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Clinical Protocol CA209025

A Randomized, Open-Label, Phase 3 Study of Nivolumab (BMS-936558) vs Everolimus in Subjects with Advanced or Metastatic Clear-Cell Renal Cell Carcinoma Who Have Received Prior Anti-Angiogenic Therapy

(CheckMate 025, CHECKpoint pathway and nivoluMAb clinical Trial Evaluation)

Revised Protocol Number: 06
Incorporates amendment: 15

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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 06	12-Aug-2015	Incorporates amendment 15
Amendment 15	12-Aug-2015	Protocol amendment is being implemented to provide modifications to the protocol based on recommendations of the study's independent Data Monitoring Committee (DMC). The DMC for the CA209025 study convened on 17-Jul-2015 to evaluate data from a planned, formal Interim Analysis of overall survival (OS). The DMC declared superiority for OS in subjects receiving nivolumab as compared to everolimus. As a result of the DMC assessment, this protocol amendment is being implemented to provide a mechanism for eligible subjects randomized to the everolimus treatment Arm B to receive subsequent nivolumab therapy as part of a nivolumab extension phase. Protocol amendment also indicates that the interim analysis results should now be considered the final primary analysis results of the protocol. Protocol amendment also indicates the assignment of Helene Hardy and Elmer Berghorn as the BMS Study Directors.
Revised Protocol 05	02-Apr-2015	Incorporates amendment 14
Amendment 14	02-Apr-2015	Updated Section 5.3.1 to include language that allows the potential for the collection of additional survival data.
Revised Protocol 04	24-Dec-2014	Incorporates amendment 13
Amendment 13	24-Dec-2014	Updated Section 4.1.3 to refer to the current Investigator Brochure for nivolumab preparation information. Clarification added to Section 6.1 and 6.4 indicating SAE and pregnancy forms are to be submitted within 24 hours of awareness of the event. Clarification indicating SAEs for subjects who were randomized but never received study treatment need to be reported for a period of 30 days from date of randomization.
Revised Protocol 03	27-Aug-2014	Incorporates amendment 12
Amendment 12	27-Aug-2014	Changed the order of secondary objectives throughout document to indicate that ORR will be first and PFS second Definition of PFS updated to include investigator assessed RECIST 1.1 or clinical progression Updated nivolumab preparation information in Section 4.1.3 regarding filter size, acceptable diluents and IV components and minimal drug concentration
Revised Protocol 02	11-Jun-2013	Incorporates amendment 09

Document	Date of Issue	Summary of Change
Amendment 09	11-Jun-2013	CA209025 protocol is additionally identified as "CheckMate 025, CHECKpoint pathway and nivoluMAb clinical Trial Evaluation" Approved generic name "nivolumab" for BMS-936558 has been added throughout the document. Clarification of 4th secondary objective added Information on Opportunistic Infections added to Summary of Safety Clarifications added to Inclusion criteria 2e and 2h and Exclusion criteria 2h and 2k Section 3.4.1 added clarification regarding palliative radiation and added information regarding palliative surgical resection. Added clarifying information on subject follow-up in section 3.6 Updated product information in Table 4.1-1 Added clarifying information on weight used for nivolumab dose in section 4.3 Added Nephrotoxicity to list of management guidelines available in IB Added clarification and guidance to Tables in section 5.1, removed HCO3, added albumin, allow for serum urea or BUN, HCV Ab or HCV RNA and added additional sample collections to Table 5.1-6 Clarifying information added to section 5.3 Safety Assessments Added Section 5.3.1 - Follow-up and Survival Procedures; including addition of EQ5D collection during the survival follow-up period. Section 5.4 added clarification regarding bone scans. Section 5.6 added clarifications throughout and information on PBMC and Peripheral Blood RNA Clarification/update to section 8.2 (Population for Analysis), 8.3(Endpoints), 8.4.2.2 (Methods for Secondary Endpoints), 8.45 (Biomarker Analyses) Section 9.3 updated to reflect criteria for Signatory Investigator Reference 50 & 51 added Additional minor clarifications and grammatical corrections made throughout document
Revised Protocol 01	05-Mar-2013	Incorporates amendment: 07
Amendment 07	05-Mar-2013	Update to the Summary of Safety section to include new preliminary reproductive toxicology data that was distributed as a Non-clinical Expedited Safety Report and to include changes to the guidance on contraception. Tables were renumbered per new model template Section 3.3.1 Inclusion criteria 3a and 3d were updated to add clarifying language for length of time of contraceptive use. Update Appendix 3 - Guide on Contraception
Original Protocol	18-Jun-2012	Not applicable

SYNOPSIS

Clinical Protocol CA209025

Protocol Title: CA209025: A Randomized, Open-Label, Phase 3 Study of Nivolumab (BMS-936558) vs Everolimus in Subjects with Advanced or Metastatic Clear-Cell Renal Cell Carcinoma Who Have Received Prior Anti-Angiogenic Therapy (CheckMate 025, CHECKpoint pathway and nivoluMAb clinical Trial Evaluation)

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Nivolumab dosed intravenously over 60 minutes at 3 mg/kg every 2 weeks or everolimus, 10 mg daily continuous oral dose, until disease progression, unacceptable toxicity or other reasons specified in the protocol.

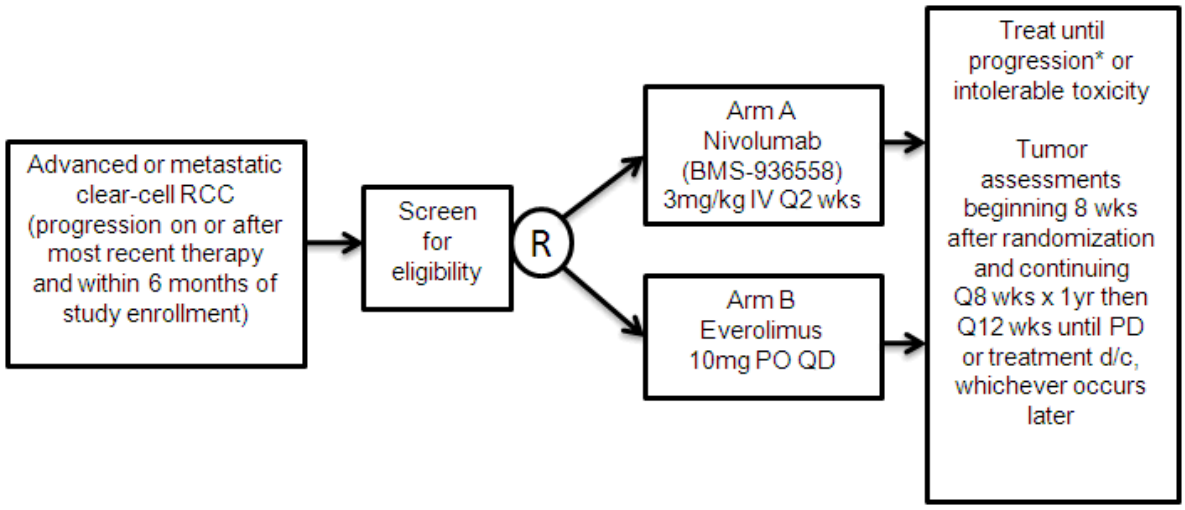
Study Phase: 3

Research Hypothesis: Treatment with nivolumab will improve overall survival (OS) when compared to everolimus in subjects with advanced or metastatic renal cell carcinoma who have received prior anti-angiogenic therapy.

Objectives: To compare the clinical benefit, as measured by the duration of OS, provided by nivolumab vs everolimus in subjects with advanced or metastatic renal cell carcinoma who have received prior anti-angiogenic therapy.

Study Design: This is a Phase 3, randomized, open-label study of nivolumab vs everolimus in subjects with advanced or metastatic RCC with a clear-cell component who have received at least one but not more than two prior anti-angiogenic therapy regimens in the advanced or metastatic setting and no more than three total prior systemic treatment regimens in the advanced or metastatic setting. Subjects must have evidence of progression on or after the last treatment regimen received and within 6 months prior to study enrollment. Approximately 822 subjects will be randomized 1:1 and stratified by region (US/Canada vs W. Europe vs Rest of World), Memorial Sloan-Kettering Cancer Center (MSKCC) risk group (favorable- vs intermediate- vs poor-risk; see Appendix 1), and number of prior anti-angiogenic therapy regimens in the advanced or metastatic setting (1 vs 2) to receive nivolumab (3 mg/kg IV every 2 weeks) on Arm A or everolimus (10 mg po daily) on Arm B. No dose increases or reductions will be allowed for nivolumab. Dose modifications for everolimus will be allowed as per the approved product label or as per standard practice in countries where everolimus is not approved for the treatment of advanced RCC. Subjects will be assessed for response (RECIST 1.1) by CT or MRI beginning 8 weeks after randomization and continuing every 8 weeks for the first year and then every 12 weeks until progression or treatment discontinuation, whichever occurs later. Subjects on both arms will be allowed to continue study therapy after initial investigator-assessed RECIST 1.1-defined progression if they are assessed by the investigator to be deriving clinical benefit and tolerating study drug. Such subjects must discontinue study therapy when further progression, as defined in the protocol, is documented. The primary endpoint of this study is OS. The final analysis of OS will occur after approximately 569 events (ie, deaths) have occurred. An interim analysis of OS will occur when at least 398 OS events (70% of total OS events needed for final analysis) have occurred. Objective response rate (ORR) and progression-free survival (PFS), each based on investigator assessments using RECIST 1.1 criteria, are key secondary endpoints that will be subject to hierarchical testing, with testing for ORR followed by testing for PFS if appropriate. Other secondary endpoints include duration of objective response, evaluation of PD-L1 as a predictive biomarker for OS, incidence of adverse events, serious adverse events, and specific laboratory abnormalities, and time to disease-related symptom progression rate.

Figure 1: **Trial Design Schema**



*Treatment beyond initial investigator-assessed RECIST 1.1-defined progression will be considered in subjects experiencing investigator-assessed clinical benefit and tolerating study therapy. Such subjects must discontinue therapy when further progression is documented.

Amendment 15 Update:

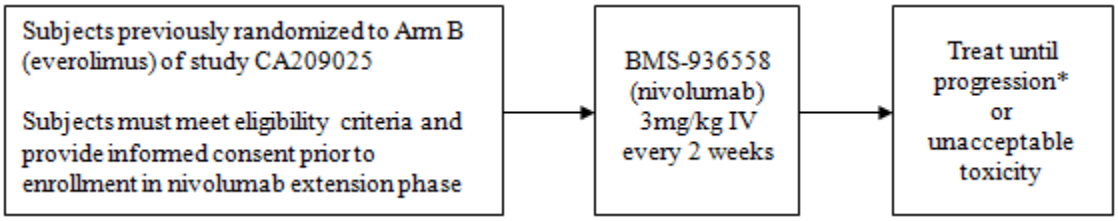
Subjects currently receiving treatment with nivolumab will continue to be treated and monitored as specified in the protocol.

With this amendment, all subjects randomized to the everolimus treatment (Arm B) who meet eligibility criteria may enter the nivolumab extension phase, according to the schema below. These subjects will follow the assessment schedules outlined in Tables 5.1-7 and 5.1-8 of the protocol.

Subjects treated with everolimus who have ended study treatment will be able to receive treatment with nivolumab via the extension phase of the study, assuming eligibility criteria are met (including a 14-day washout period for prior systemic anti-cancer therapy). Details are provided in Sections 3.3.1.1 and 3.3.2.1.

Subjects currently receiving treatment with everolimus may continue to be treated and monitored as specified in the protocol as long as they are continuing to derive benefit from everolimus in the judgment of the investigator. These subjects may receive nivolumab once they are discontinued from everolimus therapy, assuming basic eligibility criteria are met (including a 14-day washout period from the last dose of everolimus).

Nivolumab Extension Phase (schema for those previously randomized to everolimus):



*Treatment beyond investigator-assessed RECIST 1.1-defined progression may be considered for subjects meeting criteria according to Section 4.3.6. Treatment beyond progression for subjects in the nivolumab extension phase must be approved by the BMS Medical Monitor or Study Director prior to subjects receiving additional study drug. Criteria for discontinuation of treatment beyond progression are described in Section 4.3.6.

Study Population:

Key Inclusion Criteria include:

1) Men and women ≥ 18 years of age with histologic confirmation of advanced or metastatic RCC with a clear-cell component.
2) Measurable disease (as defined by RECIST 1.1).
3) Must have received at least one but not more than two prior anti-angiogenic therapy regimens in the advanced or metastatic setting. Prior cytokine therapy (eg, IL-2, IFN-α), vaccine therapy, or treatment with cytotoxics is also allowed. Must have received no more than three total prior systemic treatment regimens in the advanced or metastatic setting and must have evidence of progression on or after the last treatment regimen received and within 6 months prior to study enrollment.
4) Karnofsky Performance Score (KPS) ≥ 70%.
5) Tumor tissue (archival or recent acquisition), FFPE block or slides, must be received by the central vendor for correlative studies in order to randomize a subject to study treatment. (Note: Fine Needle Aspiration (FNA) and bone metastases samples are not acceptable for submission.)

Key Exclusion Criteria include:

1) Any history of or current CNS metastases. Baseline imaging is required within 30 days prior to the first dose.
2) Prior treatment with an mTOR inhibitor (including, but not limited to everolimus, temsirolimus, sirolimus, and ridaforolimus).
3) Any active known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
4) Any condition requiring systemic treatment with corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medication with 14 days prior to the first dose of study drug. Inhaled steroids and adrenal replacement steroid doses > 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease.
5) Uncontrolled adrenal insufficiency.
6) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).
7) Any positive test for hepatitis B or hepatitis C virus indicating acute or chronic infection.
8) Prior treatment with an 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.

Amendment 15 Update:

Specific eligibility criteria for subjects originally randomized to the everolimus Arm B and now entering the nivolumab extension phase are included in the protocol in Sections 3.3.1.1 and 3.3.2.1.

Study Assessments: Overall survival is the primary endpoint of the study. Subjects will be assessed for survival at each in-person study visit and every 3 months following the required in-person visits. Subjects will be assessed for response by CT or MRI beginning 8 weeks (± 1 week) after randomization and continuing every 8 weeks (± 1 week) for the first year and then every 12 weeks (± 1 week) until progression or treatment discontinuation, whichever occurs later. Tumor assessments will continue after treatment discontinuation in subjects who discontinue treatment for reasons other than progression.

Amendment 15 Update:

The schedule of study assessments for subjects randomized to the everolimus Arm B and now entering the nivolumab extension phase are included in the protocol in Section 5.1.

Statistical Considerations:

Sample Size: The sample size is calculated in order to compare the OS between subjects randomized to receive nivolumab and subjects randomized to receive everolimus.

Approximately 569 events (ie, deaths) with an interim analysis after 398 events (70% of total OS events needed for final analysis) provides 90% power to detect a hazard ratio of 0.76 with an overall type 1 error of 0.05 (two-sided). The HR of 0.76 corresponds to a 32% increase in the median OS, assuming a median OS of 14.8 months for everolimus and 19.5 months for nivolumab. The stopping boundaries at interim and final analyses will be derived based on the number of deaths using O'Brien and Fleming alpha spending function.

Endpoints: Approximately 822 subjects will be randomized to the two treatment arms in a 1:1 ratio. Assuming a piecewise constant accrual rate (with a maximum rate of 63 subjects/month and an average rate of 41 subjects/month), the accrual will take approximately 20 months. The total duration of the study from start of randomization to final analysis of OS is expected to be 42 months (20 months of accrual + 22 months of follow-up).

Analyses: If superiority in OS is demonstrated, a hierarchical hypothesis testing approach for the key secondary endpoints will be used to preserve a study-wise type I error rate at 0.05. The key secondary endpoints will be tested in the following hierarchical order:

1) ORR
2) PFS

The PFS and OS distributions will be compared via a two-sided log-rank test stratified by region, MSKCC risk group, and the number of prior anti-angiogenic regimens in the advanced or metastatic setting. The PFS/OS curves, medians, PFS rate at 6 months, OS rate at 12, 18, and 24 months for each randomized arm will be estimated using the Kaplan-Meier product-limit method. The hazard ratios (HR) and corresponding two-sided 95% CI's will be estimated in a Cox proportional hazards model using randomized arm as a single covariate, stratified by the above factors. ORR will be compared using a Cochran-Mantel Haenszel (CMH) test stratified by the same factors used above.

The OS distributions will be also estimated for each randomized arm within PD-L1 positive and PD-L1 negative subgroups separately. Similarly, hazard ratios between randomized arms will be estimated in each subgroup. Interaction between PD-L1 expression and randomized arm will also be tested in a Cox proportional model. Other exploratory analyses, such as associations between PD-L1 status and other efficacy endpoints and evaluations of different thresholds for PD-L1 positivity, will also be performed.

The duration of response (CR + PR) for each randomized arm will be estimated using the Kaplan-Meier product-limit method and limited to responders only.

Summary tables will be presented on safety parameters for each treatment arm. Toxicity rates (worst CTC grade per subject) of adverse events and specific laboratory tests will be tabulated.

The disease-related symptom progression rate based on FKSI-DRS and its corresponding 95% exact CI will also be calculated by Clopper-Pearson method for each randomized arm.

Amendment 15 Update:

As a result of the DMC's positive findings at the interim, the interim analysis results will be considered the final primary analysis results of the protocol.

