior (28%), 2 prior (42%), 3+ prior (21%). Among RCC subjects, 6/18 (33%) had an objective response. The disease control rate (CR, PR, or SD lasting at least 6 months) was 11/18 (61%). Progression-free survival was estimated to be 8 months (4.0 - 14 months). Consistent with the experience in melanoma, subjects treated at doses lower than 10 mg/kg had anti-tumor activity. Specifically, 2 subjects treated with 1 mg/kg experienced a CR and durable stable disease of > 250 days duration with net tumor reduction of 27%. There was no apparent relationship between clinical activity and the number of prior treatments or the use of prior immunotherapy.

Two (2) subjects developed objective responses following initial evidence of PD. One (1) subject had melanoma and 1 subject had NSCLC. Based on an exploratory method of assessing tumor responses (Immune-related Response Criteria, Section 1.4.4.5 and Appendix 3), these subjects were permitted to continue treatment and sustained durable anti-tumor activity.

Clinical Pharmacology Summary:

The Half-life of BMS-936558 determined from study MDX1106-01 is 21 - 24 days. Cmax and AUC of BMS-936558 are proportional to dose from 0.3 to 10 mg/kg.

1.4.4 Rationale

CA209010 is a randomized, double-blinded, 3-arm dose-ranging Phase 2 study. Determining the optimal BMS-936558 dose (or doses) for evaluation in Phase 3 trials is critical for the BMS-936558 program. Unlike cytotoxic chemotherapy, the optimal dose for a biologic agent is often not the MTD. As such, a Phase 2 dose-ranging study provides an opportunity to obtain efficacy and safety information across a range of doses to identify a dose (or doses) to evaluate in Phase 3 studies.

1.4.4.1 Choice of Dose Range and Schedule

Three (3) BMS-936558 arms (0.3, 2, and 10 mg/kg) were chosen for evaluation based on PK modeling, pre-clinical, and clinical data. In CA209003 (MDX1106-003), repeated dosing at 1, 3, and 10 mg/kg every 2 weeks (Q2wks) elicited clinical activity, though there was no apparent relationship between dose and anti-tumor activity, adverse event frequency, or pharmacodynamic activity in this dose range.

Although the majority of experience has been with 10 mg/kg, evaluation of lower doses (1 mg/kg and 3 mg/kg) indicates similar anti-tumor activity at these dose levels. As described in Section 1.4.3.3, similar objective response rates were observed in melanoma subjects treated with 1 mg/kg (7/14, 50%) and 3 mg/kg (5/13, 38%) as subjects treated with 10 mg/kg (5/15, 33%).

This study will utilize an every 3 week (Q3wk) schedule instead of the Q2wk schedule evaluated in CA209003 (MDX1106-003). Based on the long half-life (20-24 days), PK modeling suggests a Q3wk schedule should still result in sustained exposure between treatments. PK modeling also indicates a 2 mg/kg dose administered on a Q3wk schedule will provide similar exposure (Cmax, Cmin, and AUC) as a 1 mg/kg dose administered on a Q2wk schedule. The Q3wk schedule will also be a more convenient schedule for subjects and is aligned with ongoing studies (CA209-004, ipilimumab/BMS-936558 combination) and planned studies designed to evaluate the safety and efficacy of BMS-936558 administered concurrently with chemotherapy (commonly provided on a Q3wk schedule).

This study will evaluate a BMS-936558 dose lower than 1 mg/kg (0.3 mg/kg) because evidence suggests it should also be biologically active. Although it is unknown if 0.3 mg/kg of BMS-936558 is clinically active, pre-clinical and clinical data suggest it may be. In MDX1106-01, limited experience (n = 6 pts) with a single dose of 0.3 mg/kg did not result in objective responses or evidence of immune-related drug toxicity; however repeated dosing at 0.3 mg/kg was not explored. Based on a receptor-occupancy assay, a single dose of 0.3 mg/kg was sufficient to achieve up to 70 - 97% receptor saturation (mean 85%) with a mean plateau occupancy of 72% that was sustained for > 57 days. Pre-clinical data indicate concentrations of

BMS-936558 as low as 0.5 μg/mL result in activation of T-cells as measured by IFNγ production and doses as low as 0.005 μg/mL can stimulate T-cell proliferation. In MDX1106-02, doses of 0.03, 0.1, and 0.3 mg/kg resulted in a geometric mean Cmax of 1.4, 3.5, and 6.9 μg/mL. Preliminary assessment of BMS-936558 concentration versus time plots suggest a dose of 0.3 mg/kg may result in sustained BMS-936558 concentrations > 1 μg/mL for up to 3 weeks.

1.4.4.2 Use of Blinding

Blinding will be utilized in this study to minimize evaluation bias. At randomization, the assignment of BMS-936558 dose will be blinded to subjects, treating physicians, the physician's staff and the Sponsor. The study site pharmacist will be unblinded so as to facilitate study drug preparation.

1.4.4.3 Primary Endpoint

The primary endpoint in this study will be PFS. In RCC clinical trials, PFS is an acceptable surrogate endpoint. Tumor response evaluation will utilize RECIST 1.1 criteria.

1.4.4.4 Rationale for Permitting Continued Treatment in Select Cases of Progressive Disease

Emerging evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[47] In this study, subjects will be permitted to continue BMS-936558 treatment beyond PD as long as they meet specific criteria (Section 4.3.4). These criteria aim to ensure the risk/benefit for continuing treatment will continue to favor the subjects. For purposes of evaluating the study primary endpoint and select secondary endpoints, these subjects will be considered as progressors (PD) at the time of the initial PD event.

1.4.4.5 Rationale for Immune-related Response Criteria (irRC) and Evaluation as an Exploratory Endpoint

Accumulating clinical evidence indicates that some subjects treated with agents that activate anti-tumor immune responses may develop progression of disease (by conventional response criteria) before demonstrating clinical objective responses and/or durable stable disease.[47] Similar anti-tumor activity was observed in 2 subjects treated with BMS-936558 (Section 1.4.3.3).

Two (2) hypotheses have been put forth to explain this phenomenon. First, enhanced inflammation within tumors could lead to an increase in tumor size which would appear as enlarged index lesions and as newly visible small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease leading to overt signs of clinical improvement. Alternatively, in some individuals the kinetics of tumor growth may initially outpace anti-tumor immune activity. With sufficient time, the anti-tumor activity will dominate and become clinically apparent.

As an example, following treatment with ipilimumab, serial biopsies have provided histopathological evidence that radiographically-defined enlarging tumor lesions can be the

result of an influx of tumor infiltrating lymphocytes.[47] Therefore, early increases in lesion size detected radiographically or upon gross examination could be misinterpreted as progressive tumor growth and precede objective tumor shrinkage. In addition the appearance of new lesions may have categorized a subject to have progressive disease using conventional tumor assessment criteria despite the concurrent observation of objective tumor responses in preexisting lesions and a net reduction in global tumor burden that includes the new lesions. Hence, the appearance of new lesions in and of themselves may not necessarily constitute progressive disease.

Based on the distinct patterns of clinical responses observed in subjects treated with immunotherapy agents such as ipilimumab and which differ from those seen in subjects treated with other classes of anti-cancer agents, new exploratory immune-related Response Criteria (irRC) have been described (Appendix 3). The irRC are a refinement of conventional response criteria and were created to systematically capture tumor response in subjects on immunotherapy.[47] The major modifications to the conventional criteria are the following: 1) a requirement to "confirm" progression at least 4 weeks after scan indicating initial progression and, 2) not scoring new, small non-target lesions as evidence of progression. Rather, the net tumor burden (which may include new small non-target lesions) is used to gauge progression. In the case of ipilimumab, the irRC identified 9.7% of subjects (22/227 treated subjects) from studies CA184022 and CA184008 who demonstrated disease control in the form of stable or reduced measurable tumor burden, including new lesions, at or after disease progression.

In this study, irRC will be evaluated on an exploratory basis by the sponsor. The primary mode of tumor response assessment will be based on RECIST 1.1 criteria.

1.4.4.6 Evaluation of QTc Interval

In this study, the affect of BMS-936558 on QTc interval will be evaluated. Pre-clinical evaluation did not identify a signal indicating BMS-936558 may increase the QTc interval or affect cardiac conduction. Similar to other biologics, the likelihood BMS-936558 directly or indirectly affects QTc intervals is low. To date, no systematic evaluation of QTc intervals in subjects exposed to BMS-936558 has been conducted. Despite the low risk, such evaluation is required during the development of a therapeutic agent and the particular design of this study (randomized dose ranging study with 50 subjects per arm) is well suited for this type of evaluation. The ECGs will be assessed by an independent core laboratory. A separate manual will include additional details and instructions.

1.5 Overall Risk/Benefit Assessment

BMS-936558 appears to have a manageable safety profile that is comparable to approved therapies for subjects with clear-cell RCC. BMS-936558 has encouraging anti-tumor activity (durable responses and stable disease) in Phase 1 studies. As such, the overall assessment of risks/benefits support the further evaluation of BMS-936558 in a Phase 2 study in subjects with previously treated clear-cell RCC.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

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

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

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

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s).

