

Page: 1  
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## **Clinical Protocol CA209374**

A Phase 3b/4 Safety Trial of Nivolumab (BMS-936558) in Subjects with Advanced or Metastatic Renal Cell Carcinoma

CheckMate 374: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 374

**Revised Protocol Number: 03**  
**Incorporates Amendment 03 and Administrative Letter 01**

### **Study Director/Medical Monitor**

Yuanxin Rong MD



### **24-hr Emergency Telephone Number**

USA: 1-866-470-2267  
International: +1-248-844-7390  
PPD Safety Hotlines: 1-888-483-7729; 1-800-201-8725

### **Bristol-Myers Squibb Research and Development**


777 Scudders Mill Road  
Plainsboro, NJ 08536

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

## DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised protocol 03	31-Oct-2016	Incorporates changes for Amendment 03 and Administrative Letter 01.
Global Amendment 03	31-Oct-2016	<ul style="list-style-type: none"> <li>• Clarification to specify that brain lesion(s) will only be assessed as non-target lesions</li> <li>• <a href="#">Appendix 6</a>: Management Algorithms for Renal, Pulmonary, Hepatic, and Skin Adverse Events have been updated.</li> </ul>
Administrative Letter 01	17-May-2016	Study design schematics corrected to align with text changes made in Global Amendment 02. The study schematics will now specify that renal cell carcinoma patients enrolled with non-clear cell (preferred) or clear cell histology will be increased if the enrollment of 25 patients with brain metastases cannot be reached.
Revised protocol 02	30-Apr-2016	Incorporates changes in Amendment 02.
Global Amendment 02	30-Apr-2016	<ul style="list-style-type: none"> <li>• Eligibility changes:                             <ul style="list-style-type: none"> <li>• Patients with previous treatment with mTOR inhibitor for clear-cell RCC histology are now eligible</li> <li>• Patients with non-clear cell histology with up to 3 rather than 2 prior systemic treatments are now eligible</li> <li>• Patients with non-clear cell RCC histology will now include collecting duct and medullary RCC (<a href="#">Appendix 4</a> updated).</li> </ul> </li> <li>• New protocol section (<a href="#">Section 5.6.2</a>) for additional research that may be conducted on specimens already collected from subjects added.</li> </ul>
Revised protocol 01	02-Oct-2015	Incorporates changes in Amendment 01.
Global Amendment 01	02-Oct-2015	<p>Major changes</p> <ul style="list-style-type: none"> <li>• The title of the study has been revised to reflect changes in the study population.</li> <li>• The term immune-mediated adverse events (IMAEs), replaces the term select adverse events for consistency with nivolumab program. <a href="#">Section 6.2.2</a> has been added to specify these events.</li> <li>• Total enrollment has been changed to 150 subjects from 250 subjects, with a maximum enrollment of 75 subjects with predominant clear cell histology and approximate enrollments of 50 subjects for non-clear cell and 25 subjects with brain metastases (either histology).</li> <li>• Prior systemic treatments for subjects with non-clear cell histology may include treatment with mechanistic target of rapamycin (mTOR) inhibitor. Subjects with non clear cell histology who otherwise qualify are eligible with no prior systemic treatment.</li> <li>• Immune-related Response Criteria (irRC) has been removed from the protocol and is no longer an assessment of efficacy.</li> <li>• </li> <li>• Nivolumab will be administered to all enrolled subjects at a dose level</li> </ul>

Document	Date of Issue	Summary of Change
Original Protocol	10-Apr-2015	<p>of 240 mg IV every 2 weeks, replacing 3 mg/kg IV every 2 weeks as the dose for all enrolled subjects.</p> <ul style="list-style-type: none"> <li>• The steroid treatment and taper for brain edema is now specified in <a href="#">Section 3.4.3</a>, Permitted Therapies.</li> <li>• The FACT-G assessment tool will not be administered in this study.</li> <li>• Papillary Renal Cell Carcinoma subtype is specified in <a href="#">Appendix 4</a>.</li> <li>• Appendices of the original protocol have been renumbered to reflect the deletion of irRC (<a href="#">Appendix 2</a> in original protocol) and the addition of Patient Reported Outcomes questionnaires: FKSI-19 (<a href="#">Appendix 2</a> in the revised protocol) and EQ-5D (<a href="#">Appendix 3</a> in the revised protocol).</li> </ul>
		Not applicable

## SYNOPSIS

### Clinical Protocol CA209374

**Protocol Title:** A Phase 3b/4 Safety Trial of Nivolumab (BMS-936558) in Subjects with Advanced or Metastatic Renal Cell Carcinoma

**Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):** Nivolumab (BMS-936558), 240 mg every two weeks as a 30 minute ( $\pm$  5 minutes) IV infusion. Subjects may continue to receive treatment for a maximum of 24 months or until confirmed disease progression, unacceptable toxicity, withdrawal of informed consent or the study is discontinued by the Sponsor. Treatment can continue beyond initial assessment of progression as specified in [Section 4.5.3](#).

**Study Phase:** 3b/4

**Research Hypothesis:** The frequency of high grade (CTCAE vs 4.0 Grade 3-5) immune-mediated adverse events (IMAEs) observed in patients with advanced or metastatic renal cell carcinoma who are treated with nivolumab monotherapy will not differ from historical adverse event data in this patient population.

**Objective:**

**Primary Objective:**

- To assess the incidence of high grade (CTCAE v4.0 Grade 3-4 and Grade 5) IMAEs in subjects with advanced or metastatic renal cell carcinoma (RCC) who are treated with nivolumab monotherapy.

**Secondary Objective:**

- To characterize the outcome of all high grade (CTCAE v4.0 Grade 3 4 and Grade 5) IMAEs in subjects with advanced or metastatic RCC who are treated with nivolumab monotherapy.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**Study Design:**

This is a Phase 3b/4 safety study of nivolumab monotherapy for the treatment of patients with advanced or metastatic renal cell carcinoma. Approximately 180 subjects will undergo screening evaluations to determine eligibility within 28 days prior to first dose. Approximately 150 eligible subjects will be treated with 240 mg nivolumab IV, over 30 minutes ( $\pm$  5 minutes) every 2 weeks. Each 28-day dosing period will constitute a cycle.