TABLE OF CONTENTS

1 INTRODUCTION AND STUDY RATIONALE

1.1 Study Rationale

CA209025 (CheckMate 025, CHECKpoint pathway and nivoluMAb clinical Trial Evaluation) is a Phase 3, randomized, open-label study of nivolumab (BMS-936558) vs everolimus in subjects with advanced or metastatic renal cell carcinoma (RCC) who received prior anti-angiogenic therapy. Among all agents approved for advanced or metastatic RCC, only everolimus is approved specifically for use after the failure of treatment with anti-angiogenic therapy. This study will allow for direct comparison of the duration of overall survival (OS) provided by nivolumab vs everolimus. If nivolumab has an acceptable safety profile and is shown to improve OS vs everolimus, this study may support the approval of nivolumab in subjects with advanced or metastatic RCC who have received prior anti-angiogenic therapy, thereby providing another therapeutic option for this patient population.

1.2 Research Hypothesis

Treatment with nivolumab will improve overall survival when compared to everolimus in subjects with advanced or metastatic RCC who have received prior anti-angiogenic therapy.

1.3 Objectives

1.3.1 Primary Objective

To compare the clinical benefit, as measured by the duration of OS, provided by nivolumab vs everolimus in subjects with advanced or metastatic RCC who have received prior anti-angiogenic therapy.

1.3.2 Secondary Objectives

- To compare the objective response rate (ORR) of nivolumab vs everolimus
- To compare the duration of progression-free survival (PFS) of nivolumab vs everolimus
- To assess the duration of objective response of nivolumab vs everolimus
- To evaluate whether PD-L1 is a predictive biomarker for OS
- To assess the overall safety and tolerability of nivolumab vs everolimus
- To assess the disease-related symptom progression rate in each treatment arm based on the FKSI-DRS subscale of the FKSI-15

1.3.3 Exploratory Objectives:

- To characterize the pharmacokinetics (PK) of nivolumab and explore the exposure-response relationship
- To characterize the immunogenicity of nivolumab
- To identify potential predictive biomarkers of efficacy, other than PD-L1 expression status, in subjects receiving nivolumab by analyzing tumor specimens for expression of other proteins involved in regulating immune responses (eg, PD-1 and PD-L2)

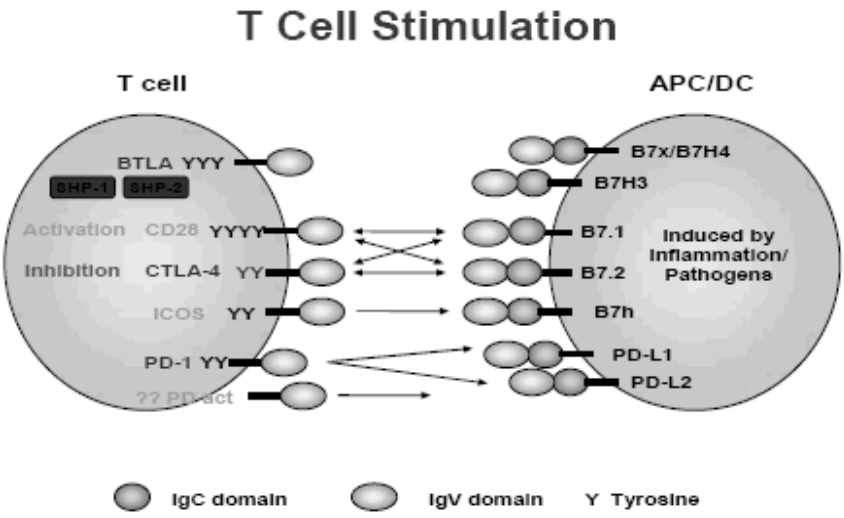
- To assess the effect of natural variation single nucleotide polymorphisms (SNPs) in select genes (eg, PD-1, PD-L1, PD-L2, CTLA-4) has on clinical endpoints and/or on the occurrence of adverse events
- To assess changes in reported global health outcomes in each treatment arm based on the EQ-5D Index score
- To assess health resource utilization (HRU) in each treatment arm during study therapy and at the first 2 follow-up visits.

1.4 Product Development Background

1.4.1 Nivolumab (BMS-936558) Mechanism of Action

Tumor progression may depend upon the acquisition of mechanisms to evade an effective immune response.[1] Immune evasion can occur by exploiting signaling checkpoints that regulate the immune response. The immunoglobulin superfamily of costimulatory receptors is large, and T-cell stimulation is a complex process involving the integration of numerous positive and negative costimulatory signals in addition to antigen recognition by the T-cell receptor (TCR) (Figure 1.4.1-1).[2] Collectively, these signals govern the balance between T-cell activation and tolerance to antigens.

Figure 1.4.1-1: T-Cell Stimulatory Molecules



Programmed death receptor-1 (PD-1, CD279), a 55 kD type I transmembrane protein, is a member of the CD28 family of T-cell costimulatory receptors that also includes CD28, CTLA-4, ICOS, and BTLA.[3] PD-1 contains an intracellular membrane proximal immunoreceptor tyrosine inhibitory motif (ITIM) and a membrane distal immunoreceptor tyrosine-based switch motif (ITSM). Two ligands specific for PD-1 have been identified: PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273). PD-L1 and PD-L2 have been shown to down-regulate T-cell activation upon

binding to PD-1 in both murine and human systems.[4,5,6] PD-1 delivers a negative signal by the recruitment of SHP-2 to the phosphorylated tyrosine residue in the ITSM in its cytoplasmic region.[7,8] 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.[9,10,11,12] The emergence of these autoimmune phenotypes is dependent upon the genetic background of the mouse strain and many of these phenotypes emerge at different times and show variable penetrance. In addition to the phenotypes of null mutations, PD-1 inhibition by antibody-mediated blockade in several murine models has been found to play a role in the development of autoimmune diseases such as encephalomyelitis, graft-versus-host disease, and type I diabetes.[11,13,14] Taken together, these results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self antigens.

Preclinical animal models of tumors have shown that blockade of 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 positive tumors as well as in tumors that are negative for the expression of PD-L1.[15,16,17,18,19,20] 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.[16,21,22,23,24,25,26,27] PD-L1 expressed by tumor cells has been shown to enhance apoptosis of activated tumor-specific T cells in vitro.[3] Moreover, the expression of PD-L1 may protect the tumor cells from the induction of apoptosis by effector T cells.[28] Retrospective analyses of several human tumor types suggest that tumor over-expression (as measured by immunohistochemistry [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.[22,26] Subjects with high tumor and/or lymphocyte PD-L1 levels are 4.5 times more likely to die from their cancer than subjects exhibiting low levels of PD-L1 expression.

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 peripheral blood mononuclear cells (PBMCs), and was evaluated by ELISA. These data indicated that BMS-936558 (nivolumab),

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 nivolumab (BMS-936558) (MDX-1106) is therefore considered a promising immunotherapeutic option.

1.4.2 Renal Cell Carcinoma: Background and Standard Treatments

Renal cell carcinoma (RCC) accounts for ~3% of all cancers in the US. This translates to 58,000 new cases a year with 13,000 associated deaths.[29] Metastatic disease is found in 30% of subjects at diagnosis. Close to 90-95% of metastatic disease is of the clear-cell histology.[30]

Until recently, the cytokines IL-2 and IFNα were the only active treatments for advanced or metastatic RCC. However, due to each of these agent's limited clinical benefit and substantial toxicity profile, newer targeted agents have largely replaced cytokines in the treatment of advanced or metastatic renal cell carcinoma.[31,32,33,34] The recognition of the importance of hypoxia inducible factor alpha (HIFα) signaling in the pathogenesis of clear-cell RCC has led to widespread study of two classes of targeted therapies, anti-angiogenic agents and mTOR inhibitors.[35] Targeting of angiogenesis is rational because constitutive HIFα activation leads to the upregulation or activation of several proteins including vascular endothelial growth factor (VEGF), which can subsequently lead to tumor proliferation and neovasculature formation. Targeting of the mTOR pathway is important because activation of the upstream PI3K/Akt/mTOR signaling pathway is one method by which constitutive HIFα activation or upregulation occurs.[35] Agents that target angiogenesis include VEGF-receptor (VEGFr) tyrosine kinase inhibitors (eg, sorafenib, sunitinib, pazopanib, axitinib, and tivozanib) and VEGF-binding monoclonal antibodies (eg, bevacizumab), while agents that target the mTOR pathway include the mTOR inhibitors (eg, everolimus and temsirolimus).

1.4.3 Treatment of Advanced or Metastatic Renal Cell Carcinoma After Prior Anti-Angiogenic Therapy

Among the five approved anti-angiogenic agents (sorafenib, sunitinib, bevacizumab, pazopanib, and axitinib) and two approved mTOR inhibitors (temsirolimus, everolimus), only everolimus is approved specifically for use after the failure of treatment with anti-angiogenic therapy. In the US, everolimus is indicated for the treatment of advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.[36] In the EU, everolimus is more broadly indicated for patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy.[37] This approval was based on the results of the randomized, double-blind, placebo-controlled Phase 3 RECORD-1 study, which included 416 subjects with metastatic RCC who received prior sunitinib, sorafenib, or both. Subjects who received everolimus experienced a 3-month improvement in median progression-free survival (mPFS) over those who received placebo (4.9 mo vs 1.9 mo, HR 0.33, $p < 0.001$).[36,38] Median PFS was longer in patients who received only one prior VEGFr TKI than in patients who received 2 prior VEGFr TKIs (5.42 mo vs 3.78 mo, respectively).[39] Objective response rates on the everolimus and placebo arms were 2% and 0%, respectively, with no complete responses observed.

Median overall survival (mOS) was not statistically significantly different between the everolimus and placebo arms (14.8 mo vs 14.4 mo, respectively, HR 0.87, p = 0.162).[40] This lack of difference in mOS between arms was thought be likely confounded by crossover to open-label everolimus for most subjects receiving placebo.

The most common (≥ 20%) treatment-emergent adverse events (AEs) reported in the RECORD-1 trial in subjects who received everolimus were stomatitis (44%), infections (37%), asthenia (33%), fatigue (31%), diarrhea (30%), cough (30%), rash (29%), nausea (26%), anorexia (25%), peripheral edema (25%), dyspnea (24%), vomiting (20%), and pyrexia (20%). The most common (≥ 5%) Grade 3/4 treatment-emergent AEs were infections (10%), dyspnea (7%), and fatigue (5%). Grade 3/4 stomatitis, dehydration, pneumonitis, abdominal, and asthenia occurred in 3 to < 5% of subjects.[36] The most common (≥ 50%) laboratory abnormalities were anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia, and increased creatinine.[36,40]

Although no drug other than everolimus has been approved specifically for the treatment of advanced or metastatic RCC after the failure of prior anti-angiogenic therapy, axitinib was approved in the US in 2012 for the treatment of advanced RCC after failure of one prior systemic therapy. This approval was based on the results of the Phase 3 AXIS trial, which compared two VEGFr TKIs, axitinib and sorafenib, in a population including subjects who received prior sunitinib, bevacizumab, temsirolimus, or cytokine therapy.[41] Median PFS in those who received prior sunitinib was 1.4 months longer on the axitinib arm than on the sorafenib arm (4.8 mo vs 3.4 mo, respectively, HR 0.741, p = 0.0002)[41], and response rates were 11% and 7% for axitinib and sorafenib, respectively. Adverse events reported more frequently with axitinib than sorafenib included hypertension (40% vs 29%), fatigue (39% vs 32%), dysphonia (31% vs 14%), and hypothyroidism (19% vs 8%). There was no difference in mOS between arms in the overall population or in those who received prior sunitinib.[41]

1.4.4 Nivolumab (BMS-936558) in Renal Cell Carcinoma

Several completed and ongoing nivolumab (BMS-936558) monotherapy studies have included patients with RCC, including CA209001 (Phase 1 single-ascending dose, dose-escalation study), CA209003 (Phase 1 multiple-ascending dose, dose-escalation study in multiple tumor types, including RCC), CA209009 (exploratory study to investigate the immunomodulatory activity of nivolumab (BMS-936558) in RCC), and CA209010 (Phase 2 dose-ranging study in RCC). A description of each of these trials, including study design, objectives, population, and results, is provided in Section 5 of the BMS-936558 Investigator Brochure.

In addition to the above-mentioned monotherapy trials in RCC, the nivolumab (BMS-936558) program includes an ongoing Phase 1 dose-escalation trial of nivolumab (BMS-936558) in combination with sunitinib or pazopanib in subjects with RCC (CA209016). There are also several ongoing or completed trials that did not enroll subjects with RCC. CA209002 is a completed Phase 1, double-blind, randomized, placebo-controlled, dose-escalation study in subjects with active hepatitis C genotype 1 infection that included 54 treated subjects.

CA209004 is an ongoing Phase 1b multidose dose escalation study of nivolumab (BMS-936558) in combination with ipilimumab administered every 3 weeks in subjects with advanced melanoma.

1.4.5 Summary of Results from Nivolumab (BMS-936558) Program

For a complete review of clinical information, please refer to the BMS-936558 Investigator Brochure.

1.4.5.1 Summary of Safety

In CA209001 (n = 39), in which subjects received a single dose of nivolumab (BMS-936558) with possible retreatment at 3 months, the most frequent AEs were fatigue (56%), nausea (44%), proteinuria (38%), constipation (33%), back pain (33%), dry mouth (28%), vomiting (28%), rash (26%), and dyspnea (26%). There was no clear or consistent relationship between the incidence or severity of AEs and the nivolumab (BMS-936558) dose level (0.3, 1, 3, or 10 mg/kg IV single dose, with possible retreatment at 3 months). Of 39 (100%) subjects who had at least one AE, 32 (82%) had Grade 3 or 4 AEs regardless of causality. Three treatment-related SAEs were reported: hypothyroidism (Grade 2), colitis (Grade 3), and anemia (Grade 2). Among 12 deaths, none were considered drug-related.

In CA209003 (n = 296), as of the database lock date of 24-Feb-2012, BMS-936558- related AEs of any grade occurred in 70% of subjects.[42] The most frequent drug-related AEs occurring in ≥ 5% of subjects included fatigue (24%), rash (12%), diarrhea (11%), pruritus (10%), nausea (8%), decreased appetite (8%), hemoglobin decreased (6%) and pyrexia (5%). The majority of events were low grade, with Grade 3/4 drug-related AEs observed in 14% of subjects. The most common Grade 3/4 drug-related AEs occurring in ≥ 1% of subjects were fatigue (2%), pneumonitis (1%), hypoxia (1%), diarrhea (1%), colitis (1%), abdominal pain (1%), AST/ALT increased (1% each), blood alkaline phosphatase increased (1%), lipase increased (1%), pneumonia (1%), hypophosphatemia (1%), and lymphopenia (1%). Drug-related serious AEs (SAEs) occurred in 11% of subjects. Grade 3/4 drug-related SAEs occurring in ≥ 1% of subjects were: pneumonitis (1%), pneumonia (1%), lipase increased (1%), and diarrhea (1%). The spectrum, frequency, and severity of BMS-936558-related AEs were generally similar across dose levels and histological subtypes. Other drug-related AEs included vitiligo, hepatitis, hypophysitis, and thyroiditis.

Hepatic or gastrointestinal events were managed with treatment interruption and administration of corticosteroids, and were generally completely reversible. Endocrine events were managed with replacement therapy. Several subjects in these categories successfully reinitiated treatment with BMS-936558. Drug-related pneumonitis occurred in 3% of subjects; Grade ≥ 3 pneumonitis developed in 3 subjects (1%). No clear relationship between the occurrence of pneumonitis and tumor type, dose level, or the number of doses received was noted. Early-grade pneumonitis was generally reversible with treatment discontinuation and corticosteroid administration. In three subjects, infliximab and/or mycophenolate were utilized for additional immunosuppression, with unclear effectiveness. There were three (1%) drug-related deaths due to pneumonitis.

In two of these cases, the subject did not receive the early and aggressive intervention (including systemic corticosteroid therapy) that is likely key in the management of this toxicity, while in the third case, other anti-cancer agents (erlotinib and vinorelbine) may have contributed to the fatal event.

Preliminary new non-clinical safety findings of adverse pregnancy outcomes and infant losses in the absence of overt maternal toxicity have been reported.[43] The findings of increased late stage pregnancy loss and early infant deaths/euthanasia in nivolumab exposed pregnant monkeys suggest a potential risk to human pregnancy if there is continued treatment with nivolumab during pregnancy.

Opportunistic Infections Related to Immunosuppression

As of 03-Apr-2013, three subjects on nivolumab (BMS-936558) clinical trials have developed opportunistic infections (2 cases of Aspergillus, and 1 case of Pneumocystis jiroveci) after receiving prolonged treatment with high dose steroids for nivolumab-related adverse events without antifungal prophylaxis. Details of these cases are available in the BMS-936558 Investigator Brochure.

Because of the potential for opportunistic infections with prolonged high dose corticosteroid administrations, the following recommendations should be considered for subjects with inflammatory events expected to require more than 4 weeks of corticosteroids or other immunosuppresants:

- Antimicrobial/antifungal prophylaxis per institutional guidelines to prevent opportunistic infections such as Pneumocystis jiroveci, bacterial and fungal infections.
- Early consultation with an infectious disease specialist should be considered. Depending on the presentation, consultation with a pulmonologist for bronchoscopy or a gastroenterologist for endoscopy may also be appropriate.
- In addition, a concomitant opportunistic infection should be considered in the differential diagnosis when patients develop recurrent adverse events in the setting of ongoing or prior immunosuppressive use.