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

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

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

2.3 Informed Consent

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

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

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

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

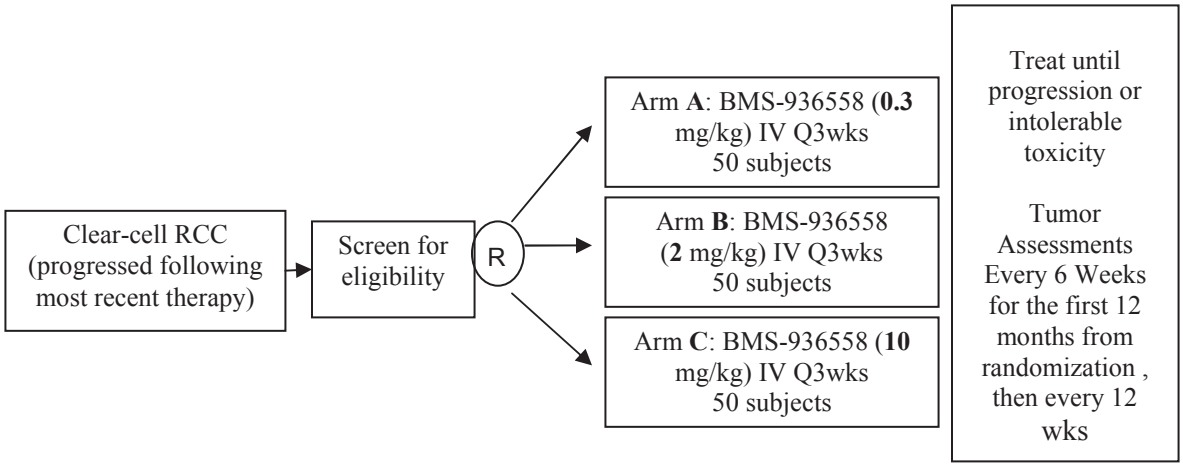
Subjects unable to give their written consent (eg, stroke patients, or subjects with severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with the subjects' understanding, and should they become capable, personally sign and date the consent form as soon as possible. The explicit wish of a subject unable to give his or her written consent, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

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

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

Figure 3.1-1: Study Design



This is a randomized, double-blinded, 3-arm dose-ranging Phase 2 study in adult (≥ 18 years old) male and female subjects with advanced/metastatic RCC (with a clear-cell component). Subjects should have received treatment with at least one anti-angiogenic therapy (eg, sunitinib, sorafenib, pazopanib, axitinib, tivozanib, bevacizumab). Progression from most recent therapy must be documented within 6 months prior to enrollment in the study. Subjects may have been treated with more than one anti-angiogenic therapy. Prior treatment with immunotherapies (eg, IL-2, IFN-2α, vaccines), cytotoxic drugs, or other targeted agents (mTOR inhibitors) is permitted. However, subjects must not have received more than 3 prior treatment regimens for metastatic disease. Subjects will be stratified by the following factors: MSKCC prognostic score (0 vs 1 vs 2/3);[48] number of prior treatments (1 or > 1) in the advanced/metastatic setting and study site; and randomized in a 1:1:1 ratio to 1 of 3 treatment arms:

Arm A: BMS-936558, 0.3 mg/kg, IV Q3 weeks
Arm B: BMS-936558, 2 mg/kg, IV Q3 weeks
Arm C: BMS-936558, 10 mg/kg, IV Q3 weeks

The subjects, treating physicians, the physician's staff and the Sponsor will be blinded to the BMS-936558 assigned dose (Arms A, B, and C). The pharmacists will be unblinded so as to facilitate accurate preparation of study drug. BMS-936558 will be administered as an IV infusion over 60 minutes on Treatment Day 1 at the assigned dose. Treatment will be administered every 3 weeks. Each treatment is considered 1 cycle. Treatment will continue until the development of progressive disease, discontinuation due to toxicity, or other reasons as indicated in Section 3.5. In select subjects, treatment beyond progression will be permitted (Section 4.3.4) as long as they meet specific criteria.

There will be no intra-subject dose escalation or reduction of BMS-936558 dose in any treatment arm.

This study will consist of 3 phases: screening, treatment and follow-up.

Screening Phase:

- Begins by establishing the subject's initial eligibility and signing of the informed consent form (ICF)
- Subject is enrolled using the Interactive Voice Response System (IVRS)
- Tumor tissue (archival or recent acquisition) must be available for correlative studies. Subjects must consent to allow the acquisition of formalin-fixed paraffin-embedded (FFPE) material (block or unstained slides) by study personnel for performance of correlative tissue studies
- Subject is assessed for complete study eligibility within the required timeframe found in Table 5.1-1.

Treatment Phase:

- Begins with the randomization call to the IVRS by the unblinded pharmacist. The subject is randomly assigned to one of the treatment arms
- Within 3 working days from randomization the subject must receive the first dose of study medication (Day 1 of Cycle 1)
- On study labs should be drawn within 72 hours of re-dosing. Adverse event assessments should be documented at each clinic visit and WOCBP must have a pregnancy test every 6 weeks
- PK samples, immunogenicity samples and ECGs will be done according to the schedule in Table 5.1-4
- Subjects are re-dosed every 3 weeks with allowances for delay up to a maximum of 3 additional weeks. (see Section 4.3)
- This phase ends when the subject is discontinued from study therapy. For a complete list of reasons for treatment discontinuation please see Section 3.5
- Treated subjects will be evaluated for response according to the RECIST 1.1 guidelines every 6 weeks (± 1 week) for the first 12 months from randomization, and then every 12 weeks (± 1 week) until disease progression is documented. For those subjects who continue study therapy after initial disease progression (Section 4.3.4), tumor assessments will continue on the Treatment Phase schedule until treatment is discontinued.

Follow-Up Phase:

- Begins when the decision to discontinue a subject from study therapy is made (no further treatment with investigational product)
- Two X follow-up visits include PK/immunogenicity samples
- Subjects that discontinue treatment for reasons other than tumor progression will continue to have tumor assessments every 6 weeks (± 1 week) for the first 12 months from

randomization and every 12 weeks (± 1 week) thereafter until tumor progression is documented

- Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline, or are deemed irreversible
- Subjects will be followed every 3 months for survival.

The study will end when analysis of survival is complete. This analysis will be conducted after 75% of the subjects have died or 2 years of follow-up time from the analysis of PFS, whichever comes first. The entire duration of the study will be less than 4 years.

3.2 Post Study Access to Therapy

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive study drug. Study drug will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of the sponsor. The sponsor reserves the right to terminate access to study drug if any of the following occur: a) the marketing application is rejected by responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

3.3 Study Population

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

3.3.1 Inclusion Criteria

1. **Signed Written Informed Consent**
   a) Willing and able to provide informed consent;
2. **Target Population**
   a) Men and women ≥ 18 years of age.
   b) Subjects with histological confirmation of RCC with a clear cell component.
   c) Measurable disease as defined by RECIST 1.1 criteria (Section 5.4).
   d) Subjects must have received treatment with at least one anti-angiogenic therapy (eg, sunitinib, sorafenib, pazopanib, axitinib, tivozanib, bevacizumab) in the advanced/metastatic setting. Previous treatment with immunotherapies (eg, IL-2, IFN-2α, vaccines), cytotoxic drugs, or other targeted agents (eg, mTOR inhibitors) is permitted.
   e) Subjects must have not received more than 3 prior treatment regimens in the advanced/metastatic setting and must have progressed from the most recent therapy within 6 months of study enrollment.
   f) Karnofsky Performance Score (KPS) ≥ 70% (Appendix 2).
   g) Tumor tissue (archival or recent acquisition) must be available (block or 5 - 15 unstained slides of FFPE tissue) for correlative studies.

3. Age and Reproductive Status

a) Women of childbearing potential (WOCBP) must use method(s) of contraception based on the tables in Appendix 4. For a teratogenic study drug and/or when there is insufficient information to assess teratogenicity (preclinical studies have not been done), a highly effective method(s) of contraception (failure rate of less than 1% per year) is required. The individual methods of contraception should be determined in consultation with the investigator. WOCBP must follow instructions for birth control when the half life of the investigational drug is greater than 24 hours, in this study contraception should be continued for a period of 23 weeks after the last dose of study drug (30 days plus the time required for the investigational drug to undergo five half lives). See Section 3.3.3 for the definition of WOCBP.

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

c) Women must not be breastfeeding.

d) Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men that are sexually active with WOCBP must follow instructions for birth control when the half life of the investigational drug is greater than 24 hours, contraception should be continued for a period of 31 weeks after the last dose of study drug (90 days plus the time required for the investigational drug to undergo five half lives).

4. Physical and Laboratory Test Findings

a) Serum creatinine ≤ 1.5 x ULN or CrCl ≥ 40 mL/min (measured or calculated using the Cockcroft-Gault formula):

$$\text{Female CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

$$\text{Male CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$$

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Active CNS metastases (including evidence of cerebral edema by CT scan or MRI, or progression from prior imaging study, any requirement for steroids, or clinical symptoms of/from CNS metastases) within 30 days of study enrollment. Subjects with known metastases must have a baseline imaging scan within 30 days of randomization.

2. Medical History and Concurrent Diseases

a) Subjects with any active autoimmune disease or a history of known autoimmune disease (See section 3.4.2).

b) Subjects with uncontrolled adrenal insufficiency

c) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix or breast.

d) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

e) Positive tests for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV RNA) indicating active or chronic infection.

f) Known drug or alcohol abuse.

g) Known or underlying medical condition (eg, a condition associated with diarrhea or acute diverticulitis) that, in the investigator's opinion, would make the administration of study drug hazardous to the subject or obscure the interpretation of toxicity determination or adverse events.

h) Prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

i) Any non-oncology vaccine therapy used for prevention of infectious diseases including seasonal (influenza) vaccinations within 4 weeks of the first dose of study drug.

j) Anti-cancer therapies must be discontinued at least 4 weeks prior to administration of study drug. Palliative, focal radiation therapy, and immunosuppressive doses of systemic corticosteroids must be discontinued at least 2 weeks before administration of study drug.

k) All toxicities attributed to prior anti-cancer therapy other than alopecia must have resolved to grade 1 (NCI CTCAE version 4) or baseline before administration of study drug.