Subjects will be enrolled into 1 of 3 treatment groups as follows:

- Group 1: Subjects with predominant clear cell histology: 75 subjects (approximate)

- Group 2: Subjects with non-clear cell histology: 50 subjects (approximate, with a minimum of 50 subjects with non-clear cell histology).
- Group 3: Subjects with brain metastases regardless of histology: 25 subjects (approximate).

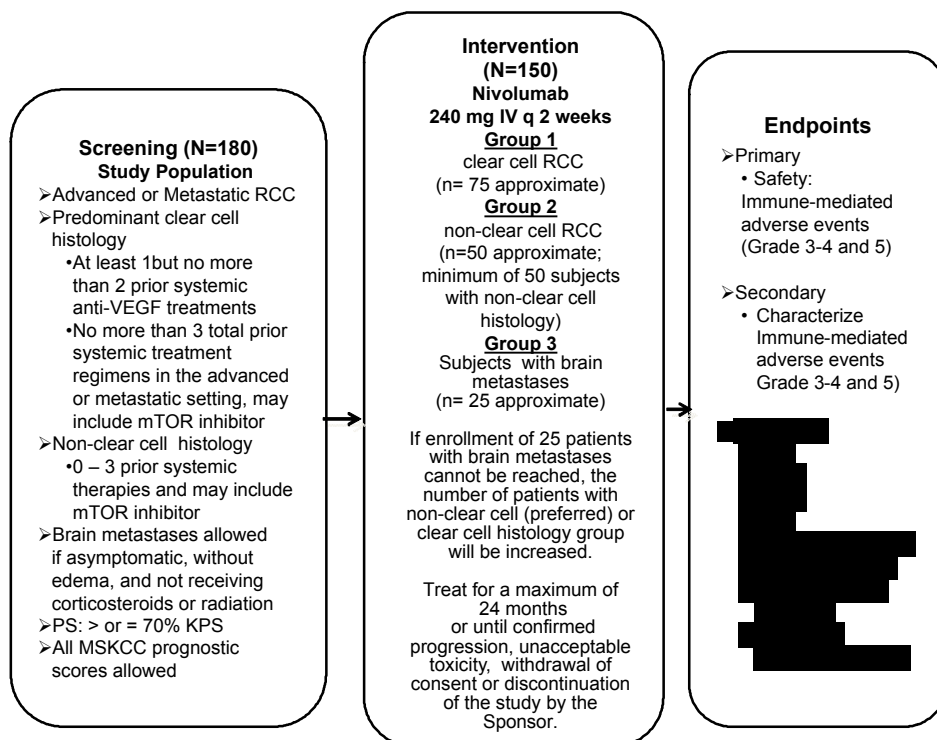
Note: If enrollment of 25 patients with brain metastases cannot be reached, the number of patients with non-clear cell (preferred) or clear cell histology group will be increased.

Subjects who are found on screening CT/MRI to have brain metastases will be enrolled to Group 3, if they do not require active treatment (radiation treatment/corticosteroids). Subjects who are found on screening CT/MRI to have brain metastases that require immediate treatment with radiation treatment/corticosteroids will be re-enrolled to Group 3 after completing active treatment. Subjects who develop brain metastases while on treatment with nivolumab will not be re-assigned to Group 3 but will remain in the group assigned at enrollment (See Section 3.4.3.2 for recommendations on palliative brain radiotherapy and resumption of treatment with nivolumab.) Brain lesions will be assessed only as non-target lesions.

After screening and enrollment, subjects will be treated for a maximum of 24 months on study, or until confirmed progression, unacceptable toxicity, withdrawal of consent, or the study is discontinued by the sponsor. Study treatment can continue beyond initial investigator assessed progression as specified in Section 4.5.3. The study will close after the last enrolled subject completes 5 years of follow up from the date of first treatment (LPFT).

Subjects treated in the study who continue to derive benefit from the study treatment after 24 months of treatment or subjects who have not completed 24 months of treatment at discontinuation of the study by the Sponsor, should continue to be treated according to standard of care following completion of the study.

The study design schematic is presented in below.



The study will continue until the last enrolled subject completes 5 years of follow up from the date of first treatment (LPFT).

**Study Population:** The study will enroll subjects with advanced (i.e., not amenable to curative surgery or radiation therapy) or metastatic (AJCC Stage IV) RCC with histological confirmation of predominant clear-cell or non-clear cell (papillary, chromophobe, translocation associated or unclassified) RCC as defined in [Appendix 4](#). Subjects with brain metastases are eligible if they are asymptomatic, without edema, and not on corticosteroids or receiving radiation treatment. Subjects with favorable, intermediate and poor risk categories per MSKCC Prognostic Score ([Appendix 5](#)) are eligible for the enrollment.

Eligible subjects with clear cell histology must have received at least 1 but no more than 2 prior anti-VEGF therapies in the advanced metastatic setting, and no more than 3 prior systemic therapies, which may include an mTOR inhibitor per Amendment 02. Subjects with non-clear cell histology are eligible with up to 3 prior systemic therapies (including m-TOR inhibitor) or with no prior systemic therapy.

No prior neoadjuvant/adjuvant therapy is allowed for subjects with either RCC histology. [REDACTED]

Subjects with uncontrolled adrenal insufficiency, known history of testing positive for human immunodeficiency virus (HIV), known acquired immunodeficiency syndrome (AIDS), or any positive test for Hepatitis B or Hepatitis C virus indicating acute or chronic infection are not eligible for this study.

**Study Drug: includes both Investigational [Medicinal] Products (IP/IMP) and Non-investigational [Medicinal] Products (Non-IP/Non-IMP) as listed:**

Study Drug for CA209374		
Medication	Potency	IP/Non-IP
Nivolumab (BMS-936558) Solution for Injection	100 mg (10 mg/mL)	IP

**Study Assessments:**

Assessments for safety include continuous monitoring for all adverse events using NCI CTCAE v. 4.0, including the IMAEs specified in [Section 8.3.1](#). Additional safety assessments include vital signs and oxygen saturation, physical measurements and target physical exam, performance status, laboratory evaluations (complete blood counts, serum chemistry, liver function, thyroid function) and pregnancy test as applicable and review of concomitant medications. To assess tumor response, CT/MRI will be performed at baseline and throughout the treatment and follow up periods as specified in [Section 5](#). Additional study procedures include assessments for biomarkers, patient reported outcomes as evaluated by FKSI-19 and EQ-5D, and healthcare resource utilization.