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

1.4.5.2 Summary of Clinical Activity

In CA209001 and CA209003, the clinical activity of nivolumab (BMS-936558) was demonstrated in a variety of tumor types, including melanoma, RCC, NSCLC, and CRC. Clinical activity was noted across a range of doses (0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg) and across dosing schedules (every 2 weeks dosing for CA209003, single administration with possibility of retreatment at 3 months in CA209001).

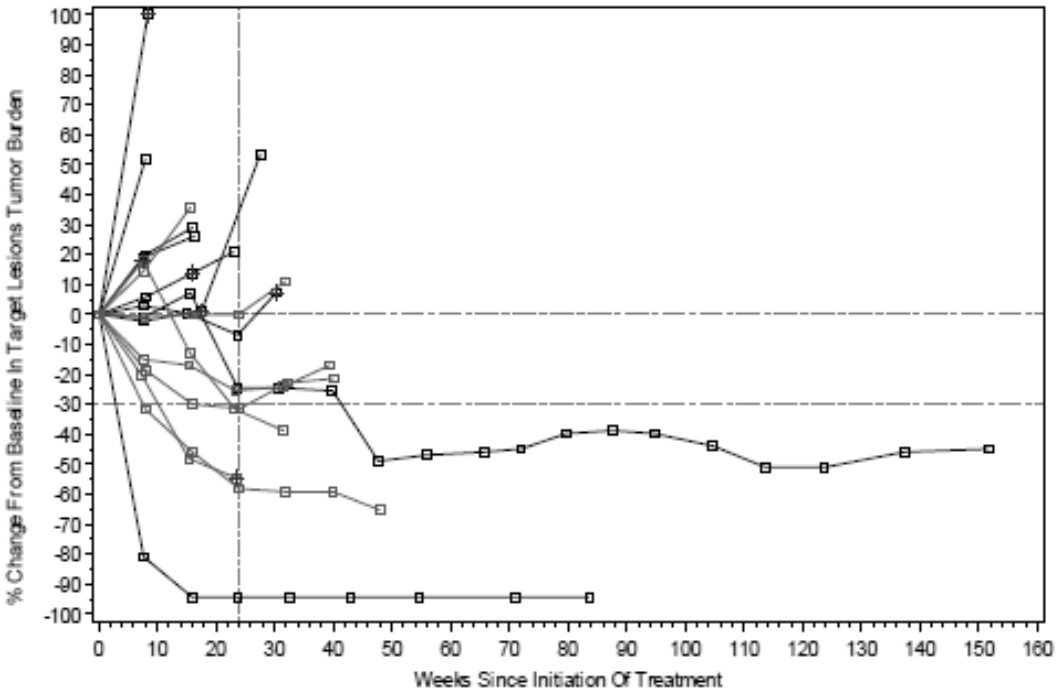
In CA209001, all treated subjects (n = 39) were evaluable for tumor response.[44] Partial response (PR) was reported in 3 subjects and stable disease (SD) was reported in 10 subjects.

Subjects with PRs included 1 subject with CRC treated at 3 mg/kg and 1 subject each with melanoma and RCC, both treated at 10 mg/kg. Tumor responses were maintained in these subjects as of their last radiological tumor assessments at 26, 3, and 18 months, respectively as of the clinical data cut-off date. The subject with RCC had received multiple prior therapies, including sunitinib and sorafenib. In 2 of the 10 subjects with SD, stable disease was maintained for more than 6 months.

In CA209003, as of the database lock date of 24-Feb-2012, a total of 203 subjects with melanoma, RCC, and NSCLC with 8 months follow-up were evaluated for clinical activity.[43] A response of either CR or PR, as determined by the investigator based on modified RECIST 1.0, has been reported at all dose levels. No responses (CR or PR) have been reported in subjects with colorectal carcinoma or castrate-resistant prostate cancer.

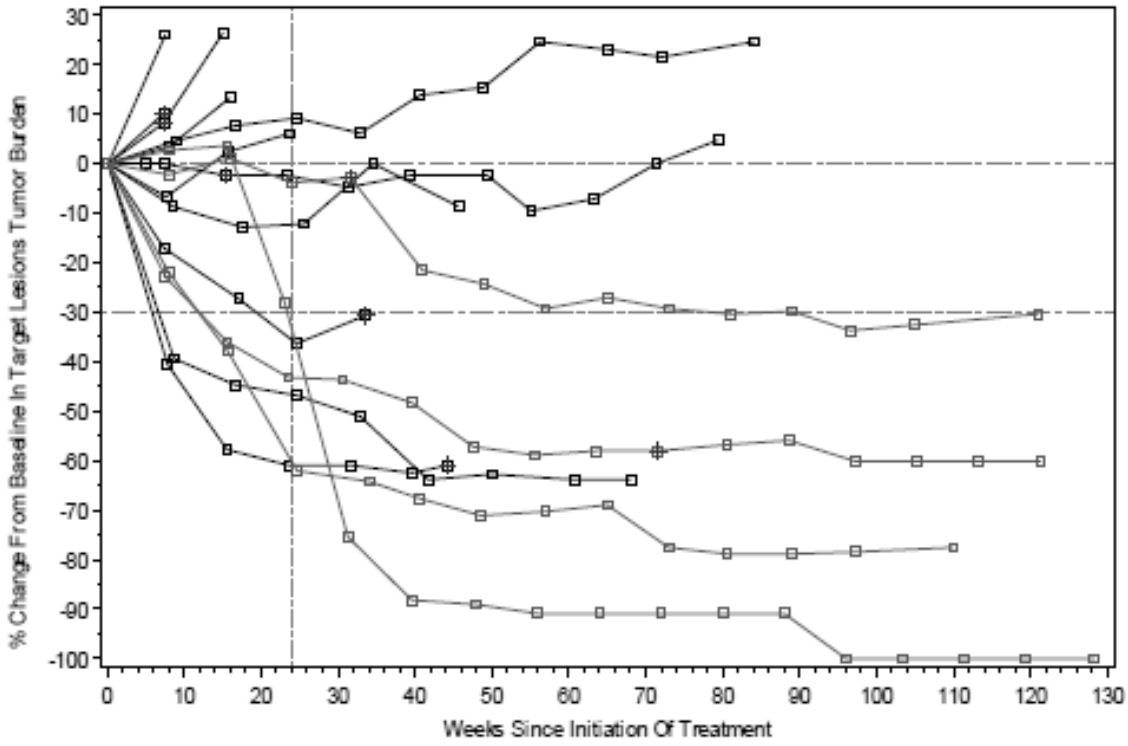
Among 33 patients with pre-treated metastatic RCC who received nivolumab (BMS-936558) and were evaluable for response, the preliminary objective response rates were 4/17 (24%) and 5/16 (31%) for RCC subjects treated at 1 and 10 mg/kg, respectively. Duration of response ranged from 5.6+ months to 17.5+ months in the 1 mg/kg RCC group and from 8.4 months to 22.3 months in the 10 mg/kg group. Stable disease ≥ 24 weeks occurred in an additional 4/17 (24%) and 5/16 (31%) RCC subjects 1 mg/kg and 10 mg/kg, respectively. The PFS-24 week rate was 47% in the 1 mg/kg RCC group and 67% in the 10 mg/kg RCC group. One RCC subject treated at 1 mg/kg attained a CR lasting greater than 1 year. Changes in tumor burden over time for subjects in the 1 mg/kg RCC group and 10 mg/kg RCC group are displayed below (Figure 1.4.5.2-1 and Figure 1.4.5.2-2).[45]

Figure 1.4.5.2-1: Tumor Burden Change Over Time for CA209003 RCC Subjects Receiving 1 mg/kg Nivolumab (BMS-936558)



+: first occurrence of new lesion

Figure 1.4.5.2-2: Tumor Burden Change Over Time for CA209003 RCC Subjects Receiving 10 mg/kg Nivolumab (BMS-936558)



+: first occurrence of new lesion

1.4.5.3 Clinical Pharmacology Summary

Single dose pharmacokinetics (PK) of nivolumab (BMS-936558) was evaluated in subjects with multiple tumor types in CA209001 whereas multiple dose PK is being evaluated in subjects in CA209003. In addition, a preliminary population pharmacokinetic (PPK) model has been developed with data from ~ 350 subjects from CA209001, CA209002, and CA209003.

Single dose PK of nivolumab (BMS-936558) was evaluated in 39 subjects with multiple tumor types in study MD1106-01 in the dose range of 0.3 to 10 mg/kg. The median Tmax across single doses ranged from 1.6 to 3 hours with individual values ranging from 0.9 to 7 hours. The PK of nivolumab (BMS-936558) is linear in the range of 0.3 to 10 mg/kg with dose- proportional increase in Cmax and AUC(INF) with low to moderate inter-subject variability observed at each dose level (ie, CV ranging from 7 to 45%). Geometric mean clearance (CL) after a single intravenous (IV) dose ranged from 0.13 to 0.19 mL/h/kg, while mean volume of distribution (Vz) varied between 83 to 113 mL/kg across doses. The mean terminal T-HALF of nivolumab (BMS-936558) is 17 to 25 days, which is consistent with half life of endogenous IgG4, indicating that the elimination mechanism of nivolumab (BMS-936558) may be similar to IgG4. Both elimination and distribution of nivolumab (BMS-936558) appear to be independent of dose in the dose range studied. Additional details are provided in the Investigator Brochure.

A preliminary PPK model was developed by nonlinear mixed effect modeling using data from 350 subjects from CA209001, CA209002, and CA209003. The body weight normalized dosing produces approximately constant trough concentrations over a wide range of body weights, and hence is appropriate for future clinical trials of BMS-936558.

1.4.6 Rationale for CA209025 Study Design

CA209025 (CheckMate 025, CHECKpoint pathway and nivoluMAb clinical Trial Evaluation) is a Phase 3, randomized, open-label study of nivolumab (BMS-936558) vs everolimus in patients with advanced or metastatic RCC who received prior anti-angiogenic therapy. The primary endpoint is overall survival (OS).

1.4.6.1 Rationale for Choice of Population

A population of subjects who received prior anti-angiogenic therapy, rather than subjects who have received any prior systemic therapy, was chosen because the type of prior regimen received has been shown to have an impact on clinical outcome in subjects with pre-treated advanced or metastatic RCC. For example, subjects who have received only prior anti-angiogenic therapy may not attain the same clinical benefit from subsequent therapy as subjects who have received cytokine therapy, as illustrated by the marked improvement in PFS in cytokine-pretreated subjects compared to sunitinib-pretreated subjects in the Phase 3 AXIS trial.[41] In an effort to include a more homogenous population in this study, the population was limited to subjects who received prior anti-angiogenic therapy.

1.4.6.2 Rationale for Choice of Comparator

Everolimus was chosen as the comparator because it is the only agent whose approval was based on the results of a Phase 3 trial limited to subjects who had received prior anti-angiogenic therapy.

1.4.6.3 Rationale for Dose and Schedule of Nivolumab (BMS-936558)

The dose and schedule of nivolumab (BMS-936558) is 3 mg/kg every two weeks, based upon the analyses of safety, efficacy, and exposure-response data from the ongoing Phase 1 study CA209003 (database lock: 24-Feb-2012; dosing data cut-off for efficacy: first dose by 01-Jul-2011). Anti-tumor activity was observed at dose levels ranging from 1 to 10 mg/kg in melanoma, NSCLC, and RCC, as well as at dose levels of 0.1 and 0.3 mg/kg in melanoma. The antitumor activity of nivolumab (BMS-936558) tended to increase with dose, as did the incidence of SAEs. The anti-tumor activity of nivolumab (BMS-936558) in RCC was investigated at dose levels 1 and 10 mg/kg, with the higher activity observed at 10 mg/kg. The observed anti-tumor activity in melanoma, and NSCLC was highest at 3 mg/kg, suggesting that anti-tumor activity approaches a plateau at dose levels of 3 mg/kg and above. Consistent with these observations, the results of the exposure-response analyses for these tumor types show that the probability of a tumor response tended to approach a plateau for trough concentrations produced by 3 and 10 mg/kg every 2 week dosing.

nivolumab (BMS-936558) was adequately tolerated up to 10 mg/kg, the highest dose level tested, and no maximum tolerated dose (MTD) was identified. Although the spectrum,

frequency, and severity of nivolumab (BMS-936558)-related AEs were generally similar across the dose levels tested, the 10 mg/kg doses level had numerically higher Grade 3/4 drug-related SAEs and AEs leading to discontinuation. Based upon the totality of the safety, efficacy, and exposure-response data, a dose of 3 mg/kg every two weeks was selected as the dose anticipated to achieve an appropriate balance of benefit and risk.

1.4.6.4 Rationale for Open-Label Design

An open-label, rather than blinded, study design was selected for multiple reasons. The management of adverse events will differ between treatment arms, given the different mechanisms of action of everolimus and nivolumab (BMS-936558). Also, divergent toxicity profiles (2% stomatitis rate for nivolumab vs 44% stomatitis rate for everolimus), different routes of administration (IV for nivolumab vs PO for everolimus), different treatment schedules (every two weeks for nivolumab vs daily for everolimus), different dose modification rules (no dose modifications for nivolumab vs allowance for dose modifications for everolimus), and the need for immunogenicity and PK samples on the nivolumab arm add complexity to any blinding strategy.

1.4.6.5 Rationale for Primary Endpoint Selection

The primary endpoint of overall survival was selected based the mechanism of action of nivolumab (BMS-936558). Given that immunotherapeutics such as nivolumab may lead to enhanced inflammation within tumors, it is expected that some patients will have evidence of enlarging lesions or new lesions secondary to this mechanism rather than as a result of true disease progression. Also, with immunotherapeutics, the kinetics of tumor growth may initially outpace anti-tumor activity.[46] For these reasons, PFS, which has served as the primary endpoint in the majority of Phase 3 trials leading to new drug approvals in advanced or metastatic RCC, may not be the optimal endpoint for this trial. OS may more accurately reflect the clinical benefit of nivolumab than PFS.

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

Emerging evidence indicates that a minority of subjects treated with immunotherapy may derive clinical benefit from continued treatment despite initial evidence of progressive disease.[47] In this study, subjects will be permitted to continue nivolumab (BMS-936558) treatment beyond initial investigator-assessed, RECIST 1.1-defined progression as long as they are experiencing an investigator-assessed clinical benefit and tolerating study drug (Section 4.3.6). These criteria aim to ensure that the benefits of continued treatment outweigh any associated risks.

In addition, as the approved product label for everolimus allows for continued treatment as long as clinical benefit is observed or until unacceptable toxicity occurs, subjects on the everolimus arm will also be permitted to continue treatment beyond initial investigator-assessed RECIST 1.1-defined progression if they meet the same criteria (Section 4.3.6). The allowance for treatment beyond progression on both arms will also help to prevent the introduction of potential bias into the study.

For statistical analyses that include the investigator-assessed progression date, subjects who continue treatment beyond initial investigator-assessed, RECIST 1.1-defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event.

1.4.6.7 Rationale for a Predictive Biomarker (Tumor PD-L1 Expression) Evaluation

Preliminary data indicate PD-L1 protein expression in tumors may correlate with nivolumab (BMS-936558) clinical activity. Sixty-one pretreatment tumor specimens from a limited subset (N = 42) of subjects in CA209003 (18 melanoma, 10 NSCLC, 7 colorectal carcinoma, 5 RCC, and 2 prostate cancer) were analyzed for tumor cell surface PD-L1 expression.[43] Biopsy specimens from 25 of 42 subjects were positive for PD-L1 expression by IHC. Among these subjects, 9 (36%) achieved an OR. Among 17 subjects with PD-L1 negative tumors, none achieved an OR. This analysis is based on optional biopsies from a non-random subset of the population, and testing of a statistical hypothesis was not pre-specified. These preliminary results must, therefore, be interpreted with caution. Importantly, only 5/42 subjects in this subset had RCC. Therefore, these data are not conclusive as to the positive or negative predictive value of PD-L1 expression in RCC, and further analyses of a larger number of samples from CA209003 are planned.

In order to more thoroughly assess the role of PD-L1 protein expression as a predictive biomarker, baseline tumor tissue will be collected prospectively from all randomized patients in this study, and a retrospective analysis of efficacy by PD-L1 expression status will be conducted. Due to the preliminary nature of the Phase 1 data and current lack of a validated IHC assay, subjects will not be selected or stratified by PD-L1 expression status. The sponsor is in the process of developing a validated IHC assay that can be used to reproducibly measure PD-L1 expression in tumor tissue. Contingent on development of an optimized assay, future studies will include prospective analyses of PD-L1 expression.

For subjects treated in the nivolumab extension phase, there will be NO tumor tissue samples collected in the extension phase.

1.5 Overall Risk/Benefit Assessment

There is a clear unmet medical need for patients with advanced or metastatic RCC who have received prior anti-angiogenic therapy. This is illustrated by the fact that everolimus, the only agent whose approval was based on the results of a Phase 3 trial limited to subjects who had received prior anti-angiogenic (RECORD-1), led to only a 3-month improvement in mPFS vs placebo (4.9 mo vs 1.9 mo). In addition, everolimus did not lead to an improvement in OS vs placebo.[40] More recently, the Phase 3 AXIS trial of axitinib vs sorafenib demonstrated only a 1.4 mo improvement in mPFS vs sorafenib (4.8 mo for axitinib vs 3.4 mo for sorafenib) in a sunitinib-refractory subgroup, with no improvement in OS.[42] Nivolumab (BMS-936558) has demonstrated clinical activity across several tumor types, including advanced or metastatic RCC, with a PFS rate at 24 weeks as high as 67%. Nivolumab (BMS-936558) has also demonstrated a

manageable toxicity profile. Although three subjects treated with nivolumab (BMS-936558) to date have experienced fatal outcome due at least in part to drug-related pulmonary toxicity, two of these subjects did not receive the early and aggressive intervention (including systemic corticosteroid therapy) that is likely key in the management of this toxicity, and the third subject received subsequent therapies which possibly contributed to the outcome. The robust clinical activity demonstrated by nivolumab (BMS-936558) in subjects with advanced or metastatic RCC, in combination with the manageable safety profile, supports the further development of nivolumab (BMS-936558) in subjects with advanced or metastatic RCC. The potential clinical benefits of administration of nivolumab (BMS-936558) outweigh the risks of toxicity.