3. Physical and Laboratory Test Findings

a) All baseline laboratory requirements will be assessed by the Central Laboratory (except the estimated creatinine clearance which should be calculated by the site) and should be obtained within -14 to -3 days of randomization

i) WBC < 2000/μL

ii) Neutrophils < 1500/μL

iii) Platelets < 100 x 10^3/μL

iv) Hemoglobin < 9.0 g/dL

v) AST > 3.0 x ULN

vi) ALT > 3.0 x ULN

vii) Bilirubin > 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL)

4. Allergies and Adverse Drug Reaction

a) History of severe hypersensitivity reactions to other monoclonal antibodies.

5. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated.

b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

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

3.3.3 Women of Childbearing Potential

Women of childbearing potential include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Post menopause is defined as:

- Amenorrhea ≥ 12 consecutive months without another cause and a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL or;
- Women with irregular menstrual periods and a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL or;
- NOTE: FSH level testing is not required for women ≥ 62 years old with amenorrhea of ≥ 1 year
- Women on hormone replacement therapy (HRT)

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

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study (unless utilized to treat a drug-related adverse event):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 3.4.3)
- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive radiation therapy, or standard or investigational agents for treatment of RCC.

Palliative and supportive care for disease related symptoms may be offered to all subjects on the trial. Palliative (limited-field) radiation therapy for bone metastases is permitted for subjects who have investigator assessed clinical benefit (eg, irSD or irPR) (Section 4.3.1). Subjects should not receive study treatment during radiation and must meet re-treatment criteria prior to resuming treatment. For purposes of evaluating the study primary and secondary endpoints, these subjects will be considered as PD at the time of the initial PD event.

Subjects may continue to receive hormone replacement therapy. Bisphosphonates and RANK-L inhibitors are allowed for bone metastases if initiated prior to randomization.

3.4.2 Other Restrictions and Precautions

Subjects with any active autoimmune disease or a history of recent known or suspected autoimmune disease or history of syndrome that required systemic corticosteroids or immunosuppressive medications, except for subjects with vitiligo or resolved childhood asthma/atopy or other syndromes which would not be expected to recur in the absence of an external trigger (eg, drug-related serum sickness or post-streptococcal glomerulonephritis) are excluded from the study. Subjects with type 1 diabetes mellitus are permitted to enroll.

3.4.3 Permitted Therapy

Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids (eg, prednisone ≤ 10 mg/day) are permitted. A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

3.5 Discontinuation of Subjects from Treatment

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

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Protocol defined reasons for discontinuation (Section 4.3.4).

All subjects who discontinue should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures including follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form (eCRF) page.

4 TREATMENTS

All protocol-specified investigational products are considered study drug.

4.1 Study Treatments

BMS-936558 100 mg (10 mg/mL) will be packaged in an open-label fashion. Ten BMS-936558 10 mL vials will be packaged within a carton. The vials are not subject or treatment group specific although there will be specific vial assignments by subject distributed by the IVRS in order to track drug usage and re-supply.

Subjects will be randomized to one of three treatment groups: 0.3 mg/kg, 2 mg/kg, or 10 mg/kg. The subject will be dosed every three weeks until subject discontinuation or the study ends. The subject, site personnel (except for the pharmacist), and BMS personnel will be blinded to the subject's dose assignment.

Table 4.1-1: Product Description - Treatment Period

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
BMS-936558	100 mg (10 mg/mL)	10 mL vial/ Open-Label	10 vials per carton/ Open-Label	Clear to opalescent, colorless to pale yellow liquid. May contain particles.	2 - 8°C

4.1.1 Investigational Product

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

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

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

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

4.1.2 Noninvestigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as noninvestigational products.

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

4.1.3 Handling and Dispensing

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

BMS-936558 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 BMS-936558 include laboratory coats and gloves.

After BMS-936558 has been prepared for administration, the total storage time (combination of refrigeration and room temperature) is not to exceed 24 hours. For details on prepared drug storage and use time under room temperature/ light and refrigeration, please refer to the Investigator Brochure section for “Recommended Storage and Use Conditions.”

Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between BMS-936558 and polyolefin bags have been observed

BMS-936558 is to be administered as a 60 minute IV infusion, using a volumetric pump with a 0.2/0.22 micron in-line filter at the protocol-specified doses. It is not to be administered as an IV

push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

Details regarding the mixing and concentrations of the blinded doses will be detailed in the pharmacy binder.

4.2 Method of Assigning Subject Identification

After the subject's initial eligibility is established and informed consent has been obtained, the subject must be enrolled into the study by calling an interactive voice response system (IVRS) to obtain the subject number. The following information is required for enrollment:

- Date of birth
- Date that informed consent was obtained

Once the subject has meet all study required criteria and is ready to be randomized, the following information is required for subject randomization:

- Date of birth
- Subject number
- MSKCC prognostic score (see Appendix 1)
- Number of prior treatment regimens in the advanced/metastatic setting

The IVRS will randomly assign the subject in a 1:1:1 ratio to 1 of 3 treatment arms of BMS-936558 stratified by the following factors: MSKCC prognostic score (0 vs 1 vs 2/3) (see Appendix 1); number of prior treatments (1 or > 1) in the advanced/metastatic setting and study site. The randomization procedure will dynamically minimize the imbalance between treatment arms within the levels of each of the stratification factors and study site. The randomization will be carried out using a Pocock and Simon dynamic balancing procedure. The exact procedures for using the IVRS will be detailed in a separate document.

4.3 Selection and Timing of Dose for Each Subject

Subjects will receive treatment with BMS-936558 as a 60 minute IV infusion on Day 1 of a treatment cycle every 3 weeks (21 days). Dosing calculations should be based on the body weight assessed at each visit as per Table 5.1-2. There will be no dose escalations or reductions allowed. Treatment may be delayed for up to a maximum of 3 weeks from the scheduled re-treatment date (See Sections 4.3.1 to 4.3.4). Subjects may be dosed no less than 19 days from the previous dose.

Subjects will be monitored continuously for AEs while on study. Treatment modifications (eg, dose delay) will be based on specific laboratory and adverse event criteria.

4.3.1 Dose Delay Criteria

BMS-936558 administration should be delayed for the following AEs:

- Any Grade 2 non-skin, drug-related adverse event, except for fatigue and laboratory abnormalities
- Any Grade 3 drug-related laboratory abnormality (except lymphopenia, AST, ALT, or T.bilirubin)
- Any 2-Grade drug-related shift from baseline in AST, ALT, or T.bilirubin
  - If a subject has a baseline AST, ALT, or T. bilirubin that is within normal limits, delay dosing for drug-related Grade 2 toxicity
  - If a subject has a baseline AST, ALT, or T. bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade 3 toxicity.
- Any Grade 3 skin drug-related AE
- Any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, warrants skipping the dose of study medication.

In some cases, the natural history of immunotherapy-related AEs can differ and be more severe than AEs caused by other therapeutic classes. Early recognition and management may mitigate severe toxicity. Evaluation and Management Guidelines were developed to assist investigators and can be found in the Investigator Brochure:

- General Guideline
- Diarrhea and Colits
- Endocrinopathies
- Hepatotoxicity (including asymptomatic LFTs).

4.3.2 Dose Reductions

BMS-936558 dose reductions are not permitted in this study.

4.3.3 Criteria to Resume Treatment with BMS-936558

Subjects may resume treatment with BMS-936558 when the drug-related AE(s) resolve(s) to Grade 1 or baseline value (except grade 2 fatigue for which subjects are not required to delay treatment). Subjects with baseline AST/ALT or total bilirubin in the grade 1 toxicity range who require dose delays for reasons other than a 2 grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin. Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 4.3.4) should have treatment permanently discontinued.

In the case of endocrine-related AEs, hormone replacement therapy may be utilized to restore physiologic function and to permit retreatment with BMS-936558. Subjects must be re-treated

within 6 weeks from the previous dose (see Section 4.3.4). If this is not possible the subject must be discontinued from study therapy.

4.3.4 Discontinuation Criteria

BMS-936558 administration should be discontinued if at least one of the following drug-related adverse event(s) occurs:

- Any ≥ Grade 2 eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any ≥ Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the exception of laboratory abnormalities, drug-related bronchospasm, and hypersensitivity reactions
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except for Grade 3 febrile neutropenia > 1 day or Grade 3 thrombocytopenia ≥ 7 days or associated with bleeding
  - Grade 3 drug-related bronchospasm, hypersensitivity reaction, or infusion reaction of any duration
- Any liver function tests (LFTs) that meet the following criteria:
  - AST or ALT > 5 - 10 x ULN for > 2 weeks
  - AST or ALT > 10 x ULN
  - T. bilirubin > 5 x ULN
  - Concurrent AST or ALT > 3 x ULN and T. bilirubin > 2 x ULN
- Any drug-related Grade 4 laboratory abnormalities, except for the following which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Any other Grade 4 drug-related adverse event
- Any dosing interruption lasting > 6 weeks, except for dosing interruptions to allow for prolonged steroid tapers to manage adverse events. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the BMS medical monitor must be consulted.
- Any adverse event, laboratory abnormality or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued BMS-936558 dosing.

4.3.5 Continued Treatment Beyond Progression of Disease

As described in Section 1.4.4.3, accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease.[47]

Subjects will be permitted to continue BMS-936558 treatment beyond confirmed PD as long as they meet the following criteria:

- Investigator assessed clinical benefit (eg, irSD; irPR) (Appendix 3), and
- Subject is tolerating BMS-936558.

Subjects that meet the above criteria and continue on study therapy must discontinue BMS-936558 upon the next documented event of PD.

The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment. The decision to continue treatment should be discussed with the BMS Medical Monitor and documented in the study records. Palliative radiotherapy or surgical resection of isolated lesions is permitted in these subjects and will not preclude the continued treatment with BMS-936558 (Section 3.4.1). For purposes of evaluating the study primary and secondary endpoints, these subjects will be considered as PD at the time of the initial PD event.