All study procedures/assessments performed during screening, during treatment with nivolumab and during follow up must be completed in accordance with [Table 5.1-1](#), [Table 5.1-2](#), and [Table 5.1-3](#).

**Statistical Considerations:**

**Sample Size:** Approximately 150 subjects will be treated with nivolumab in this study. This sample size will allow for estimating an incidence rate of 0.67% (n=1 subject with events) with a 95% CI (confidence interval) of (0.02%, 3.7%), or an incidence rate of 2% (n=3 subjects with events) with a 95% CI of (0.4%, 5.7%). Furthermore, the sample size will allow for enough events to compare incidence with historical adverse event data.

**Endpoints:**

**Primary Endpoint:** The primary objective of the study will be assessed by measuring the incidence for high grade (Grade 3-4 and Grade 5) IMAEs.

The IMAEs are the following: skin, endocrinopathy, gastrointestinal, hepatic, renal, pulmonary, and neurologic adverse events.

**Secondary Endpoints:** The secondary objective of the study will be assessed by measuring the following:

- median time to onset, median time to resolution (Grade 3-4) IMAEs.
- percentage of subjects who received immune modulating medication (e.g. corticoidsteroids, infliximab, cyclophosphamide, IVIG, and mycophenolate mofetil), or hormonal replacement therapy, the percentage of subjects who received  $\geq 40$  mg prednisone equivalents, total duration of all immune modulating medications given for the immune-mediated event.

[REDACTED]

**Analyses:**

Demographics, baseline disease characteristics and baseline laboratory results will be summarized using descriptive statistics for all treated subjects and all subjects in Groups 1, 2, and 3.

**Primary Endpoint:** The number and percentage of subjects who report high grade (Grade 3-4 and Grade 5) IMAEs will be summarized for all treated subjects. High grade (Grade 3-4 and Grade 5) IMAEs will be tabulated using worst grade per NCI CTCAE v4.0 criteria by system organ class and Medical Dictionary for Regulatory Affairs (MedDRA) preferred term.

**Second Endpoints:** Additional descriptive statistics for high grade (Grade 3 4 and Grade 5) IMAEs will include median values using the Kaplan-Meier (KM) product-limit method with 95% CI using Brookmeyer and Crowley of time to onset and time to resolution of IMAEs, and will be presented for all treated subjects in Groups 1, 2, and 3. Time to onset is calculated from first dosing date to the event onset date. If a subject never experienced the given AE, the subject will be censored at the last contact date. Time to resolution is calculated from the AE onset date to AE end date. If an AE is ongoing at the time of analysis, the time to resolution will be censored at the last contact date.

Management of high-grade (CTCAE v4.0 Grade 3-4 and Grade 5) IMAEs will be characterized by measuring percentage of subjects who received immune modulating medication (or hormonal replacement therapy), percentage of subjects who received  $\geq 40$  mg prednisone equivalents, and total duration of all immune modulating medications given for the event, in all treated subjects who have experience high-grade (CTCAE v4.0 Grade 3-4 and Grade 5) IMAEs and all subjects in Groups 1, 2, and 3.

[REDACTED]



[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**TABLE OF CONTENTS**

TITLE PAGE ..... 1

DOCUMENT HISTORY ..... 3

SYNOPSIS ..... 5

TABLE OF CONTENTS ..... 10

1 ..... 13

1.1 ..... 13

..... 14

..... 16

..... 16

..... 17

..... 17

..... 18

..... 18

..... 19

1.4 Research Hypothesis ..... 19

1.5 Objectives(s) ..... 19

    1.5.1 Primary Objectives ..... 19

    1.5.2 Secondary Objectives ..... 19

..... 20

1.6 ..... 20

..... 20

..... 22

1.7 Overall Risk/Benefit Assessment ..... 24

2 ETHICAL CONSIDERATIONS ..... 24

    2.1 Good Clinical Practice ..... 24

    2.2 Institutional Review Board/Independent Ethics Committee ..... 25

    2.3 Informed Consent ..... 25

3 INVESTIGATIONAL PLAN ..... 26

    3.1 Study Design and Duration ..... 26

    3.2 Post Study Access to Therapy ..... 28

    3.3 Study Population ..... 28

        3.3.1 Inclusion Criteria ..... 28

        3.3.2 Exclusion Criteria ..... 31

        3.3.3 Women of Childbearing Potential ..... 32

    3.4 Concomitant Treatments ..... 33

        3.4.1 Prohibited and/or Restricted Treatments ..... 33

        3.4.2 Other Restrictions and Precautions ..... 33

        3.4.3 Permitted therapies ..... 33

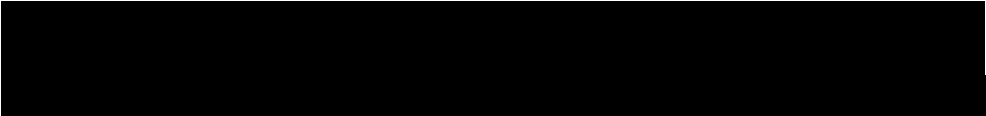
            3.4.3.1 Focal Palliative Radiation ..... 34