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 Harmonisation (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.

In situations where consent cannot be given to subjects, their legally acceptable representatives are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers 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 confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

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.

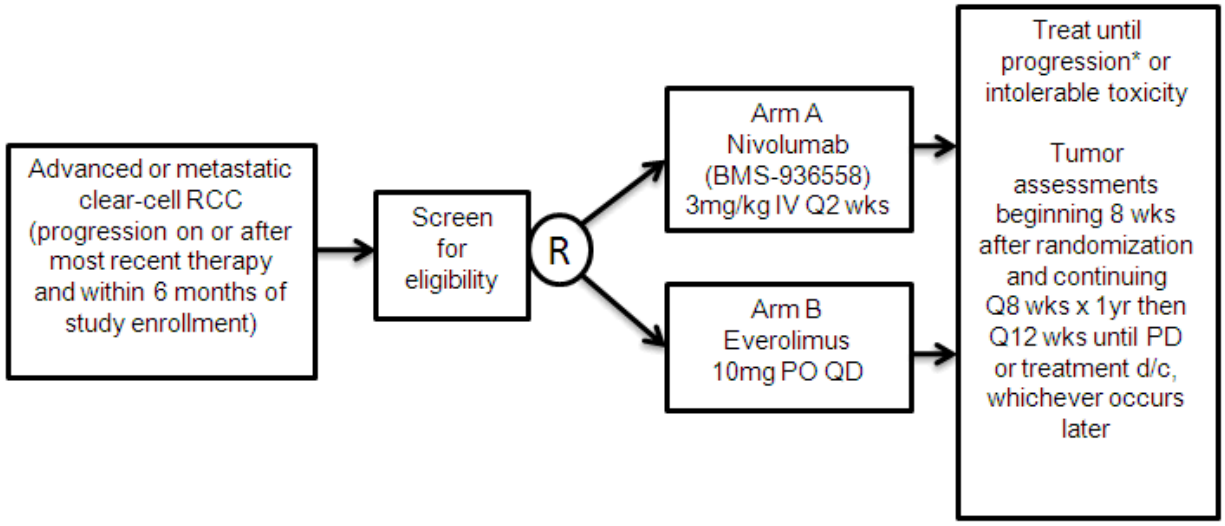
The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is a Phase 3, randomized, open-label study of nivolumab (BMS-936558) vs everolimus in subjects with advanced or metastatic RCC with a clear-cell component who have received one or two prior anti-angiogenic therapy regimens in the advanced or metastatic setting and no more than three total prior systemic treatment regimens in the advanced or metastatic setting. Subjects must have evidence of progression on or after the last treatment regimen received and within 6 months prior to study enrollment. Approximately 822 subjects will be randomized 1:1 and stratified by region (US/Canada vs W. Europe vs Rest of World), Memorial Sloan-Kettering Cancer Center (MSKCC) risk group (favorable- vs intermediate- vs poor-risk; see Appendix 1), and number of prior anti-angiogenic therapy regimens in the advanced or metastatic setting (1 vs 2) to receive nivolumab (3 mg/kg IV every 2 weeks) on Arm A or everolimus (10 mg po daily) on Arm B. No dose increases or reductions will be allowed for nivolumab. Dose modifications for everolimus will be allowed as per the approved product label or as per standard practice in countries where everolimus is not approved for the treatment of advanced RCC. Subjects will be assessed for response (RECIST 1.1) by CT or MRI beginning 8 weeks from randomization and continuing every 8 weeks for the first year and then every 12 weeks until progression or treatment discontinuation, whichever occurs later. Subjects will be allowed to continue study therapy after initial investigator-assessed RECIST 1.1-defined progression if they are assessed by the investigator to be deriving clinical benefit and tolerating study drug. Such subjects should discontinue study therapy when further progression is documented (see Section 4.3.6). The primary endpoint of this study is OS. The final analysis of OS will occur after approximately 569 events (ie, deaths) have occurred. An interim analysis of OS will occur after at least 398 events (70% of total OS events needed for final analysis) have occurred. ORR and PFS (each based on investigator assessments using RECIST 1.1 definitions) are key secondary endpoints that will be subject to hierarchical testing, with testing for ORR followed by testing for PFS, if appropriate. Other secondary endpoints include duration of objective response, association of OS with PD-L1 expression, incidence of adverse events, serious adverse events, and laboratory abnormalities, and disease-related symptom progression rate.

Figure 3.1-1: Trial Design Schema



*Treatment beyond initial investigator-assessed, RECIST 1.1-defined progression may be considered in subjects experiencing investigator-assessed clinical benefit and tolerating study drug. Such subjects must discontinue therapy when further progression is documented (see Section 4.3.6).

Amendment 15 Update:

The Data Monitoring Committee (DMC) for the CA209025 study convened on 17-Jul-2015 to evaluate the data from a planned, formal Interim Analysis of overall survival (OS). The DMC declared superiority for OS in subjects receiving nivolumab as compared to everolimus.

As a result of the DMC assessment, this protocol will provide a mechanism for eligible subjects randomized to the everolimus treatment Arm B to receive subsequent nivolumab therapy as part of a nivolumab extension phase.

All subjects previously on everolimus (Arm B), who wish to receive subsequent therapy with nivolumab, must meet the extension phase eligibility criteria and sign informed consent prior to initiation of extension phase therapy.

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 received at the central lab for correlative studies in order for a subject to be randomized. Subjects must consent to allow the acquisition of formalin-fixed paraffin-embedded (FFPE) material (block or minimum of 10 unstained slides) by study personnel for performance of correlative tissue studies.

- Subject is assessed for complete study eligibility including assessments and procedures within the required timeframe found in Table 5.1-1
- Patient-reported outcome (PRO) instruments will be completed after randomization, prior to the first dose of study therapy.

For subjects in the nivolumab extension phase, screening assessments and procedures will be followed according to Table 5.1-7.

Amendment 15 Update:

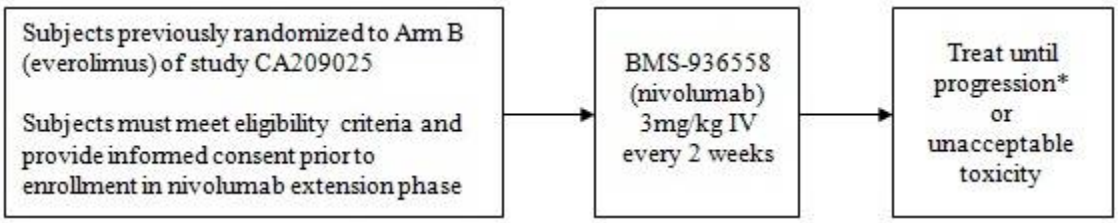
Subjects currently receiving treatment with nivolumab will continue to be treated and monitored as specified in the protocol.

With this amendment, all subjects randomized to the everolimus treatment Arm B who meet eligibility criteria may enter the nivolumab extension phase, according to the schema below. These subjects will follow the assessment schedules outlined in Table 5.1-7 and Table 5.1-8 of the protocol.

Subjects treated with everolimus who have ended study treatment will be able to receive treatment with nivolumab via the extension phase of the study, assuming basic eligibility criteria are met (including a 14-day washout period for prior systemic anti-cancer therapy). Details are provided in Sections 3.3.1.1 and 3.3.2.1.

Subjects currently receiving treatment with everolimus may continue to be treated and monitored as specified in the protocol as long as they are continuing to derive benefit from everolimus in the judgment of the investigator. These subjects may receive nivolumab once they are discontinued from everolimus therapy, assuming basic eligibility criteria are met (including a 14-day washout period from the last dose of everolimus).

Nivolumab Extension Phase (schema for those previously randomized to everolimus):



*Treatment beyond investigator-assessed RECIST 1.1-defined progression may be considered for subjects meeting criteria according to Section 4.3.6. Treatment beyond progression for subjects in the nivolumab extension phase must be approved by the BMS Medical Monitor or Study Director prior to subjects receiving additional study drug. Criteria for discontinuation of treatment beyond progression are described in Section 4.3.6.

Treatment Phase:

- Begins with the randomization call to the IVRS. The subject is randomly assigned to either the nivolumab arm (Arm A) or the everolimus arm (Arm B).

- Within 3 working days from randomization the subject must receive the first dose of study medication (Day 1 of Cycle 1).
- On-study labs (cycle 2 and beyond) should be drawn within 72 hours prior to re-dosing. Adverse event assessments should be documented at each clinic visit and women of childbearing potential (WOCBP) must have a pregnancy test at every new cycle visit.
- PK samples, immunogenicity and serum for soluble factors samples for subjects on nivolumab (Arm A) will be done according to the schedule in Table 5.1-5. and a single serum soluble factor sample for subjects on Arm B will be done according to Table 5.1-6.
- Subjects on nivolumab are re-dosed every 2 weeks with allowances for delay up to a maximum of 6 weeks from last dose (see Sections 4.3.1.1 and 4.3.3.1). Subjects on everolimus will continue daily oral dosing with allowances for delay up to a maximum of 6 weeks from last dose (see Sections 4.3.1.2 and 4.3.3.2). Subjects on both arms adhere to the same 4-week cycle length, with nivolumab arm (Arm A) subjects receiving 2 doses within the cycle.
- Treated subjects will be evaluated for response according to the RECIST 1.1 guidelines beginning 8 weeks from randomization (± 1 week) and continuing every 8 weeks (± 1 week) for the first 12 months from randomization, and then every 12 weeks (± 1 week) until disease progression or end of therapy, whichever occurs later.
- ePRO instruments will be completed according to Table 5.1-2& Table 5.1-3. For subjects in the nivolumab extension phase, PRO assessments will be done according to the schedule in Table 5.1-7 and Table 5.1-8.
- This phase ends when the subject is discontinued from study therapy. For a complete list of reasons for treatment discontinuation, see Section 3.5.

Follow-Up Phase:

- Begins when the decision to discontinue a subject from study therapy is made (no further treatment with study therapy).
- Two X follow-up visits include PK/immunogenicity samples only for subjects who received nivolumab (Arm A). Subjects in the nivolumab extension phase will have XX follow-up visits and will not provide PK and immunogenicity samples.
- Subjects that discontinue treatment for reasons other than disease progression will continue to have tumor assessments beginning 8 weeks from randomization (± 1 week) and continuing every 8 weeks (± 1 week) for the first 12 months from randomization and every 12 weeks (± 1 week) thereafter until disease 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, to include subsequent anti-cancer therapy.
- ePRO instruments will be completed according to Table 5.1-4.

The primary analysis of survival was planned to be conducted after approximately 569 subjects have died (approximately 42 months from start of randomization). One interim analysis was planned after at least 398 subjects had died. As a result of DMC's positive findings at the interim, the interim analysis results with 398 death events will be considered the final primary analysis results of the protocol. Additional survival follow-up may continue for up to 5 years from the primary analysis of survival. The study will end once survival follow-up has concluded.

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) Histological confirmation of RCC with a clear cell component.

c) Advanced or metastatic RCC.

d) Measurable disease as defined by RECIST 1.1 criteria (Section 5.4).

e) Must have received at least one but not more than two prior anti-angiogenic therapy regimens (including, but not limited to, sunitinib, sorafenib, pazopanib, axitinib, tivozanib, and bevacizumab) in the advanced or metastatic setting. Prior cytokine therapy (eg, IL-2, IFN-α), vaccine therapy, or treatment with cytotoxics is also allowed.

f) Must have received no more than three total prior systemic treatment regimens in the advanced or metastatic setting, and must have evidence of progression on or after the last treatment regimen received and within 6 months prior to study enrollment.

g) Karnofsky Performance Score (KPS) ≥ 70% (Appendix 2).

h) Tumor tissue (FFPE archival or recent acquisition) must be received by the central vendor (block or unstained slides) for correlative studies outlined in Section 5.6.1.1 in order to randomize a subject to study treatment. (Note: Fine Needle Aspiration (FNA) and bone metastases samples are not acceptable for submission.)

3) Age and Reproductive Status

a) Women of childbearing potential (WOCBP) must use method(s) of contraception based on the tables in Appendix 3. 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, contraception should be continued for a period of 30 days plus the time required for the investigational drug to undergo five half lives. For women randomized to receive nivolumab, this is equivalent to 23 weeks after discontinuation of treatment. Women randomized to receive everolimus must follow instructions for birth control as per the SmPC or package insert (8 weeks after discontinuation of treatment).

b) WOCBP 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 90 days plus the time required for the investigational drug to undergo five half lives. For men randomized to receive nivolumab, this is equivalent to 31 weeks after discontinuation of treatment. Men randomized to receive everolimus must follow instructions for birth control for 14 weeks after discontinuation of treatment.

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):

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

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

3.3.1.1 Inclusion Criteria for Entering the Nivolumab Extension Phase - Subjects Previously Randomized to Everolimus

1) Signed Written Informed Consent

a) Subjects must have signed and dated an IRB/IEC approved written Informed Consent Form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal subject care.

b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests and other requirements of the study.

2) Target Population

a) Subjects previously randomized to everolimus treatment (Arm B) on the CA209025 study.

b) Prior anti-cancer therapy, including everolimus and palliative radiotherapy, must have been completed at least 14 days prior to first dose of nivolumab.

c) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 or baseline prior to first dose of nivolumab.

d) Laboratory values must meet the following criteria and should be obtained within 14 days prior to first dose of nivolumab:

i) WBC $\geq$ 2000/μL

ii) Neutrophils $\geq$ 1500/μL

iii) Platelets $\geq 100 \times 10^3$/μL

iv) Hemoglobin $\geq$ 9.0 g/dL

v) Serum creatinine $\leq$1.5 x ULN or creatinine clearance (CrCl) $\geq$40 mL/minute (using Cockcroft/Gault formula):

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

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

vi) AST/ALT $\leq$ 3.0 x ULN ($\leq$5 x ULN for subjects with liver metastases)

vii) Total Bilirubin $\leq$ 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL.

3.3.2 Exclusion Criteria

1) Target Disease Exceptions

a) Any history of or current CNS metastases. Baseline imaging of the brain by MRI or CT scan is required within 30 days prior to the first dose of study drug.

2) Medical History and Concurrent Diseases

a) Prior treatment with an mTOR inhibitor (including, but not limited to, everolimus, temsirolimus, sirolimus, and ridaforolimus).

b) Any active known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

c) Any condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days prior to the first dose of study drug. Inhaled steroids and adrenal replacement steroid doses > 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease.

d) Uncontrolled adrenal insufficiency.

e) Any known active chronic liver disease.

f) 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.

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

h) Any positive test for hepatitis B or hepatitis C virus indicating acute or chronic infection.

i) Known medical condition (eg, a condition associated with diarrhea or acute diverticulitis) that, in the investigator's opinion, would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results.

j) Prior treatment with an 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.

k) Major surgery (eg, nephrectomy) less than 28 days prior to the first dose of study drug. Minor surgery less than 14 days prior to the first dose of study drug.

l) Anti-cancer therapy less than 14 days prior to the first dose of study drug (less than 28 days for bevacizumab) or palliative, focal radiation therapy less than 14 days prior to the first dose of study drug.

m) Presence of any toxicities attributed to prior anti-cancer therapy other than alopecia that have not resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of study drug.

n) Concurrent use of any medications or substances known to be moderate CYP3A4 or PgP inhibitors or strong CYP3A4 inhibitors or inducers (Appendix 4). Although corticosteroids are considered to be strong inducers of CYP3A4, physiologic replacement doses of corticosteroids are allowed at study entry (Section 3.4.3).

o) Presence of a malabsorption syndrome, gastrointestinal disorder, or gastrointestinal surgery that could affect the absorption of everolimus.

3) Physical and Laboratory Test Findings

a) All baseline laboratory requirements should be obtained within 14 days prior to 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)

viii. Fasting serum glucose > 1.5x ULN

ix. Fasting serum cholesterol > 300 mg/dL or >7.75 mmol/L

x. Fasting triglycerides > 2.5x ULN

4) Allergies and Adverse Drug Reaction

a) History of severe hypersensitivity reaction to any monoclonal antibody.

5) Sex and Reproductive Status

a) WOCBP who are pregnant or breastfeeding

b) Women with a positive pregnancy test at enrollment or prior to administration of study medication

6) 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.

3.3.2.1 Exclusion Criteria for Entering the Nivolumab Extension Phase - Subjects Previously Randomized to Everolimus

1) Medical History and Concurrent Diseases

a) Subjects with active, known or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

b) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days prior to the first dose of nivolumab. Corticosteroids with minimal systemic absorption (for example, topical, inhalational, or as specified in Section 3.4.3), and adrenal replacement steroid doses > 10 mg daily prednisone or equivalent are permitted in the absence of active autoimmune disease.

c) Subjects must have recovered from the effects of major surgery or significant traumatic injury at least 28 days prior to the first dose of nivolumab.

d) Prior treatment with an anti-PD-1 or anti-PD-L1 therapy.

e) Uncontrolled adrenal insufficiency.