4.3.6 Treatment of BMS-936558 Related Infusion Reactions

Since BMS-936558 contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study medical monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 4.0) guidelines.

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

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

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

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

- Stop the BMS-936558 infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms.

Corticosteroid therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further BMS-936558 will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the case report form (CRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional BMS-936558 administrations. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

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

- Immediately discontinue infusion of BMS-936558. Begin an IV infusion of normal saline, and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. BMS-936558 will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms.

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

4.4 Blinding/Unblinding

This study includes blinding of dose, but all subjects receive the same investigational product (BMS-936558). Since no dose adjustments will be permitted, there will be no need to unblind the actual BMS-936558 dose given to a study subject. Subsequent or concomitant treatment decisions would not require knowledge of the BMS-936558 dose.

Designated staff of Bristol-Myers Squibb Research and Development may be unblinded prior to database lock to facilitate the bioanalytical analysis of pharmacokinetic samples and preliminary population PK (PPK) and exposure-response (E-R) analyses (including ECG analysis). A bioanalytical scientist, pharmacokineticist, pharmacometrician, statistician and programmer would be unblinded to enable preliminary PPK and E-R analyses.

4.5 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the subject's medical record and eCRF.

4.6 Destruction and Return of Study Drug

4.6.1 Destruction of Study Drug

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

4.6.2 Return of Study Drug

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

4.7 Retained Samples for Bioavailability / Bioequivalence

Not applicable.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline (CA209010)

Procedure	Screening Visit[a]	Visit 1 Day -3 to +1	Notes
Eligibility Assessments			
Informed Consent	X		
Inclusion/Exclusion Criteria	X	X	All inclusion/exclusion criteria should be assessed prior to randomization
Medical History	X		
Tumor tissue samples	X		May be archival. 1 paraffin block or 5 - 15 FFPE unstained slides to Central Lab
ECG		X	See Table 5.1-4
Disease Assessments	X		CT or MRI
Safety Assessments			
Physical Examination	X		
Vital Signs (including Performance status)	X		
Concomitant Medication Collection	X		Within 2 weeks of randomization
Assessment of Signs and Symptoms	X		Within 2 weeks of randomization
Laboratory Tests	X		Day -14 to -3 prior to randomization by Central Lab. To central Lab; CBC w/ differential, LFTs, BUN, creatinine, Ca, Mg, Na, K, HCO3, Cl, Glucose, albumin, CRP, endocrine panel (TSH, T3, T4), Hep B/C, HIV testing
Pregnancy Test		X	Local/site. For WOCBP within 3 days of randomization (serum or urine)

Table 5.1-1: Screening Procedural Outline (CA209010)

Procedure	Screening Visit[a]	Visit 1 Day -3 to +1	Notes
Exploratory			
Biomarker Serum Sample		X	Must be obtained prior to dosing
PGx sample (Optional)	X		Can be obtained at any time after consent is signed
Clinical Drug Supplies			
Randomize		X	

[a] Within 30 days of randomization.

Table 5.1-2: On Study Procedural Outline (CA209010)

Procedure	Each cycle Q 3 wks Day 1	Q 6 weeks from Randomization	Notes
Safety Assessments			
Targeted assessments	X		Except Cycle 1. Assessments to include: Performance status, body weight, concomitant medications. Body weight measurement can be performed within 72 hours prior to re-dosing.
Adverse Events Assessment	X		
Laboratory Tests	X		Except Cycle 1. On study labs (including pregnancy testing) to be done on site/local. Within 72 hrs of re-dosing to include CBC w/ differential, LFTs, BUN, creatinine. See Section 5.3.
Pulse Oximetry	X		Prior to dosing (at rest and with exertion). Also perform if any new or worsening pulmonary symptoms present.
Pregnancy Test		X	Serum or urine
ECG			See Table 5.1-4
Pharmacokinetic Samples			
PK samples	X		See Table 5.1-4 for schedule of samples
Other samples			
Immunogenicity blood sample	X		See Table 5.1-4
Efficacy Assessments			
Disease assessment		X	By methods used at baseline. Tumor assessments should be continued every 6 wks (± 1 wk) from randomization for the first 12 months, then every 12 weeks until disease progression is documented
Clinical Drug			
Administer Study Treatment	X		Record study drug infusion start and stop times

Table 5.1-3: Follow-up Assessments (CA209010)

Procedure	X, Follow-up[a] Visit 1+ 2	Y, Survival Follow-up visits[b]	Notes
Safety Assessments			
Targeted Physical Examination	X		To assess for potential late emergent study drug related issues
Adverse Events Assessment	X	X	For study drug related adverse events only
Laboratory Tests	X		On site/local CBC w/ differential , LFTs for X01, repeat at X02 if study drug related toxicity persists
Survival Status			
Subject Status	X	X	Every 3 months (Y Survival Follow-ups may be accomplished by visit or phone contact)
Efficacy Assessments			
Disease assessment	X	X	Only for subjects without progression on study therapy. Disease assessments should be continued every 6 wks (± 1 wk) from randomization for the first 12 months, then every 12 weeks until disease progression is documented
Pharmacokinetic Samples			
PK samples	X		See Table 5.1-4
Other samples			
Immunogenicity blood sample	X		See Table 5.1-4

[a] X visits as follow, X1 = 30 days from last dose ± 15 days, X2 = 60 days from X1 ± 15 days

[b] Y, Survival visits continue every 3 months after X visits.

Table 5.1-4: Pharmacokinetic, Immunogenicity, and ECG Sampling Schedule

Study Day [a]	Time (Relative To Dosing) Hour	Time (Relative To Dosing) Hour: Min	Pharmacokinetic Blood Sample Schedule	Immunogenicity Blood Sample Schedule	ECG Measurements
Day -3 to +1 (post randomization)	0 (Predose)	00:00		X	X
Cycle 1 Day 1	1.0 (EOI)[b]	01:00	X		X[c]
Cycle 1 Day 1	3.0	3:00	X		X
Cycle1 Day 3 - 5[d]	0.0	48:00 - 96:00	X		
Cycle 1 Day 7 - 15[d]	0.0	144:00 - 336:00	X		
Cycle 2 Day 1	0.0 (predose)	00:00	X		
Cycle 4 Day 1	0.0 (predose)	00:00	X	X	
Cycle 7 Day 1	0 (Predose)	00:00	X		X
Cycle 7 Day 1	1.0 (EOI)[b]	01:00	X		X[c]
Cycle 7 Day 1	3.0	3:00	X		X
Cycle 7 Day 3 - 5[d]	0.0	48:00 - 96:00	X		
Cycle 7 Day 7 - 15[d]	0.0	144:00 - 336:00	X		
Cycle 8 dose Day 1	0 (Predose)	00:00	X		
Follow-up visit X 1 & 2			X	X	

[a] If a subject permanently discontinues study drug treatment during the sampling period, they will move to sampling at the follow up visits.

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

[c] ECGs should be done prior to the PK sample, prior to EOI

[d] One sample may be drawn at any time in the specified range.

5.2 Study Materials

The following materials will be provided at study start:

- NCI CTCAE version 4.0;
- BMS-936558 Investigator Brochure;
- Pharmacy binder

- Laboratory manuals for collection and handling of blood (including PKs, biomarker and immunogenicity) and tissue specimens;
- ECG collection manual
- Site manual for operation of interactive voice response system (randomization);
- Enrollment/randomization worksheets;
- Serious Adverse Event (or eSAE) case report form pages
- Pregnancy Surveillance Forms.

5.3 Safety Assessments

At baseline, a medical history will be obtained to capture relevant underlying conditions. Baseline signs and symptoms are those that are assessed within 2 weeks prior to randomization. The baseline physical examination should include weight, height, KPS, BP, HR and temperature and should be performed within 30 days of randomization. Concomitant medications will be collected from within 2 weeks prior to randomization through the study treatment period (see Table 5.1-1 and Table 5.1-2).

Subjects will be evaluated for safety if they have received any study drug. Toxicity assessments will be continuous during the treatment phase. During the X follow-up phase (see Table 5.1-3) toxicity assessments should be done in person. Once subjects reach the Y or survival follow-up period either in person or documented telephone calls to assess the subject's status are acceptable.

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

Performance status and body weight should be assessed at each on study visit, (body weight measurement must be performed within 72 hours prior to each subsequent scheduled cycle). Vital signs should also be taken as per institutional standard of care prior to, during and after the infusions with investigational products. The start and stop time of the study drug infusion should be documented. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse event page.

Additional measures including non-study required laboratory tests should be performed as clinically indicated.

Baseline serum chemistries (blood urea nitrogen [BUN], creatinine, ALT, AST, alkaline phosphatase, total bilirubin) and hematology (CBC plus differential) and other required labs (see Table 5.1-1) will be assessed by the Central Lab. Sites should collect these samples between -14 to -3 days from randomization to insure that results required for eligibility purposes are verified prior to the randomization call. Baseline creatinine clearance (CrCl) based on the Cockcroft-Gault formula may be calculated from the central lab supplied serum creatinine value by the site, if needed. Pregnancy testing (done locally) must be performed within 72 hours prior to the initial administration of investigational product at baseline and then every 6 weeks (± 1 week) from randomization during study therapy and at the X follow-up visits. CBC plus

differential and LFT panel should be drawn within 72 hours prior to each subsequent scheduled cycle. On study labs will be done on site/locally. Laboratory tests may be done more frequently if indicated. Additional laboratory tests should be performed as per standard of care.

Laboratory toxicities (eg, suspected drug induced liver enzyme elevations) will be monitored during the follow-up phase via on site/local labs until all study drug related toxicities resolve, return to baseline or are deemed irreversible.