            3.4.3.2 Palliative brain radiation ..... 34

    3.5 Discontinuation of Subjects following any Treatment with Study Drug ..... 35

    3.6 Post Study Drug Study Follow up ..... 35

        3.6.1 Withdrawal of Consent ..... 35

3.6.2 Lost to Follow-Up.....	36
4 STUDY DRUG.....	36
4.1 Investigational Product .....	38
4.2 Non-investigational Product .....	38
4.3 Storage and Dispensing.....	38
4.4 Method of Assigning Subject Identification.....	39
4.5 Selection and Timing of Dose for Each Subject.....	39
4.5.1 Management Algorithm for Nivolumab related adverse events .....	40
4.5.2 Dose Delay Criteria.....	40
4.5.2.1 Nivolumab Dose Delay Criteria .....	40
4.5.3 Dose Escalations and Reductions.....	41
4.5.3.1 Criteria to Resume Treatment with Nivolumab .....	41
4.5.4 Treatment Beyond Disease Progression.....	41
4.5.4.1 Treatment Discontinuation Criteria for Nivolumab .....	42
4.5.5 Treatment of Nivolumab-Related Infusion Reactions .....	43
4.6 Blinding/Unblinding .....	44
4.7 Treatment Compliance.....	44
4.8 Destruction of Study Drug .....	44
4.9 Return of Study Drug.....	45
5 STUDY ASSESSMENTS AND PROCEDURES.....	46
5.1 Flow Chart/Time and Events Schedule.....	46
5.1.1 Retesting During Screening or Lead-in Period .....	52
5.2 Study Materials .....	52
5.3 Safety Assessments.....	52
5.3.1 Screening Assessments.....	52
5.3.2 On-Study Safety Assessments and Procedures .....	52
5.3.3 Follow-up and Survival Procedures .....	53
5.3.4 Imaging Assessment for the Study.....	53
5.4 Efficacy Assessments.....	53
5.4.1 Screening (Baseline visit) and On-Study Efficacy Assessments .....	53
5.5 Pharmacokinetic Assessments .....	54
5.6  .....	54
5.7 Outcomes Research Assessments .....	55
5.8 Other Assessments .....	55
5.9 Results of Central Assessments .....	55
6 ADVERSE EVENTS.....	55
6.1 Serious Adverse Events .....	56
6.1.1 Serious Adverse Event Collection and Reporting.....	57
6.2 Nonserious Adverse Events .....	58
6.2.1 Nonserious Adverse Event Collection and Reporting.....	58
6.2.2 Adverse Events of Interest.....	58
6.3 Laboratory Test Result Abnormalities.....	59
6.4 Pregnancy.....	60
6.5 Overdose .....	60

6.6 Potential Drug Induced Liver Injury (DILI) .....	60
6.7 Other Safety Considerations .....	61
7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES .....	61
8 STATISTICAL CONSIDERATIONS.....	61
8.1 Sample Size Determination.....	61
8.2 Populations for Analyses .....	63
8.3 Endpoints .....	63
8.3.1 Primary Endpoint(s) .....	63
8.3.2 Secondary Endpoint(s).....	63
[REDACTED] .....	63
8.4 Analyses.....	64
8.4.1 Demographics and Baseline Characteristics.....	64
8.4.2 Primary Analyses .....	64
8.4.3 Secondary Analyses .....	65
[REDACTED] .....	65
8.4.5 Pharmacokinetic Analyses .....	66
[REDACTED] .....	66
8.4.7 Outcomes Research Analyses .....	66
8.4.8 Other Analyses .....	66
8.5 Interim Analyses .....	66
9 STUDY MANAGEMENT .....	67
9.1 Compliance .....	67
9.1.1 Compliance with the Protocol and Protocol Revisions .....	67
9.1.2 Monitoring .....	67
9.1.2.1 Source Documentation.....	68
9.1.3 Investigational Site Training.....	68
9.2 Records .....	68
9.2.1 Records Retention .....	68
9.2.2 Study Drug Records .....	68
9.2.3 Case Report Forms .....	69
9.3 Clinical Study Report and Publications .....	69
10 GLOSSARY OF TERMS .....	71
11 LIST OF ABBREVIATIONS.....	72
[REDACTED] .....	76
APPENDIX 1 RECIST 1.1 GUIDELINES .....	79
[REDACTED] .....	87
[REDACTED] .....	88
[REDACTED] .....	91
[REDACTED] .....	99
[REDACTED] .....	100
[REDACTED] .....	108





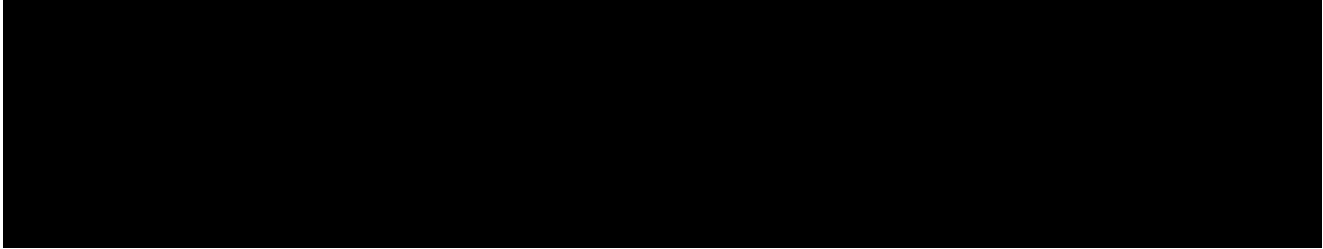












**1.4 Research Hypothesis**

The frequency of high grade (CTCAE vs 4.0 Grade 3-5) IMAEs observed in patients with advanced or metastatic renal cell carcinoma who are treated with nivolumab monotherapy will not differ from historical adverse event data in this patient population.

**1.5 Objectives(s)**

**1.5.1 Primary Objectives**

To assess the incidence of high grade (CTCAE v4.0 Grade 3-4 and Grade 5) IMAEs in subjects with advanced or metastatic renal cell carcinoma (RCC) who are treated with nivolumab monotherapy.

**1.5.2 Secondary Objectives**

To characterize the outcome of all high grade (CTCAE v4.0 Grade 3-4 and Grade 5) IMAEs in subjects with advanced or metastatic RCC who are who are treated with nivolumab monotherapy.













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.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

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

## **2.2 Institutional Review Board/Independent Ethics Committee**

Before study initiation, the investigator must have obtained written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS 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 BMS 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 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 (as per country guidelines) 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 his or her informed consent during the study, 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 or subjects with or 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 his or her understanding, and should this subject become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a subject who is unable to give his or her written consent, but who is capable of forming an opinion and assessing 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 3b/4 safety study of nivolumab monotherapy for the treatment of patients with advanced or metastatic renal cell carcinoma. Approximately 180 subjects will be screened to determine eligibility within 28 days prior to first dose. Approximately 150 eligible subjects will be treated every 2 weeks with 240 mg nivolumab, intravenously over 30 minutes ( $\pm$  5 minutes). Each 28 day dosing period will constitute a cycle.