2) Physical and Laboratory Test Findings

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

b) Known positive test for Hepatitis B virus or Hepatitis C virus indicating acute or chronic infection.

3.3.3 Women of Childbearing Potential

A Woman of Childbearing Potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. In addition, women under the age of 62 must have a documented serum follicle stimulating hormone, (FSH) level > 40 mIU/mL. Women treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used:

- 1 week minimum for vaginal hormonal products, (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products
- Other parenteral products may require washout periods as long as 6 months

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study:

- Immunosuppressive agents (except to treat a drug-related adverse event)
- Systemic corticosteroids > 10 mg daily prednisone equivalent (except as stated in Section 3.4.3 or to treat a drug-related adverse event)
- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive radiation therapy, or standard or investigational agents for treatment of cancer).
- Strong CYP3A4 inhibitors (Appendix 4)

Supportive care for disease-related symptoms may be offered to all subjects on the trial.

Palliative (limited-field) radiation therapy and palliative surgical resection are permitted, if the following criteria are met:

1. The lesion being considered for palliative radiation is not a target lesion.
2. The subject will be considered to have progressed at the time of palliative therapy and must meet criteria to continue with treatment beyond progression (Section 4.3.6)
3. The case is discussed with the BMS medical monitor or study director.

Surgical resection of lesions is otherwise not permitted.

3.4.2 Other Restrictions and Precautions

Live vaccines should be avoided, whenever possible, while on study treatment.

All subjects (either treatment arm) should avoid moderate CYP3A4 and/or PgP inhibitors and strong CYP3A4 inducers (Appendix 4). This includes grapefruit, grapefruit juice, and other foods that are known to inhibit cytochrome P450 and PgP activity, as well as St. John's Wort (*Hypericum perforatum*), which is a CYP3A4 inducer. If subjects receiving everolimus do require moderate CYP3A4 and/or PgP inhibitors or strong CYP3A4 inducers during the course of study drug treatment, dose modifications should occur as outlined in Sections 4.3.2.2 and 4.3.2.4.

3.4.3 Permitted Therapy

Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if > 10 mg/day prednisone or equivalent. 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 contact allergen) is permitted.

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

Concomitant medications are recorded at baseline, throughout the treatment phase of the study and at the two follow-up visits, in the appropriate section of the CRF. All medications (prescriptions or over the counter medications) continued at the start of the study or started during the study and different from the study drug must be documented in the concomitant therapy section of the CRF.

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 involuntary 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 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 (CRF) page.

3.6 Subject Follow-Up

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up in writing, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 TREATMENTS

Study drugs include both Noninvestigational (NIMP) and Investigational Medicinal Products (IMP) and can consist of the following:

- All products, active or placebo, being tested or used as a comparator in a clinical trial
- Study required premedication, and
- Other drugs administered as part of the study that are critical to claims of efficacy (eg, backbone therapy, rescue medications)
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection

4.1 Study Treatments

BMS-936558 (nivolumab) 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 specific although there will be specific vial assignments by subject distributed by the IVRS in order to track drug usage and re-supply.

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-936558-01 (nivolumab) Solution for Injection	100 mg (10 mg/mL)	10 mL vial Open-label	10 vials per carton/ Open-label	Clear to opalescent, colorless to pale yellow liquid. May contain particles.	2 to 8 °C. Protect from light and freezing.
Everolimus Tablets*	10 mg	Wallet/blister card containing 30 tablets Open-label	N/A	White to slightly yellow, elongated tablets with a beveled edge and no score, engraved with "UHE" on one side and "NVR" on the other.	Store at 15-25°C. Store in original container. Protect from moisture and light.
Everolimus Tablets*	5 mg	Wallet/blister card containing 30 tablets Open-label	N/A	White to slightly yellow, elongated tablets with a beveled edge and no score, engraved with "5" on one side and "NVR" on the other.	Store at 15-25°C. Store in original container. Protect from moisture and light.

* Everolimus may be obtained by the investigational sites in certain countries as local commercial product (which may be available as a different potency/package size than listed above) if local regulations allow and agreed to by BMS.

4.1.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined 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) differently than 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/are: BMS-936558 (nivolumab) and everolimus.

Everolimus will be provided by BMS as listed in Table 4.1-1 for certain countries and will be procured as local commercial product in certain countries, where allowed by local regulations (eg, by investigators or central distributor) and agreement from the sponsor (BMS). For subjects receiving treatment with BMS-936558 (nivolumab), the sites will be responsible for procuring/supplying IV bags, diluents(s), and the appropriate in-line filters.

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.

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

BMS-936558 (nivolumab) 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 (nivolumab) include laboratory coats and gloves.

For details on prepared drug storage and use time of BMS-936558 (nivolumab) under room temperature/light and refrigeration, please refer to the Investigator Brochure section for “Recommended Storage and Use Conditions” and/or pharmacy reference sheets.

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 (nivolumab) and polyvinyl chloride (PVC), non-PVC/non-DEHP (di(2-ethylhexyl)phthalate) IV components, or glass bottles have been observed.

BMS-936558 (nivolumab) is to be administered as a 60 (±10) minute IV infusion, using a volumetric pump with a 0.2 to 1.2 micron in-line filter at the protocol-specified dose. 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 0.9% Sodium Chloride Injection or 5% Dextrose Injection.

Please refer to the current version of the Investigator Brochure (IB) and/or pharmacy reference sheets for complete storage, preparation and administration information for BMS-936558 (nivolumab).

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
- Number of prior anti-angiogenic therapy regimens in the advanced or metastatic setting (1 vs 2)
- MSKCC risk group (favorable- vs intermediate- vs poor-risk)
- Region (US/Canada vs W. Europe vs Rest of World)

Site must receive acknowledgment from central lab that tumor tissue has been received prior to subject being randomized by the site. The IVRS system will not allow the site to randomize a subject without this information entered by the central lab. The IVRS will randomly assign the subject in a 1:1 ratio to either Arm A (nivolumab) or Arm B (everolimus); stratified by the following factors: MSKCC risk group (favorable- vs intermediate- vs poor-risk) (see Appendix 1); number of prior anti-angiogenic therapy regimens in the advanced or metastatic setting (1 vs 2) and region (US/Canada vs W. Europe vs Rest of World). IVRS will automatically assign correct region based on study site number. The randomization will be carried out via permuted blocks within each stratum. The exact procedures for using the IVRS will be detailed in a separate document.

Amendment 15 Update:

IVRS will be amended to allow all subjects previously randomized to Arm B (everolimus) to receive treatment with nivolumab. The IVRS will assign the nivolumab treatment for all subjects eligible for the extension phase. Procedural information will be provided in a separate document.

Subjects currently randomized to Arm B (everolimus) may also continue obtaining that treatment, as previously done so through the IVRS, as long as they are continuing to derive benefit from everolimus in the judgment of the investigator.

4.3 Selection and Timing of Dose for Each Subject

Subjects in Arm A will receive treatment with nivolumab as a 60 (± 10) minute IV infusion on Day 1 and 15 (± 2 days) of a treatment cycle. Cycles will be of a 28 (± 2 days) duration. Dosing calculations should be based on the actual body weight assessed at either:

- The day of dosing
- The start of each cycle
- Weight at Cycle 1 Day 1 and if the subject's weight on the day of dosing differs by ≥ 10% from the weight used to calculate the dose, the dose must be recalculated.

All doses should be rounded to the nearest milligram. The screening body weight may be used for dosing of cycle 1. There will be no nivolumab dose escalations or reductions allowed. Subjects may be dosed no less than 12 days from the previous dose. If a subject cannot receive the 2nd dose of the cycle within the 28 day period it will be omitted and the next dose received will be considered Day 1 of the next cycle

Subjects in Arm B will receive treatment with everolimus 10 mg as a daily oral dose. Cycles will be of a 28 day (±2 days) duration. If everolimus dosing is stopped for ≤ 7 days during a cycle, the cycle may be extended to complete the remaining doses. Everolimus dose reductions or escalations are allowed as per the approved product label (Sections 4.3.2.2 and 4.3.2.4).

On both arms, treatment may be delayed for up to 6 weeks from the last dose. Delays longer than 6 weeks are allowed only in cases where a prolonged steroid taper is required to manage drug-related adverse events or, in some cases, if the delay was due to a non-drug related cause. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the BMS medical monitor or study director **must** be consulted.

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

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.

In some cases, the natural history of AEs associated with immunotherapy can differ from and be more severe than AEs caused by agents belonging to other therapeutic classes. Early recognition and management may mitigate severe toxicity. Evaluation and management guidelines for the following types of adverse events were developed to assist investigators and can be found in the Investigator Brochure:

- Pulmonary toxicity
- Diarrhea or colitis
- Endocrinopathies
- Hepatotoxicity (including asymptomatic LFT elevations)
- Nephrotoxicity

For patients requiring more than 4 weeks of corticosteroid or other immunosuppressive agents to manage the adverse event, please consider recommendations provided in section 1.4.5.1

4.3.1 Dose Delay Criteria

4.3.1.1 Nivolumab Dose Delay Criteria

Nivolumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require treatment delay
- Any Grade 3 skin, drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, leukopenia, AST, ALT, or total bilirubin:
  - Grade 3 lymphopenia or leukopenia does not require dose delay
  - If a subject has a baseline AST, ALT or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity
  - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

4.3.1.2 Everolimus Dose Delay Criteria

Everolimus dose delays should be based on instructions in the approved product label and should be considered for any severe or intolerable drug-related adverse event.

For this protocol, the following specific drug-related adverse events require dose delay until resolution to Grade 1 or baseline:

- Grade 2 or 3 pneumonitis

- Grade 3 stomatitis
- Grade 3 infection

See Section 4.3.2.2 for details on dose reduction, including required dose reduction after delay for Grade 2 or 3 pneumonitis, Grade 3 infection, or Grade 3 stomatitis.

4.3.2 Dose Modifications

4.3.2.1 Nivolumab Dose Reductions

Nivolumab dose reductions are not permitted.

4.3.2.2 Everolimus Dose Reductions

Everolimus dose reductions are permitted as per the approved product label.

Everolimus dose reductions should be considered for any severe or intolerable drug-related adverse event. If dose reduction is required in the management of an adverse event, the suggested initial reduced dose as per the product label is 5 mg.

For this protocol, the following specific drug-related adverse events require dose reduction if treatment is re-started after requisite dose delay (Section 4.3.1.2):

- Grade 2 or 3 pneumonitis
- Grade 3 infection
- Grade 3 stomatitis

In addition, as per the approved product label, dose reduction should occur if everolimus is co-administered with moderate CYP3A4 and/or PgP inhibitors (Appendix 4). Subsequent everolimus dose increases may be considered based on patient tolerance. If the moderate inhibitor is discontinued, a washout period of approximately 2 to 3 days should be allowed before the everolimus dose is increased. If the moderate inhibitor is discontinued, the everolimus dose should be returned to the dose used prior to initiation of the moderate CYP3A4 and/or PgP inhibitor. Additional information regarding everolimus dose escalation is provided in Section 4.3.2.4.

4.3.2.3 Nivolumab Dose Escalations

Nivolumab dose escalations are not permitted, including for subjects enrolled in the extension phase.

4.3.2.4 Everolimus Dose Escalations

Everolimus dose escalations are permitted, as per the approved product label, in certain cases.

The use of concomitant strong CYP3A4 inducers (Appendix 4) should be avoided. However, if a subject is already receiving everolimus and requires the co-administration of a strong

CYP3A4 inducer, the everolimus dose may be increased from 10 mg daily to 20 mg daily in 5 mg increments. If the strong inducer is discontinued, the everolimus dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer.

Information regarding everolimus dose re-escalation after de-escalation for co-administration with moderate CYP3A4 and/or PgP inhibitors is provided in Section 4.3.2.2.

4.3.3 Criteria to Resume Treatment

4.3.3.1 Criteria to Resume Treatment with Nivolumab

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

- Subjects may resume treatment with Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Subjects with baseline 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.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Subjects with drug-related endocrinopathies adequately controlled with only physiologic replacement may resume treatment.
- If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except in cases where the delay is due to the need for a prolonged steroid taper to manage drug-related adverse events or the delay is not drug related and permission to resume treatment is granted by the BMS medical monitor or study director.

4.3.3.2 Criteria to Resume Treatment with Everolimus

If everolimus dosing is delayed for a drug-related adverse event, treatment may resume when the event has resolved to Grade 1 or baseline. If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except in cases where the delay is due to the need for a prolonged steroid taper to manage drug-related adverse events or the delay is not drug related and permission to resume treatment is granted by the BMS medical monitor or study director.

4.3.4 Discontinuation Criteria

4.3.4.1 Discontinuation Criteria for Nivolumab

Nivolumab administration should be discontinued for the following:

- Any Grade ≥ 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for laboratory abnormalities, drug-related bronchospasm, hypersensitivity reactions, and infusion reactions:
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
      - AST or ALT > 5-10x ULN for > 2 weeks
      - AST or ALT > 10x ULN
      - Total bilirubin > 5x ULN
      - Concurrent AST or ALT > 3x ULN and total bilirubin > 2x ULN
  - Grade 3 drug-related bronchospasm, hypersensitivity reaction, infusion reaction, uveitis or pneumonitis of any duration requires discontinuation
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Any dosing interruption lasting > 6 weeks with the following exceptions:
  - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the BMS medical monitor or study director must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
  - Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor or study director. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the BMS medical monitor or study director must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.

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

4.3.4.2 Discontinuation Criteria for Everolimus

As per the approved product label for everolimus, treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs.

For this protocol, subjects must permanently discontinue everolimus for:

- Any drug-related Grade 4 adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Any dosing interruption lasting > 6 weeks with the following exceptions:
  - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the BMS medical monitor or study director must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
  - Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor or study director. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the BMS medical monitor or study director must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued everolimus dosing.

4.3.5 Treatment of Nivolumab Related Infusion Reactions

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

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

For 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 nivolumab 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, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours)

Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further nivolumab 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 nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone 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 nivolumab. Begin an IV infusion of normal saline, and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. nivolumab 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).

4.3.6 Continued Treatment Beyond Progression of Disease

As described in Section 1.4.6.6, accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit from continued treatment despite initial evidence of progressive disease.[48] For this reason, subjects receiving nivolumab will be permitted to continue study therapy beyond initial investigator-assessed RECIST 1.1-defined progression as long as they meet the 2 criteria listed below. In addition, as the approved product label for everolimus allows for continued treatment as long as clinical benefit is observed or until unacceptable toxicity occurs, subjects on the everolimus arm will also be permitted to continue treatment beyond initial investigator-assessed RECIST 1.1-defined progression if they meet the same 2 criteria listed below.

Criteria for continuing treatment beyond initial investigator-assessed RECIST 1.1-defined progression:

- Investigator-assessed clinical benefit,
  and
- Subject is tolerating study drug.

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment.

All decisions to continue treatment beyond initial progression **must** be discussed with the BMS Medical Monitor or Study Director and documented in the study records.

Subjects will be re-consented with an ICF describing any reasonably foreseeable risks or discomforts.

Subjects should discontinue study therapy upon evidence of further progression, defined as an additional 10% or greater increase in tumor burden from time of initial progression (including all target lesions and new measurable lesions).

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden measurement if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have an increase in short axis to at least 15 mm).

For statistical analyses that include the investigator-assessed progression date, subjects who continue treatment beyond initial investigator-assessed, RECIST 1.1-defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event.

Amendment 15 Update:

Subjects enrolled in the nivolumab extension phase will be permitted to continue study therapy beyond initial investigator-assessed RECIST 1.1-defined progression, as defined in this section.

4.4 Blinding/Unblinding

Not applicable.

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

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible BMS Study Monitor will make arrangements for return of study drug.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.6.2 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible BMS Study Monitor.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

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 (CA209025)

Procedure	Screening[a]	Day -3 to +1 (Post Randomization)	Notes
Eligibility Assessments			
Informed Consent	X		Obtain consent prior to performing any testing for eligibility.
Inclusion/Exclusion Criteria	X	X	All inclusion/exclusion criteria should be assessed prior to randomization
Medical History	X		Include assessment of Pulmonary Risk Factors
Tumor tissue samples	X		May be archival. 1 paraffin block or a minimum of 10 FFPE unstained slides received by Central Lab prior to subject randomization. (FNA and bone metastases samples not acceptable)
Tumor Assessments	X		CT or MRI within 30 days prior to first dose of study drug. Baseline imaging of chest, abdomen, pelvis, brain, and all known sites of disease is required.
Safety Assessments			
Physical Examination	X		Within 30 days of randomization
Vital Signs (including Performance status)	X	X	Screening visit should include weight, height and KPS. Complete vitals should be performed within 3 days prior to first dose of study drug to include: body weight, BP, HR, temperature, and oxygen saturation by pulse oximetry at rest and after exertion (Section 5.3)
Concomitant Medication Collection	X		Within 14 days prior to randomization
Assessment of Signs and Symptoms	X		Within 14 days prior to randomization
Urinalysis	X		Within 14 days prior to randomization to include: protein

Table 5.1-1: Screening Procedural Outline (CA209025)			
Procedure	**Screening[a]**	**Day -3 to +1 (Post Randomization)**	**Notes**
Laboratory Tests	X		Local Labs: Within 14 days prior to randomization to include: CBC w/ differential, LFTs (AST, ALT, total bili, alk phosphatase), BUN or serum urea, creatinine, Ca, Mg, Na, K, Cl, albumin, endocrine panel (TSH, free T3, free T4), fasting serum lipids profile including total cholesterol, triglycerides, LDL, and HDL; fasting glucose and Hep B and C testing (HBV sAg, HCV Ab or HCV RNA).
Pregnancy Test	X	X	For WOCBP at screening and within 24 hours of the first dose of study drug (serum or urine) Local/site.
Exploratory Samples		X	Must be obtained prior to dosing. See Table 5.1-6
PGx sample (Optional)		X	Can be obtained at any time after PGx consent is signed
Clinical Drug Supplies			
Randomize		X	First dose of study medication must be administered within 3 working days of randomization.
Other			
Patient-Reported Outcome Measurements		X	After randomization and prior to first dose: FKSI-DRS and EQ-5D (Use Cycle 1 visit on ePRO tablet for this visit)

[a] All testing listed to be performed within 30 days prior to randomization, unless otherwise specified

Note: Screening period is not limited to 30 days, provided testing is performed within time frames noted.