ECGs: Electrocardiogram recording should be obtained prior to PK samples at each time point as indicated in Table 5.1-4. The ECGs will be assessed by an independent core laboratory. A separate manual will include additional details and instructions

All ECG tests will be in performed in triplicates (ie, 1 ECG test equals 3 consecutive individual 12 lead ECGs performed within a 4 minute period). Special Restrictions: Subjects should refrain from strenuous physical activity and use of (methyl) xanthenes (eg, coffee, tea, cola, chocolate) or alcohol on the days when ECG measurements will be obtained.

Pulse oximetry should be obtained prior to each dose of BMS-936558 and at any time a subject has any new or worsening respiratory symptoms. A reading at rest and on exertion should be obtained at each time point. The extent of the exertion should be based on the judgment of the investigator, but should remain consistent for each individual subject throughout the study. If the patient's status changes the investigator can alter the extent of exertion based on their medical judgment. If a subject shows changes on pulse oximetry or other pulmonary-related signs (hypoxia, fever) or symptoms (eg. dyspnea, cough, fever) consistent with possible pulmonary adverse events, the patient should be immediately evaluated to rule out pulmonary toxicity. An algorithm for the management of suspected pulmonary toxicity can be found in Appendix 1 of the Investigator's Brochure.

5.4 Efficacy Assessments

Study evaluations will take place in accordance with the flow charts in Section 5. Baseline assessments should be performed within 30 days of randomization utilizing CTs/MRI. All known sites of disease should be assessed at baseline and subsequent assessments using the same method. Subjects will be evaluated for tumor response every 6 weeks (± 1 week) for the first 12 months from randomization and every 12 weeks (± 1 week) thereafter, until tumor progression is documented or the primary endpoint of PFS is analyzed by the sponsor.

Change in tumor measurements and tumor responses will be assessed by the investigator using the RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) criteria.[49]

5.4.1 Primary Efficacy Assessment

Progression free survival is the primary efficacy assessment of this trial. The analysis of PFS will be conducted after approximately 116 events (progression or death) have been observed from 150 subjects.

5.4.2 Secondary Efficacy Assessment

Response rate per RECIST 1.1 criteria and OS are the secondary efficacy assessments of this trial.

5.4.3 Assessment of Overall Tumor Burden and Measurable Disease

To serially evaluate tumor response to therapy, it is necessary to estimate the *overall tumor burden at baseline* and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable tumor lesion. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

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

5.4.3.1 Measurable Lesions

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

- 10 mm by CT/MRI scan - (CT/MRI scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest x-ray
- *Malignant lymph nodes*: To be considered pathologically enlarged *and* measurable, a lymph node must be ≥ 15 mm in ***short*** axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the ***short*** axis will be measured and followed.

5.4.3.2 Non-measurable Lesions

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

Special Considerations Regarding Lesion Measurability

Bone lesions

- Bone scan, PET scan or plain films are ***not*** considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

5.4.3.3 Lesions with Prior Local Treatment

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

5.4.4 Specifications by Methods of Measurements

5.4.4.1 Measurement of Lesions

All measurements should be recorded in metric notation (mm). All baseline evaluations should be performed as close as possible to the treatment start and never more than 30 days before the beginning of the treatment.

5.4.4.2 Method of Assessment

The **same method of assessment and the same technique should be used** to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

5.4.4.3 CT/MRI Scan

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

5.4.4.4 Chest X-ray

Chest CT is preferred over chest x-ray, particularly when progression is an important endpoint, since CT is more sensitive than x-ray, particularly in identifying new lesions. However, lesions

on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

5.4.4.5 Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As previously noted, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

5.4.4.6 Ultrasound

Ultrasound is ***not*** useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

5.4.4.7 Endoscopy, Laparoscopy

The utilization of these techniques for objective tumor evaluation is ***not*** advised.

5.4.4.8 Tumor Markers

Tumor markers ***alone*** cannot be used to assess objective tumor response.

5.4.5 Baseline Documentation of 'Target' and 'Non-target' Lesions

5.4.5.1 Target Lesions

When more than one measurable lesion is present at baseline all lesions up to **a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as *target lesions*** and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their **size** (lesions with the longest diameter), be representative of all involved organs, and should lend themselves to ***reproducible repeated measurements*.**

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

5.4.5.2 Lymph Nodes

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a **short axis of ≥ 15 mm by CT scan**. Only the *short* axis of these nodes will contribute to the baseline sum.

Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

5.4.5.3 Non-target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as *non-target lesions* and should also be recorded at baseline. Measurements are not required and these lesions should be followed as **'present', 'absent', or in rare cases 'unequivocal progression'.** In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

5.4.6 Tumor Response Evaluation

5.4.6.1 Evaluation of Target Lesions

Complete Response (CR): **Disappearance of all target lesions.** Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a **30% decrease in the sum of diameters of target lesions,** taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a **20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study*** (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an **absolute increase of at least 5 mm**. (*Note:* the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

5.4.6.2 Special Notes on the Assessment of Target Lesions

5.4.6.3 Lymph Nodes

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a **short axis of ≥ 15 mm by CT scan**. Only the *short* axis of these nodes will contribute to the baseline sum. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

5.4.6.4 Target Lesions that Become 'Too Small to Measure'

All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). If the radiologist is able to provide an actual measurement, that should be recorded, even if it is below 5 mm.

However, when such a lesion becomes difficult to assign an exact measure to then:

- if it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- if the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (note: in case of a lymph node believed to be present and faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).

5.4.6.5 Target Lesions That Split or Coalesce On Treatment

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

5.4.7 Evaluation of Non-target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) above the normal limits.

Progressive Disease (PD): *Unequivocal progression* of existing non-target lesions. (*Note:* the appearance of one or more new lesions is also considered progression).

5.4.7.1 When the Subject Has Measurable Disease

- To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status.

5.4.8 New Lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example,

some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the subject's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was *not* scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and while on study has a CT or MRI brain scan ordered which reveals metastases. The subject's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

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

5.4.9 Response Criteria (RECIST 1.1)

5.4.9.1 Time Point Response

For subjects who have **measurable disease** at baseline Table 5.4.9.1-1 provides a summary of the overall response status calculation at each time point.

Table 5.4.9.1-1: Time Point Response: Subjects With Target (± Non-target) Disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

5.4.9.2 Missing Assessments and Not Evaluable Designation

When no imaging/measurement is done at all at a particular time point, the subject is **not evaluable (NE)** at that time point. If only a subset of lesion measurements are made at an assessment, the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not have changed the assigned time point response.

5.4.9.3 Confirmation Scans

- **Verification of Response**: Confirmation of response is not required since it will not add value to the interpretation of trial results.
- **Verification of Progression**: Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered to not have progressive disease.

5.4.10 Best Overall Response: All Time Points

The *best overall response* is determined once all the data for the subject is known. It is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. For subjects who continue study therapy beyond RECIST progression, the best overall survival response should be assessed at the time of RECIST progression. The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Best response is defined as the best response across all time points (for example, a subject who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR).

When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the subject's best response depends on the subsequent assessments. For example, a subject who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same subject lost to follow-up after the first SD assessment would be considered not evaluable.

5.4.11 Duration of Response

5.4.11.1 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

5.4.11.2 Exploratory Efficacy Assessments

To estimate the immune-related response rate (ir-RR) and ir-PFS using criteria in Appendix 3

5.5 Pharmacokinetic Assessments

Pharmacokinetic blood samples will be drawn from study subjects at the time points indicated in Table 5.1-4. Blood samples should be drawn from a site other than the infusion site

(ie, contralateral arm) on days of infusion. All samples collected pre-dose should be taken just prior to the administration, and end-of-infusion (EOI) samples should be taken as close to EOI as possible (preferably 2 minutes prior to EOI) on the contralateral arm (ie, the arm not for the infusion). If the infusion was interrupted, the reason for interruption should also be documented on the CRF. Blood samples will be processed to collect serum. Serum samples will be analyzed for BMS-936558 by a validated ELISA method. Further details of pharmacokinetic sample collection, processing and shipment will be provided to the site in the lab procedure manual.

BMS-936558 concentration data obtained from this study will be combined with data from other studies for population pharmacokinetic modeling and will be reported separately.

5.6 Pharmacodynamics Assessments

Not applicable.

5.7 Pharmacogenomic/Pharmacogenetic Assessments

Blood samples will be collected at any time during the study from consenting subjects to explore possible associations of single nucleotide polymorphisms (SNPs) in specific genes and clinical activity or adverse events associated with BMS-936558 therapy. Genes of interest include, but are not limited to, PD-1, PD-L1, PD-L2 and CTLA-4. Blood samples will be submitted to a central location specified by the Sponsor.

5.8 Outcomes Research Assessments

Not applicable.

5.9 Other Exploratory Assessments

Expression of PD-L1, PD-L2, PD-1 and other markers of immune cells will be measured in tumor tissues by immunohistochemistry techniques or quantitative real time polymerase chain reaction (qRT-PCR). Archival tumor tissue (paraffin block or 5 - 15 unstained slides of formalin fixed paraffin embedded tissue) will be required from all subjects. If archived tumor tissues are not available, a fresh tumor biopsy will be required. Tissue block or slides will be submitted to a central location specified by the Sponsor.

Blood samples will be collected and processed as serum samples for analysis of candidate predictive markers including, but not limited to, chemokines (CXCL9, CXCL10), cytokines (IL-17, IFNγ) and soluble PD-L1. Blood samples will be submitted to a central location specified by the Sponsor.

Blood samples for immunogenicity analysis will be collected from all subjects according to the schedule provided in Table 5.1-4. Samples will be evaluated for the presence of Anti-Drug Antibody (ADA) in subjects by a validated electrochemiluminescent (ECL) immunoassay in human serum.

6 ADVERSE EVENTS

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

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

6.1 Serious Adverse Events

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

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Potential drug induced liver injury (DILI) is also considered an important medical event (See Section 6.6 for the definition of potential DILI).