Subjects will be enrolled to 1 of 3 groups as follows:

- **Group 1:** Subjects with predominant clear cell histology: 75 subjects (approximate)
- **Group 2:** Subjects with non-clear cell histology: 50 subjects (approximate, with a minimum of 50 subjects with non-clear cell histology).
- **Group 3:** Subjects with brain metastases regardless of histology: 25 subjects (approximate).

- Subjects who are found on screening CT/MRI to have brain metastases will be enrolled to Group 3 if they do not require active treatment (radiation treatment/corticosteroids)
- Subjects who are found on screening CT/MRI to have brain metastases that require immediate treatment (radiation treatment/corticosteroids) will be re-enrolled to Group 3 after completing active treatment
- Subjects who while on treatment with nivolumab develop brain metastases will not be reassigned to Group 3 but will remain in the group assigned at enrollment. (See [Section 3.4.3.2](#) for recommendations on palliative brain radiotherapy and resumption of treatment with nivolumab.)
- Brain lesion(s) will only be assessed as non-target lesions.

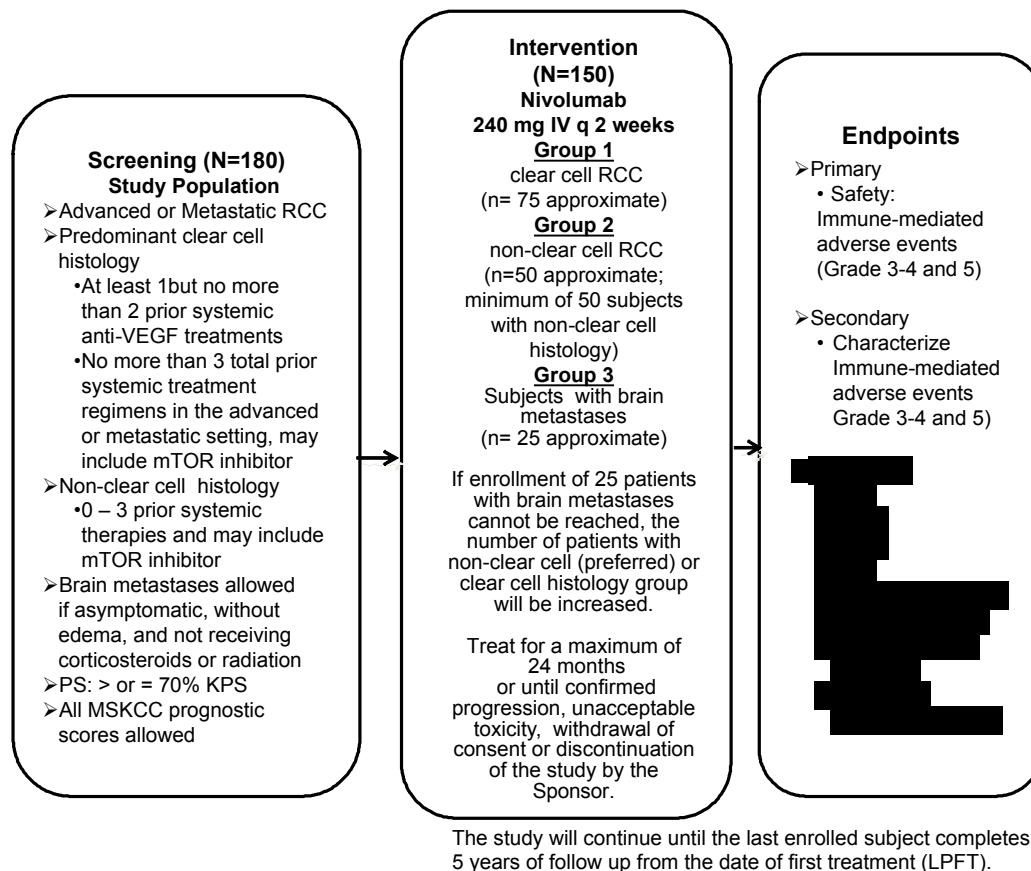
Note: If enrollment of 25 patients with brain metastases cannot be reached, the number of patients with non-clear cell (preferred) or clear cell histology group will be increased.

After screening and enrollment, subjects will be treated for a maximum of 24 months on study, or until confirmed progression, unacceptable toxicity, withdrawal of consent, or the study is discontinued by the sponsor. Study treatment can continue beyond initial investigator assessed progression as specified in [Section 4.5.4](#). The study will close after the last enrolled subject completes 5 years of follow up from the date of first treatment (LPFT).

Subjects treated in the study who continue to derive benefit from the study treatment after 24 months of treatment or subjects who have not completed 24 months of treatment at discontinuation of the study by the Sponsor, should continue to be treated according to standard of care following completion of the study.

The study design schematic is presented in [Figure 3.1-1](#).

**Figure 3.1-1: Study Design Schematic**



### 3.2 Post Study Access to Therapy

At the end of the study, BMS will not continue to provide BMS supplied study drug to subjects/investigators unless BMS chooses to extend the study. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study,

### 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) 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) Histological confirmation of RCC subjects with:

- i) Predominant clear-cell as defined in [Appendix 4](#).
- ii) Non-clear cell histology as defined in [Appendix 4](#) including:
  - (1).papillary
  - (2).chromophobe
  - (3).translocation associated.
  - (4).collecting duct
  - (5).medullary
  - (6).any pathology unclassified.
- b) Advanced (not amenable to curative surgery or radiation therapy) or metastatic (AJCC Stage IV) RCC.
- c) For subject with predominant clear cell histology:
  - i) Must have received at least 1 but not more than 2 prior anti-VEGF therapy regimens (including, but not limited to sunitinib, sorafenib, pazopanib, axitinib, tivozanib, and bevacizumab) in the advanced or metastatic setting
  - ii) Must have received no more than 3 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.
  - iii) Subjects with prior treatment with mTOR are eligible per Amendment 02.
- d) For subjects with non clear cell histology:
  - i) Must have received no more than 3 total prior systemic treatment regimens in the advanced or metastatic setting. Subjects with non clear cell histology and no prior systemic treatment are eligible for enrollment.
- e) Karnofsky Performance Status (PS) of at least 70% ([Appendix 7](#)).
- f) Measurable disease as per RECIST v1.1 ([Appendix 1](#)). Subject must have extracranial metastasis as measurable disease.
- g) Subjects with favorable, intermediate and poor risk categories will be eligible for the study (MSKCC Prognostic Score, [Appendix 5](#)).
- h) Subjects with brain metastases will be allowed if they are asymptomatic, without edema, and not on corticosteroids or receiving radiation treatment. Brain lesion(s) will only be assessed as non-target lesions.

Subject Re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subjects who have not been treated). If re-enrolled, the subject must be re-consented and will receive a new patient identification number (PID).

### 3. Age and Reproductive Status

- a) Males and Females, ages  $\geq 18$  years.
- b) Women of childbearing potential (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 study drug.

- c) Women must not be breastfeeding.
- d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab plus 5 half-lives of nivolumab (19 weeks) plus 30 days (duration of ovulation cycle) for a total of 23 weeks post-treatment completion.
- e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab plus 5 half-lives of the study drug (19 weeks) plus 90 days (duration of sperm turnover) for a total of 31 weeks days post-treatment completion.
- f) Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed below:

### **HIGHLY EFFECTIVE METHODS OF CONTRACEPTION**

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena<sup>®</sup> by WOCBP subject or male subject's WOCBP partner. Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- Nonhormonal IUDs, such as ParaGard<sup>®</sup>
- Tubal ligation
- Vasectomy.
- Complete Abstinence\*

\*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

### **LESS EFFECTIVE METHODS OF CONTRACEPTION**

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge
- Male Condom without spermicide
- Progestin only pills by WOCBP subject or male subject's WOCBP partner
- Female Condom\*.

\* A male and female condom must not be used together

### **3.3.2 Exclusion Criteria**

#### **1. Medical History and Concurrent Diseases**

- a) Not applicable per Amendment 02: ie, subjects with predominant clear cell histology and prior treatment with an mTOR inhibitor (including, but not limited to, everolimus, temsirolimus, sirolimus, and ridaforolimus) are no longer excluded from this study.
- b) Subjects with any active autoimmune disease or a history of known 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 corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days prior to first dose of study drug. Inhaled steroids and adrenal replacement steroid doses >10mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
- d) Subjects with uncontrolled adrenal insufficiency.
- e) 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.
- f) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).
- g) Any positive test for Hepatitis B or Hepatitis C virus indicating acute or chronic infection.
- h) Known or underlying medical condition (eg, a condition associated with diarrhea or acute diverticulitis) that, in the investigator's opinion, would make the administration of study drug hazardous to the subject or obscure the interpretation of toxicity determination or adverse events.
- i) Major surgery (eg nephrectomy) less than 28 days prior to first dose of study drug. Minor surgery less than 14 days prior to first dose of study drug.
- j) Prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways); subjects who participated in CA209016 or were randomized in CA209214 are not eligible.

- k) Anti-cancer therapies, including prior treatment with mTOR inhibitor must be discontinued at least 14 days prior to administration of study drug. If patient has received prior bevacizumab, then therapy must have been discontinued at least 21 days prior to administration of study drug. Palliative, focal or whole brain radiation therapy must be discontinued at least 2 weeks before administration of study drug.
- l) All toxicities attributed to prior anti-cancer therapy other than alopecia must have resolved to grade 1 (NCI CTCAE version 4) or baseline before administration of study drug.

## 2. Physical and Laboratory Test Findings

All baseline laboratory parameters should be obtained within 14 days (unless otherwise specified in [Table 5.1-1](#)) of first dose of study drug.

- i) WBC < 2000/ $\mu$ L
- ii) Neutrophil < 1500/ $\mu$ L
- iii) Platelets < 100 x 10<sup>3</sup>/ $\mu$ L
- 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) Serum creatinine of > 2.0 X ULN (upper limit of normal) or creatinine clearance < 30 mL/minute (using Cockcroft/Gault formula)
  - Female CrCl =  $\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$
  - 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. Allergies and Adverse Drug Reaction

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

## 4. 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 that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

### 3.3.3 *Women of Childbearing Potential*

A Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in



a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.

\*Females 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. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is >40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal:

- 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 (unless utilized to treat a drug related adverse event):

█ [REDACTED]

█ [REDACTED]

█ [REDACTED]

Prior radiotherapy must have been completed at least 2 weeks prior to starting study treatment. See Section 3.4.3 for guidance on concomitant palliative radiotherapy.

#### **3.4.2 Other Restrictions and Precautions**

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

Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of starting treatment are excluded. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

#### **3.4.3 Permitted therapies**

Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for

prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted. Steroid treatment specified as  $\leq 16$  mg dexamethasone PO daily tapered in  $\leq 4$  weeks is allowed only for the treatment of brain edema.

Concomitant palliative and supportive care for disease related symptoms (including bisphosphonates and RANK-L inhibitors) is allowed if initiated prior to first dose of study therapy.

### **3.4.3.1 Focal Palliative Radiation**

The potential for overlapping toxicities with radiotherapy and nivolumab currently is not known. Therefore, palliative radiotherapy is not recommended while receiving nivolumab. If palliative radiotherapy is required for bone metastases then nivolumab should be withheld for at least 1 week before, during, and 1 week after radiation. Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs should resolve to Grade  $\leq 1$  prior to resuming nivolumab. Only bone lesions may receive palliative radiotherapy. Details of palliative radiotherapy should be documented in the source records and electronic case report form (eCRF). Details in the source records should include: dates of treatment, anatomical site, dose administered and fractionation schedule, and adverse events. Subjects receiving limited field palliative radiation therapy will be considered to have unequivocal progression of disease in the non-target lesion. Symptoms requiring palliative radiotherapy should be evaluated for objective evidence of disease progression. Administration of additional nivolumab to subjects who received limited field palliative radiation should follow guidelines specified in [Section 4.5.4, Treatment beyond Disease Progression](#)

### **3.4.3.2 Palliative brain radiation**

The potential for overlapping toxicities with brain radiotherapy and nivolumab is not known. Therefore palliative brain radiotherapy is not recommended while receiving nivolumab.