Table 5.1-2: On-Study Procedural Outline Arm A- Nivolumab (BMS-936558)				
Procedure	**Each Cycle Day 1**	**2nd Dose of Cycle**	**Q 8 wks from Randomization**	**Notes**
Safety Assessments				
Targeted assessments	X			Except Cycle 1. Assessments within 48 hrs of dosing to include: Targeted physical exam, performance status and weight. Oxygen saturation by pulse oximetry at rest and after exertion (Section 5.3).
Adverse Events Assessment	X	X		eSAEs should be approved in TAO by Investigator within 4 days from entry.
Concomitant Medications	X	X		Note: Immunosuppressive agents are recorded on a separate log page
Laboratory Tests	X			Cycle 2 and beyond: (within 72 hrs of dosing) CBC w/differential, LFTs, BUN or serum urea, creatinine. Even cycles only (within 72 hours of dosing): Fasting serum lipids profile (total cholesterol, triglycerides, LDL, and HDL), fasting glucose, and TSH (See Section 5.3).
		X		LFTS only (within 72 hours of dosing)
Pregnancy Test	X			For WOCBP Serum or urine (Note: perform q6 weeks if cycle start is delayed)
Study Samples				PK, Immunogenicity, soluble factors, miRNA, peripheral blood RNA and PBMC. See Table 5.1-5 and Table 5.1-6 for schedule of samples
Efficacy Assessments				
Tumor Assessments			X	By methods used at baseline. Tumor assessments at week 8, 16, 24, 32, 40, 48, and 56 (± 1 wk) from randomization, then every 12 wks (± 1 wk) until disease progression is documented or treatment is discontinued, whichever occurs later.

Table 5.1-2: On-Study Procedural Outline Arm A- Nivolumab (BMS-936558)				
Procedure	**Each Cycle Day 1**	**2nd Dose of Cycle**	**Q 8 wks from Randomization**	**Notes**
Clinical Drug				
Administer Study Treatment	X	X		Record study drug infusion start and stop times for nivolumab (Arm A). Doses of nivolumab should not be given less than 12 days from the previous dose. If the 2nd dose cannot be given within a 28 day window, it will be omitted and the next dose received will be Day 1 of the next cycle.
Other				
Patient-Reported Outcome Measurements	X			Prior to any study-related procedures: FKSI-DRS and EQ-5D
Health Resource Utilization	X			Except cycle 1. (Section 5.8.1)

Table 5.1-3: On-Study Procedural Outline Arm B- Everolimus			
Procedure	**Each Cycle Q 4 Weeks Day 1**	**Q 8 wks from Randomization**	**Notes**
Safety Assessments			
Targeted assessments	X		Except Cycle 1. Assessments within 48 hrs of dosing to include: Targeted physical exam, performance status and weight. Oxygen saturation by pulse oximetry at rest and after exertion (Section 5.3).
Adverse Events Assessment	X		eSAEs should be approved in TAO by Investigator within 4 days from entry.
Concomitant Medications	X		Note: Immunosuppressive agents are recorded on a separate log page
Laboratory Tests	X		Cycle 2 and beyond: (within 72 hrs prior to each new cycle) CBC w/differential, LFTs, BUN or serum urea, creatinine. Even cycles only (within 72 hours prior to each new cycle): Fasting serum lipids profile (total cholesterol, triglycerides, LDL, and HDL), fasting glucose, and TSH (See Section 5.3).
Pregnancy Test	X		For WOCBP Serum or urine (Note: perform q6 weeks if cycle start is delayed)
Efficacy Assessments			
Tumor Assessments		X	By methods used at baseline. Tumor assessments at week 8, 16, 24, 32, 40, 48, and 56 (± 1 wk) from randomization, then every 12 wks (± 1 wk) until disease progression is documented or treatment is discontinued, whichever occurs later.
Clinical Drug			
Administer Study Treatment	X		First dose of study medication must be administered within 3 working days of Randomization
Study Samples			Soluble factors, miRNA, peripheral blood RNA, PBMC See Table 5.1-5and Table 5.1-6 for schedule of samples
Other			
Patient-Reported Outcome Measurements	X		Prior to any study-related procedures: FKSI-DRS and EQ-5D
Health Resource Utilization	X		Except cycle 1. (Section 5.8.1)

Table 5.1-4: Follow-Up Assessments (CA209025) - ALL Subjects			
Procedure	**X or XX, Follow-Up Visit 1+ 2** [a]	**Y or YY, 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		All new and continuing adverse events need to be documented and followed until 100 days after last dose (X02 or XX02 visit). If drug related events continue at second follow-up visit they need to be followed to resolution or until they are deemed irreversible by the investigator. eSAEs should be approved in TAO by Investigator within 4 days from entry.
Concomitant Medications	X		
Laboratory Tests	X		For X01 (and XX01) ONLY, repeat at X02 (and XX02) if study drug related toxicity persists. To include CBC w/ differential, LFTs, BUN, creatinine, fasting serum lipids profile (total cholesterol, triglycerides, LDL, and HDL), fasting glucose, and TSH
Pregnancy Test	X		Serum or urine
Survival Status			
Subject Status	X	X	Every 3 months (Y and YY Survival Follow-ups may be accomplished by visit or phone contact), to include subsequent anti-cancer therapy.
Efficacy Assessments			
Tumor Assessments	X	X	Only for subjects without progression on study therapy. Tumor assessments should be continued every 8 wks (± 1 wk) from randomization (or first dose of nivolumab for the nivolumab extension phase) for the first 12 months, then every 12 weeks (± 1 wk) until disease progression is documented
Study Samples Arm A Only			
PK Samples	X		See Table 5.1-5; Only for subjects ORIGINALLY randomized to Arm A, not required for nivolumab extension phase
Immunogenicity Blood Sample	X		See Table 5.1-5; Only for subjects ORIGINALLY randomized to Arm A, not required for nivolumab extension phase

Table 5.1-4: Follow-Up Assessments (CA209025) - ALL Subjects			
Other			
Patient-Reported Outcome Measurements	X	X	Collect FKSI-DRS and EQ-5D at both "X" and "XX" follow-up visits Collect EQ-5D information either in person or via telephone at "Y" and "YY" survival visits, q3 months for 1 year, then q6 months (sect. 5.3.1)
Health Resource Utilization	X		

[a] X visits as follow, X1 = 30 days from last dose ± 7 days, or may be on date of discontinuation ± 7 days if the date of discontinuation is more than 37 days after last dose. X2 = 100-121 days from last dose (ie, 70-84 days from X1); XX01 and XX02 follow the same timeframe, but from last dose from the nivolumab extension phase

[b] Y, Survival visits continue every 3 months after X visits; YY, Survival visits continue every 3 months after the XX visits (nivolumab extension phase).

Table 5.1-5: Pharmacokinetic and Immunogenicity Sampling Schedule for Subjects Originally Randomized to the Nivolumab Arm

Study Day[a]	Time (Relative to Dosing) Hour	Time (Relative to Dosing) Hour: Min	Pharmacokinetic Blood Sample Schedule	Immunogenicity Blood Sample Schedule
Day -3 to +1 (post randomization)	0 (Predose)	00:00		X
Cycle 1 Day 1	1.0 (EOI)[b]	01:00	X	
Cycle 1 Dose 2	0 (Predose)	00:00	X	X
Cycle 2 Day 1	0 (Predose)	00:00	X	
Cycle 3 Day 1	0 (Predose)	00:00		
Cycle 4 Day 1	0 (Predose)	00:00	X	X
Cycle 4 Day 1	1.0 (EOI)[b]	01:00	X	
Q 4th Cycle Day 1[c]	0 (Predose)	00:00	X	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 preferably within 2 minutes prior to the end of infusion. If the end of infusion is delayed to beyond the nominal infusion duration of 1 hour, the collection of this sample should also be delayed accordingly.

[c] Every 4th cycle from cycle 4 until discontinuation of nivolumab. Predose ONLY. Example: cycle 8, 12, 16 etc.

Note: Predose samples can be obtained any time prior to starting administration on day of dosing for Cycle 1 Dose 2 and forward.

Table 5.1-6: Serum Sampling Schedule for All Subjects, Except in the Nivolumab Extension Phase

Study Day	Time (Relative to Dosing) Hour	Time (Relative to Dosing) Hour: Min	Serum (for soluble factors and miRNA).	Peripheral Blood RNA	PBMC	Whole Blood (SNP)
Day -3 to +1 (post randomization; prior to dosing)	0 (Predose)	00.00	X	X	X	X
Cycle 2 Day 1	0 (Predose)	00.00	X	X	X	
Cycle 3 Day 1	0 (Predose)	00:00	X	X	X	

Note: Predose samples can be obtained any time prior to starting administration on day of dosing for Cycle 2 and Cycle 3 Day 1 samples

Table 5.1-7: Screening Procedural Outline (CA209025) For Subjects Previously Randomized to Everolimus Entering Nivolumab Extension Phase

Procedure	Screening	Notes
Eligibility Assessments		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	Assessed prior to calling IVRS and registering subject for extension phase
Medical History	X	
Safety Assessments		
Vital Signs and Oxygen Saturation	X	Temperature, BP, HR, RR, O_2 saturation by pulse oximetry Obtain vital signs within 72 hours of first dose of nivolumab
Physical Examination (including Performance Status)	X	Includes Weight, and Karnofsky performance status Focused physical exam may be performed at screening, if clinically indicated
Laboratory Tests	X	Labs performed locally within 14 days prior to first dose of nivolumab (unless otherwise specified): CBC with differential, Serum chemistry (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, and glucose), AST, ALT, total bilirubin, alkaline phosphatase, LDH, TSH, free T3, free T4
Pregnancy Test	X	Performed within 24 hours prior to first dose of nivolumab (serum or urine for WOCBP only)
Assessment of Signs and Symptoms	X	After obtaining Informed Consent, assess all signs and symptoms within 14 days prior to first dose of nivolumab
Concomitant Medication Collection	X	Within 14 days prior to first dose of nivolumab
Efficacy Assessments		
Radiographic Tumor Assessment (Chest, Abdomen, Pelvis)	X	Should be performed within 28 days prior to first dose of nivolumab. MRI of brain (with contrast, unless contraindicated) is required in subjects with a known history of brain metastases. Additional sites of known or suspected disease (including CNS) should be imaged prior to first dose of nivolumab.
Other		
Patient-Reported Outcome Measurements	X	Prior to first dose of nivolumab: FKSI-DRS and EQ-5D

Table 5.1-8: On-Study Procedural Outline (CA209025) For Subjects Previously Randomized to Everolimus Entering Nivolumab Extension Phase

Procedure	Each Cycle Day 1	2nd Dose of Cycle	Q8 wks from First Dose of Nivolumab	Notes
Safety Assessments				
Targeted assessments	X			Except first cycle. Assessments within 48 hrs of dosing to include: targeted physical exam, performance status and weight. Oxygen saturation by pulse oximetry at rest and after exertion (Section 5.3).
Adverse Events Assessment	X	X		eSAEs should be approved in TAO by Investigator within 4 days from entry.
Concomitant Medications	X	X		Note: Immunosuppressive agents are recorded on a separate log page
Laboratory Tests	X			Cycle 2 and beyond: (within 72 hrs of dosing) CBC w/differential, LFTs, BUN or serum urea, creatinine. Even cycles only (within 72 hours of dosing): glucose, and TSH *(with reflexive free T4/free T3)*. (See Section 5.3).
		X		LFTS only (within 72 hours of dosing)
Pregnancy Test	X			For WOCBP Serum or urine (Note: perform q6 weeks if cycle start is delayed)
Efficacy Assessments				
Tumor Assessments			X	By methods used at screening. Tumor assessments at Week 8, 16, 24, 32, 40, 48, and 56 (± 1 wk) from first dose of nivolumab, then every 12 wks (± 1 wk) until disease progression is documented or treatment is discontinued, whichever occurs later.

Table 5.1-8:	**On-Study Procedural Outline (CA209025) For Subjects Previously Randomized to Everolimus Entering Nivolumab Extension Phase**			
Procedure	**Each Cycle Day 1**	**2nd Dose of Cycle**	**Q8 wks from First Dose of Nivolumab**	**Notes**
Clinical Drug				
Administer Study Treatment	X	X		Record study drug infusion start and stop times for nivolumab. Doses of nivolumab should not be given less than 12 days from the previous dose. If the 2nd dose cannot be given within a 28 day window, it will be omitted and the next dose received will be Day 1 of the next cycle.
Other				
Patient-Reported Outcome Measurements	X			Prior to any study-related procedures: FKSI-DRS and EQ-5D
Health Resource Utilization	X			Except cycle 1. (Section 5.8.1)

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;
- Site manual for operation of interactive voice response system, including enrollment/randomization worksheets;
- Manual for entry of local laboratory data
- Serious Adverse Event (or eSAE) case report form pages
- Pregnancy Surveillance Forms
- Manual for electronic capture of Patient Reported Outcomes

5.3 Safety Assessments

At baseline, a medical history will be obtained to capture relevant underlying conditions. History should include assessment of possible pulmonary risk factors; asthma, allergic rhinitis, eczema, allergic conjunctivitis, other allergies, pulmonary fibrosis, pneumonitis, other lung disorders and pneumonia. Baseline signs and symptoms are those that are assessed within 14 days prior to randomization. The baseline physical examination can be done within 30 days prior to randomization and should include KPS for eligibility purposes. The following measurements: weight, KPS, BP, HR, temperature, and oxygen saturation by pulse oximetry at rest and after exertion should be performed within 3 days prior to the first dose of study drug (including Cycle 1 Day 1 prior to dosing). Concomitant medications will be collected from within 14 days prior to randomization through the study treatment period (see Table 5.1-1, Table 5.1-2 and Table 5.1-3).

Baseline local labs should be done within 14 days prior to randomization to include: CBC w/ differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea, creatinine, Ca, Mg, Na, K, Cl, albumin, endocrine panel (TSH, free, T3, and free T4), Fasting serum lipid profile including total cholesterol, triglycerides, LDL, and HDL; fasting glucose, Hep B and C testing (HBV sAg, HCV Ab or HCV RNA), and urinalysis; including protein (see Table 5.1-1). Pregnancy testing for WOCBP (done locally) must be performed within 24 hours prior to the initial administration of study drug and then at the start of each cycle, or at a minimum every 4-6 weeks if the start of a cycle is delayed during study therapy and at the X follow-up visits.

Subjects will be evaluated for safety if they have received any study drug. Toxicity assessments will be continuous during the treatment phase. During the X follow-up phase (see Table 5.1-4) 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 new cycle visit. Vital signs should also be taken as per institutional standard of care prior to, during, and after the infusion of nivolumab. Oxygen saturation by pulse oximetry at rest and after exertion should be assessed prior to each new dosing of study medication. The start and stop time of the nivolumab infusion are to be documented. Some of the previously referred to assessments may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician.

If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse event page.

On-study labs should be done within 72 hours prior to the next new cycle (except 1) to include: CBC w/ differential, LFTs, BUN or serum urea, creatinine. For subjects on the nivolumab arm (Arm A), LFTs should also be assessed prior to the 2nd dose of each cycle. The results of these labs should be reviewed prior to dosing.

In addition, for subjects on both treatment Arms A and B, the following tests will be assessed every even cycle (2, 4, etc): serum lipids profile (total cholesterol, triglycerides, LDL, and HDL) fasting glucose, and TSH. If TSH is abnormal, free T3 and free T4 should be assessed.

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

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

Oxygen saturation by pulse oximetry should be obtained prior to each new cycle for subjects on both treatment arms 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 subject's status changes, the investigator can alter the extent of exertion based on their medical judgment. If a subject shows changes on pulse oximetry or other pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary adverse events, the subject 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.

Amendment 15 Update:

For subjects moving into the nivolumab extension phase, please refer to Table 5.1-7 and Table 5.1-8 for the schedule of screening and on-study assessments.

5.3.1 Follow-up and Survival Procedures

Subjects will be monitored for safety according to Table 5.1-4. During the 100 days after the last dose of study treatment, subjects will have two follow-up visits for safety. Safety assessments will include: review of concomitant medications, physical examination measurements, vital signs, performance status, laboratory measurements (CBC, serum chemistry, liver function and thyroid function), and assessment of signs and symptoms including AEs and SAEs. Beyond 100 days from the last dose of study treatment, subjects will be followed for ongoing drug-related adverse events until resolved, return to baseline or deemed irreversible, or until lost to follow-up, or withdrawal of study consent, or start of a subsequent anti-cancer therapy.