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

Although pregnancy, overdose, cancer and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs for data transmission purposes (See Section 6.1.1 for reporting pregnancies).

NOTE:

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

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

6.1.1 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs, of any causality, must be collected that occur during the screening period and within 90 days of discontinuation of dosing for those subjects that receive study therapy (within 30 days of last visit for enrollment failures). If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

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

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

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

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

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number:

For US and Canadian Sites: Central Facsimilie Station: (609) 818-3804
For all other sites: See Contact Information list.

SAE Telephone Contact (required for SAE and pregnancy reporting):

For US and Canadian Sites:
Name: Ian Waxman, MD
Office: (609) 252-4190
Mobile: (609) 651-5681
24 Hour (USA): (866) 470-2267

For all other sites: See Contact Information list.

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

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

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

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

In the event that a subject has a late emerging (post 30 days from last dose of study drug) non-laboratory, study drug related toxicity, it should be reported as an adverse event.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Laboratory Test Abnormalities

The following laboratory abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

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

6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 6.1.1 for reporting details.).

6.6 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1. for reporting details).

Potential drug induced liver injury is defined as:

1. Aminotransferase (ALT or AST) elevation > 3 times upper limit of normal (ULN)
   AND
2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),
   AND
3. No other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, progression of disease, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.7 Other Safety Considerations

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

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Not applicable.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

PFS is the primary endpoint of this trial. The analysis of PFS will be conducted after approximately 116 events (progression or death) have been observed from 150 subjects. If the enrollment rate is assumed to be 15 subjects per month, it is expected that accrual will be completed after 10 months and the final analysis of PFS will be conducted after 19 months from start of study.

If the median PFS in the three treatment arms are 4, 5.7, and 8.1 months respectively, then with 116 PFS events, the study will have 90% power with a 1-sided 10% alpha to detect a dose response relationship using a log-rank trend test. If the HR of any of the two high doses of BMS-936558 arms relative to the low dose BMS-936558 arm is 0.6, then the two-sided 80% CI will be (0.45, 0.79). If the HR is 0.75, then the 80% CI will be (0.57, 0.99).

Response rate (RR) is a secondary endpoint in this trial. If the RR in the three BMS-936558 arms are 5%, 12%, and 20% respectively, the study will have 85% power using a Cochran-Armitage trend test with a 1-sided 10% alpha to detect a dose response relationship. If the observed RR in any of the higher dose of BMS-936558 arms (2 and 10 mg/kg) is 20% and is 5% in the low dose BMS-936558 arm then with 50 subjects per arm, the two-sided 80% CI for the difference in RR

will be (6% - 24%). If the observed RRs are 12% and 5% respectively, then the two-sided 80% CI will be (0.01 - 14%).

8.2 Populations for Analyses

- Enrolled subjects: All subjects who signed the informed consent form and obtained an enrollment number
- Randomized subjects: all subjects in the study that are randomized to any treatment arm. This is the primary data set for analyses of efficacy and baseline characteristics
- Treated subjects: All subjects who received any study treatment (BMS-936558). This is the primary data set for dosing, and safety
- Exploratory data sets: Treated subjects with biomarker measures available at baseline
- The Immunogenicity data *set* consists of all available data from the subjects who receive BMS-936558 and have at least 1 sample
- The Pharmacokinetic data set includes all available data from the subjects who receive any BMS-936558 medication and have PK samples available
- The ECG evaluable population will consist of all treated subjects who had a baseline ECG and at least one on-study ECG.

8.3 Endpoint Definitions

The primary objective (to evaluate dose response relationship in the 0.3, 2, 10 mg/kg BMS-938558 arms) will be measured by the primary endpoint of progression-free survival (PFS). PFS will be defined as the time from randomization to the date of first documented disease progression per RECIST 1.1. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last tumor assessment. Subjects who did not have any on study tumor assessments will be censored on the date they were randomized. Tumor assessments are performed at baseline and then every 6 weeks during the 1st year from randomization and every 12 weeks thereafter until progression or discontinuation of study therapy whichever comes last. Survival status is collected at each visit and every 3 months in follow-up.

The first secondary objective (to estimate PFS in the BMS-936558 arms) will be also measured by the primary endpoint of PFS in each arm. Definition of PFS and schedule of assessments are described above.

The second secondary objective (to estimate the response rate in the BSM-936558 arms) will be measured by the secondary endpoint of Best Overall Response Rate (BORR) per RECIST 1.1. BORR is defined as the proportion of randomized subjects whose best response is either partial response (PR) or complete response (CR). Best Overall Response is the best tumor response recorded from the randomization until disease progression or discontinuation of study therapy. Tumor assessments are performed at baseline and then every 6 weeks during the 1st year from randomization and every 12 weeks thereafter until progression or discontinuation of study therapy whichever comes last

The third secondary objective (to estimate the Overall Survival (OS) in the BMS-936558 arms) will be measured by the secondary endpoint of Overall Survival. Overall Survival is defined as the time from date of randomization until date of death. If the subject did not die, overall survival will be censored on the last date the subject was known to be alive. Survival status is collected at each visit during treatment and every 3 months during follow-up.

The fourth secondary objective (to estimate the rate of adverse events in the BMS-936558 arms) will be measured by the secondary endpoint of incidence of adverse events. Adverse events are collected on Day 1 of each cycle, on Days 30 and 90 after last dose and then every 3 months (only drug related adverse event are collected after last dose)

The first exploratory endpoint (to evaluate the changes in QTc in each treatment arm) will be measured by ECG performed at baseline, on Day 1 of Cycle 1 at end of infusion (1 hour) and 3 hour after start of infusion, on Day 1 of Cycle 7 at pre dose, at end of infusion(1 hour) and 3 hour after start of infusion.

The second exploratory endpoint (to estimate the immune-related response rate (irRR) and irPFS in the 2 and 10 mg/kg BMS-936558 arms relative to the 0.3 mg/kg arm) will be measured by the exploratory endpoints of Immune-Related Best Overall Response Rate (irBORR) per immune-related RECIST 1.1 (defined in Appendix 3 of the protocol) and immune-related PFS. irBORR and irPFS are defined in the same way as BORR and PFS. Tumor assessments are performed at baseline and then every 6 weeks during the 1st year from randomization and every 12 weeks thereafter until progression or discontinuation of study therapy whichever comes last

The third exploratory objective (to explore associations between PD-L1 expression in tumors another immune response biomarkers on clinical outcome) will be measured by the endpoint of PD-L1 and other markers expression measured at baseline. Clinical outcome consists in the endpoint of BORR.

The last exploratory objective (to characterize the PK of BMS-936558 and to explore exposure-safety and exposure-efficacy relationship) will be measured by the exploratory endpoint of PK of BMS-936558, derived from serum concentration versus time date Measurements will be performed on Day 1 of Cycle 1 after 1 hour [end of infusion] , after 3 hours, after 72 hours [Day 4], after 240 hours [Day 11], on Day 1 of Cycle 2 and Cycle 4 at pre-dose, on Day1 of Cycle 7 at predose, 1hour [end of infusion], after 3 hours, after 72 hours [Day 4], after 240 hours [Day 11], on Day 1 of Cycle 8 at predose, on Day 30 and 90 after last dose.

8.3.1 Analyses

8.3.1.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics.

8.3.2 Efficacy Analyses

The final analyses of PFS and RR will be conducted after approximately 116 PFS events have been observed from all randomized subjects. Analysis of survival will be conducted after 75% of the subjects have died or 2 years of follow-up time from the analysis of PFS, whichever comes first.

8.3.2.1 Primary Efficacy Analysis

The analysis of PFS will be conducted on all randomized subjects. A two-sided, $\alpha = 0.2$ level, log-rank trend test, stratified by MSKCC prognostic score (0 vs 1 vs 2/3) and number of prior treatment regimens (1 or > 1) in the advanced/metastatic setting will be used to evaluate the dose response relationship.

The PFS distribution of each randomized arm will be estimated using the Kaplan-Meier product-limit methods. A two-sided, 80% confidence interval for median PFS in each arm will be computed using the Brookmeyer and Crowley method. Six month PFS rates along with 80% confidence intervals will be estimated from the Kaplan-Meier curve for each treatment arm.

The hazard ratio of the two high doses of BMS-936558 (2 mg/kg and 10 mg/kg) relative to 0.3 mg/kg will be estimated using the Cox proportional hazard model stratified by MSKCC prognostic score (0 vs 1 vs 2/3) and number of prior treatments (1 or > 1) in the advanced/metastatic setting, with randomized treatment arm as the single covariate. A two-sided 80% confidence interval for the hazard ratio will be calculated.

8.3.2.2 Secondary Efficacy Analyses

Overall response rate, duration of response, time to response, and overall survival are secondary endpoints for this study.

The analyses of tumor response will be based on the best overall response as determined by the investigators.

The tumor response rate will be computed in each treatment arm for all randomized subjects. An exact two-sided 80% confidence interval for the response rate will be computed using the method of Clopper and Pearson. A dose response relationship will be evaluated using a two-sided $\alpha = 0.2$ Cochran-Armitage trend test.

Time to response for each treatment arm will be summarized using descriptive statistics (median, minimum, and maximum). No formal statistical comparisons are planned.

The duration of overall response in each arm will be estimated using the Kaplan-Meier product limit method. Kaplan-Meier curves by randomized arm will be produced. A two-sided 80% confidence interval for median duration will be computed using the methods of Brookmeyer and Crowley. No formal statistical comparisons are planned.

The overall survival distribution of each randomized arm will be estimated using the Kaplan-Meier product-limit methods. A two-sided, 80% confidence interval for median OS in each arm will be computed using the Brookmeyer and Crowley method.