Subjects receiving limited field palliative brain radiation therapy will be considered to have unequivocal progression of disease in the non-target lesion. Administration of additional nivolumab to subjects who received limited field palliative radiation should follow guidelines specified in [Section 4.5.4, Treatment beyond Disease Progression](#).

If subjects require palliative brain radiation, nivolumab will be held for at least one week prior to brain radiation, during and 2 weeks following radiation. Subjects should be closely monitored for potential toxicity during and after receiving radiotherapy and AEs should resolve to Grade  $\leq 1$  prior to resuming treatment with nivolumab.

### 3.5 Discontinuation of Subjects following any Treatment with Study Drug

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

- Subject's request to stop study treatment
- 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
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Study specific criteria for discontinuation of treatment with nivolumab are presented in [Section 4.5.4.1](#).

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

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

If study drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

**NOTE: A 4-week washout (minimum) of nivolumab is recommended for subjects who are discontinued from treatment with nivolumab for any reason and are being considered for treatment with mTOR inhibitor.**

### 3.6 Post Study Drug Study Follow up

In this study, safety is a key endpoint of the study. Post study follow-up is of critical importance and is essential to 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.

#### 3.6.1 *Withdrawal of Consent*

Subjects who request to discontinue study drug 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 STUDY DRUG**

Study drug includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) see [Table 4-1](#) 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, background 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 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.

For this study the investigational product is BMS-936558 (nivolumab).

#### **4.2 Non-investigational 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 non-investigational products.

#### **4.3 Storage 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 BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Study drug not supplied by BMS will be stored in accordance with the package insert.

Investigational product documentation (whether supplied by BMS or not) 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).

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 BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Investigational product documentation (whether supplied by BMS or not) 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).

Infusion-related supplies (eg IV bags, in-line filters, 0.9% NaCl solution) will not be supplied by the sponsor and should be purchased locally if permitted by local regulations.

For non-investigational product, if marketed product is utilized, it should be stored in accordance with the package insert, summary of product characteristics (SmPC), or similar.

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

Nivolumab (BMS-936558) vials must be stored at a temperature of 2°C to 8°C and should be protected from light, freezing, and shaking. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

For details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the BMS-936558 (nivolumab) 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 antimicrobial preservative or bacteriostatic agent. No incompatibilities between nivolumab and polyolefin bags have been observed.

Please refer to the current BMS-936558 (nivolumab) Investigator Brochure: Preparation instructions for details on the administration of nivolumab.

#### **4.4 Method of Assigning Subject Identification**

After the subject’s eligibility is established and informed consent has been obtained, the subject will be enrolled and a number will be assigned through an interactive voice response system (IVRS). Also, the IVRS will be used to manage enrollment of subject subgroups. Specific instructions and procedures for using IVRS will be provided to the investigational site in a separate document/ manual.

The investigator (or designee) will register the subject for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

- Date of informed consent
- Date of birth
- Gender at birth
- Confirmed RCC histology
- Confirmed presence or absence of brain metastases

#### **4.5 Selection and Timing of Dose for Each Subject**

Subjects will receive treatment every 2 weeks with 240 mg of nivolumab as a 30 minute ( $\pm$  5 minutes) IV infusion.

There will be no dose escalations or reductions of nivolumab allowed. Subjects may be dosed no less than 12 days from the previous dose. There are no premedications recommended for nivolumab on the first cycle. If an acute infusion reaction is noted, subjects should be managed according to [Section 4.5.5](#).

#### **4.5.1 Management Algorithm for Nivolumab related adverse events**

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Nivolumab is considered an immuno-oncology agent in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity.

Management Algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological

The above algorithms are found in the nivolumab Investigator Brochure, and can also be found in [Appendix 6](#) of this protocol.

For subjects expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage and adverse event, consider recommendations provided in Adverse Event Management Algorithms in Appendix 6.

#### **4.5.2 Dose Delay Criteria**

Tumor assessments for all subjects should continue as per protocol even if dosing is delayed.

##### **4.5.2.1 Nivolumab Dose Delay Criteria**

Nivolumab administration should be delayed for the following:

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



### **4.5.3 Dose Escalations and Reductions**

There will be no dose modification of nivolumab.

#### **4.5.3.1 Criteria to Resume Treatment with Nivolumab**

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

- 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 should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment
- If treatment is delayed  $>$  6 weeks, the subject must be permanently discontinued from study therapy, except as specified in Treatment Discontinuation criteria

#### **4.5.4 Treatment Beyond Disease Progression**

As described in [Section 1.3.3](#), accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD. Subjects treated with nivolumab will be permitted to continue treatment beyond initial RECIST 1.1 defined progressive disease (PD) as long as the following criteria are met:

- 1) Investigator-assessed clinical benefit
- 2) Tolerance of study drug
- 3) Stable performance status
- 4) Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- 5) Subject provides written informed consent prior to receiving additional nivolumab treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options.

The decision to continue treatment beyond initial progression should be discussed with the BMS medical Monitor and documented in the study records.

A radiographic assessment/ scan should be performed within 8 weeks of original PD to determine whether there has been a decrease in the tumor size, or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab.

If the investigator feels that the nivolumab subject continues to achieve clinical benefit by continuing treatment, the subject should remain on the trial and continue to receive monitoring according to the Time and Events Schedule on [Table 5.1-2](#).

For the subjects who continue nivolumab study therapy beyond progression, further progression is defined as an additional 20% increase in tumor burden volume from time of initial PD. This includes an increase in the sum of all target lesions and/ or the development of new measurable lesions. Treatment should be discontinued permanently upon documentation of further disease progression

New lesions are considered measureable 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 measureable and therefore included in the tumor burden volume if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm).