Blood samples will be collected for pharmacokinetics and immunogenicity as noted in Table 5.1-5 (only for subjects randomized to nivolumab at the first 2 follow-up visits up to 100 days from the end of treatment, except for subjects that withdraw consent). For subjects treated in the nivolumab extension phase, blood samples for pharmacokinetics and immunogenicity will NOT be collected in the extension phase.

Patient reported outcome (PRO) assessments (FKSI-DRS and EQ-5D) will be administered at the first two follow-up visits prior to any study related procedures. Beyond the 100 days after discontinuation, the EQ-5D will be administered once every 3 months for the first 12 months, then once every 6 months thereafter, as permitted by local law. Each site will be provided with a touch screen electronic PC tablet for the subject's responses of the PRO questionnaire. Subjects will either enter the data directly on to the electronic PC tablet at the time office visits (direct contact) or will respond to the script version of the PRO questionnaire via telephone contact. If the responses are given by telephone, site personnel will enter the responses onto the PC tablet. The data will then be transferred to the ePRO vendor.

The PRO data collection will be according to Table 5.1-4 until death, withdrawal of study consent, or lost to follow-up.

In this study, overall survival is a key endpoint. Post study follow-up is of critical importance and is essential in preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

BMS may request that survival data be collected on all randomized subjects outside of the protocol defined window (Table 5.1-4). At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contact.

Amendment 15 Update:

For subjects moving into the nivolumab extension phase, the same procedures, with the exception of any PK or immunogenicity sample collections, should be followed, therefore, please continue to refer to Table 5.1-4 for follow-up procedures.

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 prior to the first dose of study drug utilizing CTs/MRI. In addition to chest, abdomen, pelvis, and brain, all known sites of disease should be assessed at baseline. Subsequent assessments should include chest, abdomen and pelvis, and all known sites of disease and should use the same imaging method as was used at baseline. If a bone scan is utilized at baseline to document bone disease, it will need to be repeated only when complete response is identified in target disease or when progression in bone is suspected. Subjects will be evaluated for tumor response beginning 8 weeks (± 1 week) from date of randomization and continuing every 8 weeks (ie, weeks 8, 16, 24, etc) (± 1 week) for the first 12 months from randomization and every 12 weeks (± 1 week) thereafter, until disease progression is documented or treatment is discontinued (whichever occurs later). The same schedule should be followed for subjects in the nivolumab extension phase, but based off of first dose of nivolumab and not randomization. Tumor assessments for ongoing study treatment decisions will be completed by the investigator using the RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) criteria.[48]

5.4.1 Primary Efficacy Assessments

This primary endpoint is overall survival (OS). See Section 8.3.1 for the definition of OS.

5.4.2 Secondary Efficacy Assessments

Objective response rate (ORR) and progression-free survival (PFS), each based on RECIST 1.1 using investigator assessments, are the secondary efficacy assessments of the study that will be subject to hierarchical testing. See Sections 8.3.2.1 and 8.3.2.2 for the definitions of ORR and PFS, respectively. OS by PD-L1 expression is an additional secondary efficacy assessment. See Section 5.6 for details of PD-L1 biomarker assessment and Section 8.3.1 for the definition of OS.

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 as measurable or non-measurable as follows in Sections 5.4.3.1, 5.4.3.2, and 5.4.3.3.

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 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 Frequency of Tumor Re-evaluation

Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certain non-target organs may be evaluated less frequently. For example, bone

scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

5.4.7 Tumor Response Evaluation

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.

5.4.7.1 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.

5.4.7.2 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'.

5.4.8 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).

5.4.8.1 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 qualify for unequivocal progression status.

5.4.9 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.*

5.4.10 Response Criteria (RECIST 1.1)

5.4.10.1 Time Point Response

For subjects who have **measurable disease** at baseline, Table 5.4.10.1-1 provides a summary of the overall response status calculation at each time point.

Table 5.4.10.1-1: 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

Table 5.4.10.1-1: Time Point Response - Subjects With Target (Non-target) Disease			
Target lesions	**Non-target lesions**	**New lesions**	**Overall response**
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.

5.4.10.2 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.

5.4.10.3 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.

5.4.11 Best Overall Response: All Time Points

The best overall response (BOR) is determined once all the data for the subject is known. BOR is defined as the best response designation, as determined by the investigator, recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 or the date of subsequent anti-cancer therapy, whichever occurs first. For subjects without documented progression or subsequent anti-cancer therapy, all available response designations will contribute to the BOR determination. For subjects who continue treatment beyond progression, the BOR should be determined based on response designations recorded up to the time of the initial RECIST 1.1-defined progression. The subject's BOR assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

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.

For purposes of this study, the minimum duration between baseline and first on-study scan in order to determine best response of SD is 7 weeks.

5.4.12 Duration of Response

5.4.12.1 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).

5.5 Pharmacokinetic Assessments

Pharmacokinetic blood samples will be drawn from study subjects originally assigned to nivolumab treatment arm A at the time points indicated in Table 5.1-5. 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 are able to be obtained any time prior to the administration on the day of dosing, and end-of-infusion (EOI) samples should be taken just prior to the EOI (preferably within 2 minutes prior to EOI) from the contralateral arm (ie, the arm not used for the infusion). If the infusion was interrupted, the interruption details will also be documented on the CRF. Blood samples will be processed to collect serum and stored at -70^{o}C preferably (short term storage for up to 2 months at -20^{o}C is acceptable). Serum samples will be analyzed for nivolumab by a validated immunoassay method.

Further details of pharmacokinetic sample collection and processing will be provided to the site in the lab manual.

5.6 Biomarker Assessments

A variety of factors that may impact immunomodulation and efficacy will be investigated in peripheral blood and in tumor specimens taken from all randomized subjects prior to treatment and as outlined in Table 5.1-1, Table 5.1-5 and Table 5.1-6. Data from these investigations will be evaluated for pharmacodynamic effects, for associations with efficacy endpoints, (Response, OS, PFS), and/or for associations with safety (adverse events). Comparative analyses between the two treatment arms will be used to identify biomarkers with predictive versus prognostic value. Complete instructions on the collection, processing, handling, and shipment of all samples described herein will be provided in a separate lab procedure manual.

5.6.1 Peripheral Blood

Serum-Soluble Factors:

Protein concentrations of serum soluble factors involved in immune function and/or prognostic factors for RCC will be measured in all subjects prior to initiating treatment and pre-dose on C2D1 and C3D1 to detect pharmacodynamic effects and early predictive serum markers of clinical benefit. A panel of cytokines, chemokines, and other relevant immunomodulatory factors will be investigated by ELISA, seromics, and/or other relevant multiplex-based protein assay methods. Examples of analytes to be assessed include but are not limited to factors induced by IFNγ signaling (eg, T cell chemoattractants CXCL9 and CXCL10), soluble PD-L1 (sPD-L1), soluble VEGF, and lactate dehydrogenase (LDH), which may play an important role in immune tolerance and disease progression.

Serum miRNA:

MicroRNAs are broadly expressed, small RNAs that regulate the abundance of mRNA transcripts and their translation into protein. Global miRNA expression profiling has become increasingly common in cancer research, and miRNA signatures that are correlated to stage of disease or to clinical outcomes are now available for a variety of cancer types, including RCC. Expression profiling of miRNA may also be useful in identifying molecular markers for the prediction of drug-responses and for prospective stratification. Intriguingly, miRNAs are stable in serum and may represent miRNAs over-expressed in tumors and/or reflect immune system activity. Serum taken at baseline from subjects randomized to each treatment arm will be analyzed for miRNA content by microarray and/or by similar methodologies (eg, quantitative RT-PCR). The resulting miRNA expression profiles will be evaluated for associations with response and survival data. Of particular interest will be the expression of miRNAs that have been implicated in the regulation of genes involved in PD-1 signaling (eg, miR-513, which has been shown to regulate PD-L1 and to act as part of an IFNγ-induced signaling cascade) and how the expression of such miRNAs correlate with the expression of immunoregulatory proteins within tumors. Ultimately, this approach may lead to the identification of unique miRNA signatures associated with response to nivolumab treatment.

Whole Blood SNP:

Whole blood will be collected from all subjects prior to the first dose to generate genomic DNA for candidate-based and/or whole-genome single nucleotide polymorphism (SNP) analyses. Candidate-based analyses will focus on SNPs within genes associated with PD-1 and other immunoregulatory signaling pathways to determine if natural variation within those genes is associated with clinical benefit from nivolumab and/or with adverse events during treatment. A similar approach will be taken with putative genome-wide association studies (GWAS). Additional use of these data may include correlative analyses aimed at identifying genotypic associations with clinically relevant biomarkers identified by other methodologies described in this section.

Peripheral Blood Mononuclear Cells (PBMC)

Immunological monitoring of patients treated with immunotherapeutic agents, such as nivolumab and ipilimumab, has provided insights into the mechanism of action of such agents on immune cells both within the periphery as well as within the tumor microenvironment. To characterize the immunomodulatory properties of such agents and to identify candidate predictors of benefit or toxicity, peripheral blood samples have been collected and analyzed to measure the frequency of specific populations of immune cells as well as expression of markers of interest on these cells. In clinical studies of ipilimumab, associations have been reported between benefit and increases of, for example, absolute lymphocyte count, $CD8^+$ cells, Th17 cells, or $CD4^+ICOS^{high}$ T cells. [49] Corresponding data for nivolumab are limited to phase 1 studies, largely in melanoma and RCC patients (unpublished).

To understand the relationship between nivolumab treatment, benefit and immunologic endpoints in RCC patients, PBMC specimens will be collected at baseline and on-treatment and evaluated using flow cytometry and other methods. These analyses will be completed to quantify increases or decreases from baseline in various immune cell populations, including but not limited to, T cells, B cells, NK cells, or subpopulations of the aforementioned immune cell types. These samples may also be used to assess immune cell function, antigen specific T cell proliferation, or activation pending emerging information from other nivolumab studies. Evaluation of T cell diversity (by sequencing T cell rearrangements) may also be pursued.

Peripheral blood samples will be taken prior to initiation of study therapy and at designated timepoints on-treatment (see Table 5.1-6 for additional details on the blood sample collection schedule) for PBMC preparation. Samples must be shipped immediately to a BMS-designated central laboratory for processing.

Peripheral Blood RNA

Gene expression analyses of RNA derived from whole blood may provide information on the broad effects of nivolumab immune modulation. Transcriptional profiling of tumors[50] and of whole blood (unpublished) has been conducted within clinical studies of ipilimumab and identified genes that are differentially expressed upon ipilimumab treatment or whose expression is associated with benefit. To determine whether these or other genes are similarly associated with nivolumab treatment or clinical outcome, genomic expression patterns of whole blood collected at baseline and during on-study treatment will be analyzed (see Table 5.1-6 for additional details on the blood sample collection schedule). Gene expression may be assessed by Affymetrix microarray profiling, qRT-PCR or other technology, with an emphasis on genes with relevant immune function.

5.6.1.1 Tumor Specimens

A formalin-fixed, paraffin-embedded tumor tissue block or unstained slides of tumor sample (archival or recent) for biomarker evaluation must be available for all subjects at study entry, and received by the central lab prior to subject randomization. In the case of unstained slides, a minimum of 10 slides are necessary to conduct the planned biomarker analyses. If a recent

biopsy has been collected and submitted, submission of archival tissue, if available, is still highly encouraged. In cases where retrospective H&E staining by the central lab determines insufficient tumor tissue is present for biomarker analyses, additional archived tissue may be requested by the sponsor, if available. Complete instructions on the collection, processing, handling, and shipment of all samples, including archival and fresh tumor biopsies, will be provided in a separate procedure manual. Samples sent must be from excisional, incisional or core needle biopsy. Fine needle aspiration and bone metastases are not adequate for submission.

A reference laboratory will receive the samples for IHC-based analyses aimed at determining the abundance of expression of proteins involved in PD-1 signaling, such as PD-1, PD-L1, and PD-L2. Additional IHC analyses may be completed to determine the relative abundance of other protein markers associated with T and NK cells and macrophages or with RCC disease progression, such as Carbonic anhydrase IX (CAIX). The abundance of each protein monitored (or combinations of proteins) will be correlated with clinical endpoints.

FFPE tissue may also be evaluated by fluorescent in-situ hybridization (FISH), genetic mutation detection methods, and/or by qRT-PCR as part of additional exploratory analyses of putative biomarkers thought to be associated with response or resistance to therapeutics used in the treatment of RCC. Such analyses will be completed retrospectively and within the scope of informed consent.

5.7 Outcomes Research Assessments

Patient-reported outcomes (PROs) will be measured using two validated subject self-reported questionnaires: the Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI)-DRS scale and the EuroQol Group's EQ-5D.

Subjects will be asked to complete the questionnaires before any clinical activities, after randomization (before cycle 1 dosing) and on Day 1 of each cycle (starting with cycle 2) as well as at the X follow-up visits.

Questionnaires will be provided in the subject's preferred language.

Amendment 15 Update:

For subjects treated in the nivolumab extension phase of the study, the patient reported outcomes (PRO) will be measured according to Table 5.1-7 and Table 5.1-8, as well as Table 5.1-4 for follow-up visits.

5.8 Other Assessments

5.8.1 Health Resource Utilization

During the study, health resource utilization (HRU) data associated with medical encounters related to disease or treatments or both will be collected for all subjects. Specifically, HRU is evaluated based on the number of medical care encounters such as hospital admissions and their duration, outpatient visits, diagnostic tests and procedures, concomitant medications, and reasons

for the encounters. HRU data will be collected on all randomized subjects during the treatment period and for the first 2 follow-up visits.

5.8.2 Immunogenicity Assessments:

Blood samples for immunogenicity analysis will be collected from subjects assigned to nivolumab arm according to schedule given in Table 5.1-5. Samples will be evaluated for development of Anti-Drug Antibody (ADA) for nivolumab in subjects by a validated electrochemiluminescent (ECL) immunoassay in human serum. Samples may also be analyzed for neutralizing ADA response to nivolumab. (Neutralizing ADA testing conditioned upon validated assay availability.)

Further details of the immunogenicity sample collection and processing will be provided to the site in the lab manual.

5.9 Results of Central Assessments

Not Applicable

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.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

> Related: There is a reasonable causal relationship between study drug administration and the AE.
>
> Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

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 <u>any dose</u>:

- 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. (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)
- admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols).

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 must be collected that occur during the screening period and within 100 days of discontinuation of dosing**. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

Subjects, who are randomized and never treated with study drug, must have SAEs collected for 30 days from the date of randomization.

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, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). When using paper forms, the reports are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number:

For US and Canadian Sites: Central Facsimile Station: (609) 818-3804

For all other countries/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 countries/sites: See Contact Information list.

For studies capturing SAEs/pregnancies through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

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 and continue until 100 days from the last dose 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.

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 or Study Director of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours of awareness of the event 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

ALT or AST elevation > 3 times upper limit of normal (ULN)

AND

Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, 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

To provide independent oversight of safety, efficacy, and study conduct, a data monitoring committee (DMC) will be instituted. The DMC will meet regularly to ensure that subject safety is carefully monitored. The DMC will convene additional ad hoc meetings if necessary. Following each meeting, the DMC will recommend continuation, modification, or discontinuation of the study based on observed toxicities. The DMC will also review the interim analysis results and determine whether stopping criteria for superiority are met at that time. A separate DMC charter will describe the activities of this committee in more detail.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The sample size is calculated in order to compare the overall survival (OS) between subjects randomized to receive nivolumab and subjects randomized to receive everolimus.

Approximately 569 events (ie, deaths) with an interim analysis after 398 events (70% of total OS events needed for final analysis) provides 90% power to detect a hazard ratio (HR) of 0.76 with an overall type 1 error of 0.05 (two-sided). The HR of 0.76 corresponds to a 32% increase in the median OS, assuming a median OS of 14.8 months for everolimus and 19.5 months for nivolumab. The stopping boundaries at interim and final analyses will be derived based on the number of deaths using O'Brien and Fleming α spending function. It is projected that an observed hazard ratio of 0.845 or less, which corresponds to a 2.7 months or greater improvement in median OS (14.8 mo vs 17.5 mo), would result in a statistically significant improvement in OS for nivolumab at the final OS analysis.

Approximately 822 subjects will be randomized to the two arms in a 1:1 ratio. Assuming a piecewise constant accrual rate (with a maximum rate of 63 subjects/month and an average rate of 41 subjects/month), the accrual will take approximately 20 months. The total duration of the study from start of randomization to final analysis of OS is expected to be 42 months (20 months of accrual + 22 months of follow-up).

Table 8.1-1 summarizes the expected timing of each analysis.

Table 8.1-1: Schedule of Analyses

	Interim Analysis	Final Analysis
Conditions	at least 398 OS events	569 OS events
Expected timing	30 months (20 months of accrual + 10 months of follow-up)	42 months (20 months + 22 months of follow-up)
Alpha level	Interim OS projected at 0.0148 level[a]	Final OS analysis projected at 0.0455 level[a]

[a] Using O'Brien and Fleming alpha spending function in case exact 398 OS events are observed at the interim OS analysis.