8.3.2.3 Exploratory Efficacy Analyses

Exploratory analyses may also be conducted to evaluate the effect of treatment on PFS and ORR when adjusted for other baseline prognostic factors. Logistic and Cox regression models will be used to determine factors that may be associated with tumor response or PFS. Some of the risk factors that will be used for this analysis include; use of prior immunotherapy and number of disease sites. Other factors that may emerge from the current study or other studies may be considered as well.

Analysis of irRR and irPFS will be conducted similar to the analysis of ORR and PFS. Median irPFS and hazard ratios along with 80% CI will be estimated. irRR along with 80% CI will also be computed for each treatment arm.

8.3.3 Safety Analyses

Summary tables will be presented on safety parameters for each treatment arm. Toxicity rates (worst CTC grade per subject) of adverse events and laboratory tests, both of any occurrence or severe (Grade 3 - 4) events will be tabulated.

ECG Analyses

For subjects with serial ECG measurements, changes in heart rate (ΔHR) and in the ECG intervals QTc, QRS, and P-R interval (ΔQTc, ΔQRS, and ΔP-R, respectively) will be tabulated by treatment (BMS-936558 dose) and study day. Frequency distributions of max QTc values, max ΔQTc, max QRS, max P-R, and of max heart rate in pre-specified categories will be tabulated by treatment. Scatter plots of heart rate, ΔHR, QTc, ΔQTc, QRS, and P-R vs time-matched BMS-936558 concentrations will be provided. A concentration-response effect of BMS-936558 on QTc will be assessed by a linear mixed effects regression model for ΔQTc on plasma BMS-936558 concentration, both stratified by study day, as well as pooled across days. The predicted maximum effect (at mean maximum BMS-936558 concentration) will be estimated by these models at each dose by point estimates and confidence intervals.

8.3.4 Pharmacokinetic Analyses

Summary statistics will be tabulated for PK concentrations by treatment, study day and scheduled sampling time.

The concentration vs time data obtained in this study combined with PK data from additional studies in the clinical development program will be used to develop a population PK model using a non-linear mixed-effects modeling approach. This model will be used to evaluate the effects of various covariates on the PK of BMS-936558 and to derive individual steady state exposure parameters such as Cminss, Cmaxss, Cavgss. Exposure-efficacy and Exposure-safety analyses

will be conducted for selected efficacy and safety end points. Results of population PK analyses and exposure-response will be reported separately.

8.3.5 Pharmacodynamic Analyses

Not applicable.

8.3.6 Pharmacogenomic Analyses

Exploratory analyses of tumor tissue and pre-treatment serum and/or plasma will be conducted. Slides from FFPE-tumor tissue (archival or recent acquisition) will be analyzed for expression of PD-L1 and other immune-response biomarkers by immunohistochemistry. Pre-treatment serum will be analyzed for quantities of immune-system markers. Associations between expression of PD-L1 and other immune-response biomarkers and clinical outcome will be expressed as summary statistics or presented graphically.

8.3.7 Outcomes Research Analyses

Not applicable.

8.3.8 Other Analyses

8.3.8.1 Immunogenicity Analysis

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

8.4 Interim Analyses

An interim analysis will occur when all subjects have been randomized. Approximately 63 randomized subjects will have a minimum of 12 weeks follow-up when the last patient is randomized; therefore, a sufficient amount of data will be available for a qualitative assessment of differences in safety and efficacy at the time of the interim analysis.

The purpose of this interim analysis is to obtain preliminary information on the safety and efficacy profile of the different doses of BMS-936558 for future study planning. Data will be unblinded and analysed by the Sponsor.

Data analysis will focus primarily on the secondary endpoints of adverse event rates and objective response rates. Additional analyses of tumor burden change over time, incidence of laboratory abnormalities and extent of exposure will be also performed. The analyses will be kept descriptive and no formal comparison between arms will be performed. In addition,

exposure-response relationships with selected efficacy and safety parameters will be explored. More details will be provided in the statistical analysis plan.

In order to protect the integrity of the study, access to results of this interim analysis will be limited to the sponsor. Since the purpose of this interim analysis is to inform the planning of future studies, the study protocol and the study conduct will remain unchanged after this interim unless it is determined that the benefit-risk profile for one or more dose levels is not favorable.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

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

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

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

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

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

9.1.2 Monitoring

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source documents: PK sample pages. In addition, the study may be evaluated by BMS internal

auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

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

9.1.3 Investigational Site Training

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

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

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

9.2.2 Study Drug Records

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

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

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

9.2.3 Case Report Forms

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

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

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

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

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

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

9.3 Publications

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

10 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or the sponsor as related to the investigational product
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product)

11 LIST OF ABBREVIATIONS

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

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

Abbreviation	Term
TEAE	Treatment-emergent adverse event
TNF	Tumor necrosis factor
WOCBP	Women of child bearing potential

12 REFERENCES

1 Pardoll D. Does the immune system see tumors as foreign or self? Annu Rev Immunol 2003;21:807-39.

2 Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2004;23:515-48

3 Cancer Facts and Figures 2010. American Cancer Society. Atlanta: American Cancer Society; 2010.

4 Cancer of the Kidney: Section 3. W. Marston Linehan, Brian I. Rini, James C. Yang, in Cancer: Principles & Practice of Oncology / edited by Vincent T. DeVita, Samuel Hellman, Steven A. Rosenberg. Philadelphia: Lipincott-Raven; 8th edition.

5 Aldesleukin (IL-2) Prescribing Information, April 2010.

6 Fyfe G, Fisher RI, Rosenberg SA, et al. Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. J Clin. Oncol. 1995; 139: 688-696.

7 Coppin, C., Porzsolt F., Autenrieth M., Kumpf J., Coldman A., Wilt T., Immunotherapy for advanced renal cell cancer (Review). The Cochrane Library. 2008, Issue 4.

8 Interferon alfa-2b, recombinant, Prescribing Information, August 2009.

9 Mulders, P. Vascular endothelial growth factor and mTOR pathways in renal cell carcinoma: differences and synergies of two targeted mechanisms. 2009. BJU International 104: 1585-1589.

10 Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib in patients with metastatic renal cell carcinoma. NEJM 2007; 356: 115-124.

11 Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with inteferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol. 2009; 27: 3584-3590.

12 Rini BI, Halabi S, Rosenberg JE, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. J. Clin Oncol. 2010; 28(13): 2137-2143.

13 Escudier B, Bellmunt J, Negrier S, et al. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. J Clin Oncol 2010; 28(13):2144-2150.

14 Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 2010; 28(6): 1061-1068.

15 Motzer RJ, Rini BI, Bukowski RM, et al. Sunitinib in patients with metastatic renal cell carcinoma. JAMA 2006; 295: 2516-2524.

16 Escudier B, Eisen T, Stadler WM, et al. Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. J Clin Oncol 2009; 27(20): 3312-3318.

17 Hudes G, Carducci M, Tomczak P. et al. Temsirolimus, Interferon Alfa, or both for advanced renal-cell carcinoma. NEJM 2007; 356: 2271-2281.

18 Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet 2008; 372: 449-456.

19 Everolimus Prescribing Information. May 2010.

20 Nishimura H, Honjo T. PD-1: an inhibitory immunoreceptor involved in peripheral tolerance. Trends Immunol 2001; 22(5):265-8.

21 Freeman GJ, Long AJ, Iwai Y, 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.

22 Latchman Y, Wood CR, Chernova T, et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. Nat Immunol 2001;2(3):261-8.

23 Carter LL, Fouser LA, Jussif J, et al. PD-1:PD-L inhibitory pathway affects both CD4+ and CD8+ T cells and is overcome by IL-2. Eur J Immunol 2002; 32(3):634-43.

24 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.

25 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 PKC-theta. FEBS Letters 2004 Sep 10; 574(1-3):37-41.

26 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.

27 Nishimura H, Okazaki T, Tanaka Y, et al. Autoimmune dilated cardiomyopathy in PD-1 receptor-deficient mice. Science 2001;291(5502):319-22.

28 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.

[29] Okazaki T, Tanaka Y, Nishio R, et al. Autoantibodies against cardiac troponin I are responsible for dilated cardiomyopathy in PD-1-deficient mice. Nat Med 2003;9(12):1477-83.

[30] Salama AD, Chitnis T, Imitola J, 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.

[31] Blazar BR, Carreno BM, Panoskaltsis-Mortari A, 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.

[32] 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.

[33] 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.

[34] Strome SE, Dong H, Tamura H, et al. B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma. Cancer Res 2003; 63:6501-5.

[35] Dong H, Strome SE, Salomao DR, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med 2002; 8(8):793-800

[36] Hirano F, Kaneko K, Tamura H, et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. Cancer Res 2005;65(3):1089-96.

[37] Blank C, Brown I, Peterson AC, 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.

[38] 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.

[39] Thompson RH, Gillett MD, Cheville JC, 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.

[40] Ohigashi Y, Sho M, Yamada Y, 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.

[41] Tsushima F, Tanaka K, Otsuki N, et al. Predominant expression of B7-H1 and its immunoregulatory roles in oral squamous cell carcinoma. Oral Oncol 2006; 42(3): 268-74.

[42] Thompson RH, Webster WS, Cheville JC, et al. B7-H1 glycoprotein blockade: a novel strategy to enhance immunotherapy in subjects with renal cell carcinoma. Urology 2005; 66(5A):10-14.

[43] Thompson RH, Gillett MD, Cheville JC, et al. Costimulatory Molecule B7-H1 in primary and metastatic clear cell renal cell carcinoma. Cancer 2005 Nov 15; 104(10):2084-91.

[44] Dong H, Chen L. B7-H1 pathway and its role in the evasion of tumor immunity. J Mol Med 2003;81(5)281-7.

[45] 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.

[46] Non-Clinical Expedited Safety Report for Nivolumab (Ad Hoc CARES #54344.1); BMS DCN 930067627 1.0

[47] Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: Immune-related response criteria. Clin Can Res 2009; 15(23): 7412-7420.

[48] Motzer RJ, Bacik J, Schwartz LH, Reuter V, et al. Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. J Clin Oncol 22: 454-463.

[49] E.A. Eisenhauera, P. Therasseb, J. Bogaertsc, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 4 5 (2009): 228 - 247

APPENDIX 1 MSKCC PROGNOSTIC SCORE

PREVIOUSLY TREATED PATIENTS

Parameter	Risk Factor	Value	Subject value	IF subject meets criteria value enter 1
KPS	Low KPS	< 80%		
Corrected Calcium	High Corrected Calcium	> 10 mg/dL		
Hemoglobin	Low Hemoglobin	Males: < 13 g/dL Females: < 11.5 g/dL		
	Sum above =	**MSKCC prognostic score**		

Corrected Calcium = ([4 - plasma albumin in g/dL] X 0.8 + serum calcium)

Risk Factors

Favorable Risk: 0
Intermediate Risk: 1
Poor Risk: 2 or 3

APPENDIX 2 PERFORMANCE STATUS SCALES

STATUS	SCALES		STATUS
	KARNOFSKY	ZUBROD-ECOG-WHO	
Normal, no complaints	100	0	Normal activity
Able to carry on normal activities Minor signs or symptoms of disease	90	0	Symptoms, but fully ambulatory
Normal activity with effort	80	1	
Cares for self. Unable to carry on normal activity or to do active work	70	1	Symptomatic, but in bed < 50% of the day.
Requires occasional assistance, but able to care for most of his needs	60	2	
Requires considerable assistance and frequent medical care	50	2	Needs to be in bed > 50% of the day, but not bedridden
Disabled. Requires special care and assistance	40	3	
Severely disabled. Hospitalization indicated though death non imminent	30	3	Unable to get out of bed
Very sick. Hospitalization necessary. Active supportive treatment necessary	20	4	
Moribund	10	4	
Dead	0	5	Dead

APPENDIX 3 IR RECIST 1.1

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

1 EVALUATION OF LESIONS

1.1 Evaluation of Target Lesions

Immune-related Complete Response (irCR): **Disappearance of all target lesions.** Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Immune-related Partial Response (irPR): At least a **30% decrease in the sum of diameters of target lesions and all new measurable lesions** (ie Percentage Change in Tumor Burden)**,** taking as reference the baseline sum diameters.

Note: the appearance of new measurable lesions is factored into the overall **Tumor Burden**, but does not automatically qualify as progressive disease until the sum of the diameters increases by ≥ 20% when compared to nadir.

Immune-related Progressive Disease (irPD): At least a **20% increase in Tumor Burden** (ie the sum of diameters of target lesions, and any new measurable lesions) taking as reference the ***smallest sum on study*** (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an **absolute increase of at least 5 mm**. Tumor assessments using immune-related criteria for progressive disease incorporates the contribution of new measurable lesions. Each net percentage change in tumor burden per assessment accounts for the size and growth kinetics of both old and new lesions as they appear.

Immune-related Stable Disease (irSD): Neither sufficient shrinkage to qualify for irPR nor sufficient increase to qualify for irPD, taking as reference the smallest sum diameters while on study.

1.1.1 Special Notes on the Assessment of Target Lesions

1.1.1.1 Lymph Nodes

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a **short axis of ≥ 15 mm by CT scan**. Only the *short* axis of these nodes will contribute to the baseline sum. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

1.1.1.2 Target Lesions that Become 'Too Small to Measure'

All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). If the radiologist is able to provide an actual measurement, that should be recorded, even if it is below 5 mm.

However, when such a lesion becomes difficult to assign an exact measure to then:

- if it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- if the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (note: in case of a lymph node believed to be present and faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).

1.1.1.3 Target Lesions that Split or Coalesce on Treatment

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

1.2 Evaluation of Non-target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Immune-related Complete Response (irCR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Immune-related Progressive Disease (irPD): Increases in number or size of non-target lesion(s) does not constitute progressive disease unless/until **Tumor Burden** increases by 20% (ie, the sum of the diameters at nadir of target lesions and any new measurable lesions increases by the required amount)

Note: Non-target lesions are not considered in the definition of Stable Disease and Partial Response.

1.3 New Lesions

The appearance of new lesions alone does not denote disease progression. However their contribution to total tumor burden is included in the sum of the diameters which in turn feeds into the irRECIST 1.1 assessment of tumor response.

2 RESPONSE CRITERIA

2.1 Time Point Response

A response assessment should occur at each time point specified in the protocol.

- **Immune-related Complete Response (irCR)**: Complete disappearance of all tumor lesions (target and non-target), together with no new measurable or unmeasurable lesions, for at least

4 weeks from the date of documentation of irCR. All lymph nodes short axes must be < 10 mm.

- **Immune-related Partial Response (irPR)**: The sum of the diameters of all target lesions is measured and captured as the sum of diameters at baseline. At each subsequent tumor assessment, the sum of the diameters of all target lesions and of new measurable lesions are added together to provide the Immune Response Sum of the Diameters (irSD). A decrease, relative to baseline of the irSD of 30% or greater is considered an irPR, in the absence of irCR. Must be confirmed no less than 4 weeks from the first irPR.
- **Immune-related Stable Disease (irSD)**: irSD is defined as the failure to meet criteria for immune complete response or immune partial response, in the absence of progressive disease.
- **Immune-related Progressive Disease (irPD)**: It is recommended in difficult cases (eg, increase in the sum of the diameters accompanied with significant individual lesion regression, "mixed response", or in presence of stable or improving performance status/clinical condition) to confirm PD at the following tumor assessment. Any of the following will constitute progressive disease:
  - At least 20% increase in the Sum of the Diameters of all target lesions over the nadir Sum of the Diameters calculated for these lesions.
  - At least a 20% increase in the Sum of the Diameters of all target lesions and new measurable lesions over the nadir Sum of the Diameters calculated for the target lesions.

Table 2.1: irRECIST 1.1 Definitions

Target Lesion Response	Non-target Lesion Response	New Measurable Lesions	New Non-measurable Lesions	% Change in Tumor Burden (including measurable new lesions when present)	Overall ir-response
CR	CR	Any	Any	-100%	irCR
PR	Any	Any	Any	≤-30%	irPR
				> -30% to < +20%	irSD
				≥ +20%	irPD
SD	Any	Any	Any	> -30% to < +20%	irSD
				≥ +20%	irPD
PD	Any	Any	Any	≥ +20%	irPD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, ir = Immune response

2.1.1 Confirmation Scans

- **Verification of Response:** irPR must be confirmed no less than 4 weeks from the initial irPR.

2.2 Best overall response: All timepoints

Best Overall Response and Date of Progression Using irRECIST 1.1 (irBOR): The investigator will be asked to provide all responses on study and date(s) of progression, if applicable, and the best overall response will be calculated by the sponsor or designee based on the time point responses and tumor measurements provided by the investigator.

APPENDIX 4 GUIDANCE ON CONTRACEPTION

ACCEPTABLE METHODS FOR PROTOCOLS WITH A TERATOGENIC DRUG OR WHEN THERE IS INSUFFICIENT INFORMATION TO DETERMINE TERATOGENICITY

(CHOOSE ONE OF THE FOLLOWING 3 OPTIONS)[a]

OPTION 1: Any TWO of the following methods

- Hormonal methods of contraception[b, c, d]
- IUD[c, d, e]
- Vasectomy[d, f]
- Tubal Ligation[d]
- A Barrier method (Female or Male Condom with spermicide, Cervical Cap with spermicide, Diaphragm with spermicide)

OPTION 2: Male condom (with spermicide) and diaphragm[g]

OPTION 3: Male condom (with spermicide) and cervical cap[g]

[a] The theoretical failure rate for any of the options listed is considerably less than 1% per year

[b] Excludes progestin-only pills

[c] Hormonal contraceptives may not be used for contraception unless a drug-drug interaction study has demonstrated that the pharmacokinetics of the hormone based contraceptive has not been adversely affected by the investigational drug in the protocol or there is compelling evidence to substantiate that investigational product(s) or con-meds will not adversely affect contraception effectiveness. The PK scientist and MST chair must agree that the use of hormone-based contraception is safe and efficacious for WOCBP. The use of hormone-based contraceptives is not otherwise restricted

[d] A highly effective method of birth control with a failure rate less than 1% per year

[e] IUDS used should have a failure rate less than 1% (highly effective method), such as Mirena and ParaGard

[f] Must be at least 90 days from date of surgery with a semen analysis documenting azoospermia

[g] These 2 barrier methods together are acceptable for a teratogenic drug

UNACCEPTABLE METHODS OF CONTRACEPTION

Abstinence (including periodic abstinence)

No method

Withdrawal

Rhythm

Vaginal Sponge

Any barrier method without spermicide

Spermicide

Progestin only pills

Concomitant use of female and male condom

In countries where spermicide is not available or its use is not considered compatible with male condoms, use of a male condom without spermicide in conjunction with a hormonal method, IUD, or tubal ligation will be acceptable to fulfill this recommendation. Any barrier method when used alone (without spermicide) or the concomitant use of a female and male condom, is not considered a sufficient method of contraception, as each carries a failure rate of >1%.

Women of childbearing potential (WOCBP) receiving BMS-936558 (nivolumab) will be instructed to adhere to contraception for a period of 23 weeks after the last dose of investigational product. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product. These durations have been calculated using the upper limit of the half-life for BMS-936558 (nivolumab) (25 days) and are based on the protocol requirement that WOCBP use contraception for 5 half-lives plus 30 days and men who are sexually active with WOCBP use contraception for 5 half-lives plus 90 days after the last dose of BMS-936558 (nivolumab).