8.2 Populations for Analyses

- All enrolled subjects: All subjects who signed an informed consent form and were registered into the IVRS
- All randomized subjects: All subjects who were randomized to any treatment arm in the study. This is the primary dataset for analyses of efficacy and baseline characteristics
- All treated subjects: All subjects who received any dose of nivolumab or everolimus. This is the primary dataset for dosing and safety
- PK subjects: All subjects with available serum time-concentration data from randomized subjects dosed with nivolumab
- Immunogenicity subjects: All subjects with available data from randomized subjects dosed with nivolumab
- All randomized PD-L1 measurable subjects: All randomized subjects with a measurable PD-L1 expression result (ie excludes indeterminable and unknown)
- Biomarker subjects: All subjects with available biomarker data from randomized subjects

8.3 Endpoints

The primary objective (ie, clinical benefit comparison) will be measured by the primary endpoint of overall survival as defined in Section 8.3.1.

The secondary objectives of assessment of objective response rate (ORR), progression-free survival (PFS) and duration of objective response will be measured by the secondary endpoints defined in Sections 8.3.2.1, 8.3.2.2, and 8.3.2.3.

The second secondary objective (To evaluate whether PD-L1 expression is a predictive biomarker for OS) will be measured by the same primary endpoint, ie. OS.

The secondary objective related to the safety profile of both drugs will be measured by the endpoints defined in Section 8.3.2.4.

The last secondary objective (ie, evaluation of patient-reported outcomes) will be measured by the endpoint of disease-related symptom progression rate defined in Section 8.3.2.5.

8.3.1 Primary Endpoint

Overall Survival (OS) is defined as the time from randomization to the date of death. A subject who has not died will be censored at last known alive date.

Subject status will be followed every 2 - 4 weeks while on treatment and then every 3 months.

8.3.2 Secondary Endpoints

8.3.2.1 Objective Response Rate

Objective response rate (ORR) is defined as the number of subjects with a best response of CR or PR divided by the number of randomized subjects. Best overall response (BOR) is defined as

the best response designation, as determined by the investigator, recorded between the date of randomization and the date of objectively documented progression per RECIST v1.1 or the date of subsequent therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR determination. For subjects who continue treatment beyond progression, the BOR should be determined based on response designations recorded up to the time of the initial RECIST 1.1-defined progression.

Tumor response assessments will be performed every 8 weeks (± 1 week) after randomization during the first year and every 12 weeks (± 1 week) thereafter until investigator-assessed progression or treatment discontinuation, whichever occurs later.

8.3.2.2 Progression-Free Survival

Progression-free survival (PFS) is defined as the time from randomization to the date of the first documented tumor progression as determined by the investigator (per RECIST 1.1 criteria or clinical) or death due to any cause whichever occurs first. 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 evaluable tumor assessment. Subjects who did not have any on-study tumor assessments and did not die will be censored on the date they were randomized. Subjects who received any subsequent anti-cancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the subsequent anti-cancer therapy.

Progression will be assessed by CT or MRI every 8 weeks (± 1 week) during the first year and every 12 weeks (± 1 week) thereafter, until investigator-assessed progression or treatment discontinuation, whichever occurs later.

8.3.2.3 Duration of Objective Response

Duration of objective response is defined as the time from first response (CR or PR) to the date of the first documented tumor progression as determined by the investigator using RECIST 1.1 criteria or death due to any cause, whichever occurs first. For subjects who neither progress nor die, the duration of objective response will be censored at the same time they were censored for the primary definition of PFS. This endpoint will only be evaluated in subjects with objective response of CR or PR. Tumor response assessments will be performed every 8 weeks (± 1 week) during the first year and every 12 weeks (± 1 week) thereafter until investigator-assessed progression or treatment discontinuation, whichever occurs later.

8.3.2.4 Safety

Safety will be analyzed through the incidence of adverse events, serious adverse events and specific laboratory abnormalities (worst grade) in each treatment arm. Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Adverse event assessment is performed on an ongoing basis while on treatment and for up to 100 days after the last dose of study drug (ie, during the X follow-up visits).

Laboratory tests are performed at baseline, on Day 1 of each cycle (within 72 hours prior to dose for all cycles except 1 (see Table 5.1-2), and at the first visit in follow-up. Tests at second visit in follow-up will be repeated if study drug related toxicity persists.

8.3.2.5 Disease-Related Symptom Progression Rate

Disease-related symptom progression rate is defined as the proportion of randomized subjects who have disease-related symptom progression as measured by the FKSI-DRS.

The nine items of the FKSI-DRS are summarized into a symptom scale ranging in score from zero (0) to thirty six (36), with zero being the worst possible score and thirty six being the best possible score.[51] The minimum important change in the FKSI-DRS used to define symptom progression is approximately a change of two points and that definition has been used for this mRCC symptom scale in other mRCC trials.[40,51,52]

Disease-related symptom progression is defined as a decrease of two points in the FKSI-DRS relative to the subject's baseline FKSI-DRS score without returning to above that point during the remainder of the study.

FKSI-DRS questionnaire is completed at baseline, on Day 1 of each cycle (starting with cycle 2), and then at the X and XX follow-up visits.

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by randomized treatment arm using descriptive statistics

8.4.2 Efficacy Analyses

All hypothesis testing will be two-sided on a significance level of 0.05 except for OS. A group sequential testing procedure will be applied to OS to control the overall type I error for interim and final analyses. The α spending function is described in Section 8.1. If superiority in OS is demonstrated, a hierarchical hypothesis testing approach for the key secondary endpoints will be used to preserve a study-wise type I error rate at 0.05. The key secondary endpoints will be tested in the following hierarchical order:

1. ORR
2. PFS

The formal statistical testing for ORR will take place only if OS is statistically significant and the statistical testing for PFS will take place only if both OS and ORR are statistically significant.

8.4.2.1 Methods of Primary Endpoint

The OS distributions will be compared in two randomized arms at the interim and final analyses via two-sided, log-rank tests, stratified by region, MSKCC risk group, and number of prior anti-angiogenic therapy regimens in the advanced or metastatic setting. The interim analysis for OS is planned after 398 deaths have been observed. This formal comparison of OS will allow for early stopping for efficacy and the stopping boundaries will be derived based on the O'Brien and Fleming alpha spending function in EAST v5.4. If the analysis is performed exactly at 398 events, the study could be stopped by the DMC for efficacy if the p-value is ≤ 0.0148. The nominal significance level for the final look of OS after 569 events would then be 0.0455. The OS curve, median and OS rates at 12, 18, and 24 months for each randomized arm will be estimated using the Kaplan-Meier product-limit method. Two-sided, 95% confidence intervals for median OS will be computed by Brookmeyer and Crowley method.[53] Similarly, two-sided, 95% confidence intervals for OS rates at 12, 18, and 24 months will be computed by Greenwood method. The hazard ratio (HR) and corresponding two-sided 100(1-α)% (adjusted for the interim analysis) CI will be estimated in a Cox proportional hazards model using randomized arm as a single covariate, stratified by the above factors.

8.4.2.2 Methods for Secondary Endpoint

ORR will be compared using a Cochran-Mantel Haenszel (CMH) two-sided test stratified by the same factors used above. An associated odds ratio and 95% CI will be calculated. The ORR and its corresponding 95% exact CI will also be calculated by Clopper-Pearson method for each randomized arm.

The PFS distributions will be compared in two randomized arms via a two-sided, log-rank test stratified by the same factors as for OS. Sensitivity analyses will be performed using different PFS definitions to assess the robustness of the primary analysis. The PFS curve, median and PFS rate at 6 months for each randomized arm will be estimated using the Kaplan-Meier product-limit method. Two-sided, 95% confidence intervals for median PFS will be computed by Brookmeyer and Crowley method.[54] Similarly, two-sided, 95% confidence interval for PFS rate at 6 months will be computed by Greenwood method. The hazard ratio (HR) and corresponding two-sided 95% CI's will be estimated in a Cox proportional hazards model using randomized arm as a single covariate, stratified by the above factors.

The duration of objective response (CR + PR) and its median will be estimated for each randomized arm using the Kaplan-Meier product-limit method and limited to responders only. Two-sided, 95% confidence intervals for median duration of objective response will be computed by Brookmeyer and Crowley.[54]

PD-L1 IHC data and tumor sample characteristics will be listed and summarized. The distribution of PD-L1 expression will be investigated graphically by summary plots and individual subject plots. Summary statistics of PD-L1 expression by treatment group and across treatment groups will be provided.

To assess the potential association between PD-L1 expression and OS, OS curves and medians with 95% CIs will be estimated using Kaplan-Meier methodology by treatment group for each PD-L1 expression quartile and for subjects with a missing or indeterminate PD-L1 IHC result.

Potential associations with ORR and PFS will also be examined. If there is an indication of a meaningful association, additional analyses may be performed to further evaluate PD-L1 expression as a predictive biomarker.

8.4.3 Safety Analyses

Summary tables will be presented on safety parameters for each treatment arm. Toxicity rates (worst CTCAE grade per subject) of adverse events and specific laboratory tests will be tabulated.

8.4.4 Pharmacokinetic Analyses

The concentration vs time data obtained in this study will be combined with data from other studies in the clinical development program to develop a population PK model. This model will be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of nivolumab and to determine measures of individual exposure (such as steady-state peak, trough, and time-averaged concentration). Model determined exposures will be used for exposure-response analyses of selected efficacy and safety end points. Results of population PK and exposure-response analyses will be reported separately.

8.4.5 Biomarker Analyses

Pharmacodynamic Analyses

To assess pharmacodynamic effects in serum, blood RNA, or PBMC obtained from subjects on each treatment arm, summary statistics for biomarkers of immunoregulatory activity (eg, IFNγ-inducible proteins, miRNAs, antibodies to tumor antigens, gene expression, immune cells) and their corresponding changes (or percent changes) from baseline will be tabulated by planned study visit. In addition, the time course of biomarker outcomes will be investigated graphically. If there is indication of a meaningful pattern across time, further analysis may be completed to characterize the relationship. Possible associations between changes in biomarker measures of interest and exposure to study drug will be explored graphically.

Pharmacogenomic and Exploratory Analyses

Potential relationships between biomarker data and efficacy or safety endpoints will be investigated as part of an analysis plan aimed at identifying baseline biomarkers that may be used to prospectively identify patients likely (or not likely) to respond to nivolumab and to identify subjects who may be predisposed to having adverse reactions to treatment. These exploratory predictive biomarker analyses will be completed with biomarkers measured in blood and in tumor samples and will focus primarily, as outlined in the exploratory objectives, on SNPs in select genes associated with immunity or on the expression of selected proteins in tumor

specimens, such as PD-1, PD-L1, and PD-L2. Similar analyses will be completed with data regarding serum-soluble factors, blood RNA and/or immune cell types.

Associations between biomarkers and efficacy measures will be analyzed on all subjects treated with at least one dose of study medication and with corresponding efficacy and biomarker measurements. Efficacy measures will include response, PFS, and OS. Demographic and case-history factors will be examined to determine whether stratification or adjustments should be made within the subsequent statistical analyses, and if necessary, the appropriate stratification or adjustment will be made.

Biomarkers will be summarized graphically as they relate to efficacy and safety endpoints, as applicable. Summary statistics will be tabulated. SNP allele frequencies will be summarized. The relationships between binary measures (eg, response) and candidate biomarkers will be investigated using logistic regression. Associations will be summarized in terms of point and interval estimates of hazard ratios, odds ratios, or other statistics, as appropriate for the analyses completed. Models to predict clinical activity based on combinations of biomarkers may also be investigated.

Additional post hoc statistical analyses not specified in the protocol, such as alternative modeling approaches may be completed. All analyses described in this section are based on the availability of the data.

8.4.6 Outcomes Research Analyses

FKSI-DRS questionnaire completion rate, defined as the proportion of questionnaires actually received out of the expected number (ie, the number of subjects still on treatment or in follow-up), will be calculated and summarized at each assessment point.

The disease-related symptom progression rate and its corresponding 95% exact CI will also be calculated by the Clopper-Pearson method for each randomized arm. The same analysis will be conducted, where death and radiographic progression will be also considered as disease-related symptom progression.

The EQ-5D will be used to assess each subject's overall health status. The following two measures from EQ-5D are used for this study: a population preference-based health state utility score (EQ-5D Index) and each subject's overall health state on a visual analog scale (EQ-VAS). Both the EQ-5D Index and EQ-VAS have been shown to be reliable and valid for assessing health-related PROs in cancer patients.

The health resource utilization data will be utilized to conduct economic analyses.[54,55,56]

8.4.7 Other Analyses

8.4.7.1 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 ADA at any time point will be provided. The frequency of subjects with at least one positive ADA assessment and the

frequency of subjects with an increase in ADA levels from baseline will be tabulated. The frequency of neutralizing antibodies will be provided based on data availability. 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.

8.5 Interim Analyses

As described in Section 8.1, an interim analysis of OS will be performed after at least 398 OS events (70% of total OS events needed for final analysis) have occurred. This analysis will be reviewed by the DMC while the Sponsor remains blinded. From Table 8.1-1, the estimated timing of this analysis is around 30 months after the start of randomization.

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.

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 paper or electronic 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 or electronic 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 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected considering the following criteria:

- External Principal Investigator designated at protocol development
- Involvement in trial design

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
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
BMS	Bristol-Myers Squibb
BOR	Best overall response
BUN	Blood urea nitrogen
CMV	Cytomegalovirus
CR	Complete response
CRC	Colorectal cancer
CrCl	Creatinine clearance
CRF	Case report form
CRPC	Castrate-resistant prostate cancer
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCF	Data clarification form
DILI	Drug-induced liver injury
DLT	Dose-limiting toxicity
DMC	Data monitoring committee
DRS	Disease-related symptoms
ECG	Electrocardiogram
ECL	Electrochemiluminescent
eCRF	Electronic case report form
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
EOI	End of infusion
ePRO	Electronic patient reported outcome
FFPE	Formalin-fixed paraffin-embedded
FKSI	Functional Assessment of Cancer Therapy-Kidney Symptom Index

Abbreviation	Term
FSH	Follicle-stimulating hormone
FU	Follow-up
GCP	Good clinical practices
GMP	Good manufacturing practices
HCV	Hepatitis C virus
HBV	Hepatitis B virus
HDL	High-density lipoprotein
HIFα	Hypoxia inducible factor α
HIPAA	Health Information Portability and Accountability Act
HRT	Hormone replacement therapy
HRU	Health Resource Utilization
ICF	Informed consent form
ICH	International Conference on Harmonisation
IHC	Immunohistochemistry
ITIM	Immunoreceptor tyrosine inhibitory motif
ITSM	Immunoreceptor tyrosine-based switch motif
IV	Intravenous
IFN	Interferon
IRB/IEC	Institutional review board/independent ethics committee
IRC	Independent review committee
IVRS	Interactive voice response system
KPS	Karnofsky Performance Score
LDL	Low-density lipoprotein
LFT	Liver function test
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MEL	Metastatic melanoma
miRNA	Micro-ribonucleic acid
MLR	Mixed lymphocyte reaction
MRI	Magnetic resonance imaging

Abbreviation	Term
MSKCC	Memorial Sloan-Kettering Cancer Center
MTD	Maximum-tolerated dose
mTOR	Mammalian target of rapamycin
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1
PD-L2	Programmed death-ligand 2
PFS	Progression-free survival
PK	Pharmacokinetics
PO	Per os (by mouth)
PR	Partial response
PRO	Patient-reported outcome
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase - polymerase chain reaction
SAE	Serious adverse event
sAg	Surface antigen
SD	Stable disease
SNP	Single nucleotide polymorphism
SOP	Standard operating procedures
TCR	T-cell receptor
TKI	Tyrosine kinase inhibitor
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal

Abbreviation	Term
US	United States
VEGF	Vascular endothelial growth factor
VEGFr	Vascular endothelial growth factor receptor
WOCBP	Women of child bearing potential

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APPENDIX 1 MSKCC PROGNOSTIC SCORE

Determination of Prognostic Score in Previously Treated Patients

Parameter	Risk Factor	Criteria Value	Subject Value	If subject value 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 total of above = MSKCC Prognostic Score:

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

Risk Group Based on MSKCC Prognostic Score

Risk Group	MSKCC Prognostic Score
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 GUIDANCE ON CONTRACEPTION[1, 2, 3, 4, 5, 6, 7, 8]

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, 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, are not considered sufficient methods of contraception, as they carry a failure rate of > 1%. Hormonal contraceptives may be used in this study for contraception.

Women of childbearing potential (WOCBP) receiving 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 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.

Women randomized to receive everolimus must follow instructions for birth control as per the SmPC or package insert (8 weeks after discontinuation of treatment).

Men randomized to receive everolimus must follow instructions for birth control for 14 weeks after discontinuation of treatment.

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APPENDIX 4 CYP3A4 AND PGP INHIBITORS AND INDUCERS

Strong CYP3A4 Inhibitors

- Ketoconazole
- Itraconazole
- Posaconazole
- Voriconazole
- Clarithromycin
- Telithromycin
- Nefazodone
- Saquinavir
- Ritonavir
- Atazanavir
- Darunavir
- Indinavir
- Nelfinavir

Moderate CYP3A4 and/or PGP Inhibitors

- Amprenavir
- Fosamprenavir
- Aprepitant
- Erythromycin
- Fluconazole
- Verapamil
- Diltiazem
- Cyclosporine oral

Strong CYP3A4 Inducers

- Phenytoin
- Carbamazepine
- Rifampin
- Rifabutin
- Rifapentine
- Phenobarbital
- Corticosteroids (eg, dexamethasone, prednisone, prednisolone)
- Efavirenz
- Nevirapine

Notes:

Grapefruit, grapefruit juice and other foods that are known to inhibit CYP3A4 and PgP activity should be avoided during treatment.

St. John's Wort (*Hypericum perforatum*) is known to be an inducer of CYP3A4 and should be avoided during treatment.