Subjects with global deterioration of health status (as determined by the investigator) who require discontinuation of treatment without objective evidence of disease progression at the time of treatment discontinuation should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression (ie, radiographic confirmation) even after discontinuation of treatment.

#### **4.5.4.1 Treatment Discontinuation Criteria for Nivolumab**

Tumor assessments for all subjects should continue as per protocol even if dosing is discontinued.

- **Nivolumab treatment should be permanently 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 retreatment period OR requires systemic treatment
  - Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions:
    - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
    - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except
      - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
      - Any drug-related liver function test (LFT) abnormality that meets the following criteria requires 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
  - Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events:

- Grade 4 neutropenia  $\leq$  7 days does not require discontinuation
  - Grade 4 lymphopenia or leukopenia does not require discontinuation
  - 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 do not require discontinuation
  - Isolated Grade 4 amylase or lipase abnormalities those are not associated with symptoms or clinical manifestations of pancreatitis. The Sponsor Medical Monitor designee should be consulted for Grade 4 amylase or lipase abnormalities.
- Any dosing interruption lasting  $>$  6 weeks with the following exceptions:
- Dosing interruptions to manage drug-related adverse events, such as prolonged steroid tapers, are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting  $>$  6 weeks, the Sponsor Medical Monitor designee 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 Sponsor Medical Monitor designee. Prior to re-initiating treatment in a subject with a dosing interruption lasting  $>$  6 weeks, the Sponsor Medical Monitor designee 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.

#### **4.5.5 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, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study medical monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 4.0) guidelines.

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

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

- Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg 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 acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/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.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

**For Grade 3 or 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 1:1000 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 of the symptoms.

In 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).

#### **4.6 Blinding/Unblinding**

Not applicable.

#### **4.7 Treatment Compliance**

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

#### **4.8 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 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 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.

#### **4.9 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 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.

Arrangements for the return of study drug will be made by the responsible Study Monitor.

## 5 STUDY ASSESSMENTS AND PROCEDURES

### 5.1 Flow Chart/Time and Events Schedule

<b>Table 5.1-1: Screening Procedural Outline (CA209374)</b>		
<b>Procedure</b>	<b>Screening (28 days prior to dosing unless otherwise specified)</b>	<b>Notes</b>
Eligibility Assessments		
Informed Consent	X	Obtain consent prior to performing any testing for eligibility
IVRS	X	An IVRS will be used to assign subject numbers
Inclusion/Exclusion Criteria	X	
Medical History	X	
Safety Assessments		
Physical measurements (including performance status)	X	Includes height, weight, performance status (Karnofsky); baseline EKG, and a focused physical exam is to be performed at screening.
Vital Signs	X	Temperature, BP, HR, RR. Obtain vital signs at screening and within 48 hours of first dose.
Assessment of Signs and Symptoms	X	After obtaining Informed Consent, assess all signs and symptoms within 14 days of first dose, prior to study treatment initiation.
Concomitant medications	X	Within 14 days of first dose.
Laboratory Tests	X	Labs performed locally within 14 days prior to first dose (unless otherwise specified): CBC with differential, serum chemistry (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, bicarbonate, and glucose), liver function tests (AST, ALT, total bilirubin, alkaline phosphatase, albumin, LDH).  The following labs can be performed locally within 28 days prior to first dose: TSH, free T3, free T4, hepatitis B surface antigen (HBV sAg) and Hepatitis C antibody (HCV Ab) or Hepatitis C RNA (HCV RNA).
Pregnancy Test	X	Within 24 hours prior to first dose for WOCBP only (serum or urine at the site).

<b>Table 5.1-1: Screening Procedural Outline (CA209374)</b>		
<b>Procedure</b>	<b>Screening (28 days prior to dosing unless otherwise specified)</b>	<b>Notes</b>
Radiographic Tumor Assessment (Chest, Abdomen, Head)	X	Within 28 days prior to first dose. CT/MRI of brain (with contrast, unless contraindicated) required for all subjects. Additional sites of known or suspected disease (including pelvis) should be imaged at screening.
Archived Tumor Tissue or Recent Tumor Biopsy	X	One formalin-fixed paraffin embedded tumor tissue block, or 15 minimum FFPE unstained slides are to be submitted, if available. Submit a copy of the original pathology report along with the sample. Tissue samples from different biopsy procedures are to be submitted if available with each matching pathology report and biopsy date. Tissue sample from the metastatic tumor can be submitted if the primary tumor tissue is not available.

<b>Table 5.1-2: On-Study Procedural Outline (CA209374)</b>				
<b>Procedure</b>	<b>Each Cycle Day 1</b>	<b>2nd Dose of Cycle</b>	<b>Q 8 wks from Day 1 Cycle 1</b>	<b>Notes</b>
<b>Safety Assessments</b>				
Targeted assessments	X			Cycle 2 and beyond. Assessments within 48 hrs prior to dosing to include: Targeted physical exam, performance status and weight. Oxygen saturation by pulse oximetry at rest and after exertion for patients who complain of dyspnea or other respiratory symptoms
Adverse Events Assessment	Continuously assessed using NCI CTCAE v. 4.0.			
Concomitant Medications	X	X		
Laboratory Tests	X			Cycle 2 and beyond: (within 72 hrs prior to dosing) CBC w/differential, LFTs, BUN or serum urea, creatinine. TSH (reflex to free T3 and free T4 if abnormal result).
		X		LFTS only (within 72 hours prior to dosing)
Pregnancy Test	X			
<b>Efficacy Assessments</b>				
Radiographic Tumor Assessments			X	At Week 8 ( $\pm$ 1 week) and every 8 weeks $\pm$ 1 week thereafter, regardless of dosing schedule for the first 13 months then every 12 weeks $\pm$ 1 week until progression or treatment discontinuation whichever occurs later. Subjects with a history of brain metastasis perform surveillance CT/MRI approximately every 12 weeks, or sooner if clinically indicated.



<b>Table 5.1-2: On-Study Procedural Outline (CA209374)</b>				
<b>Procedure</b>	<b>Each Cycle Day 1</b>	<b>2nd Dose of Cycle</b>	<b>Q 8 wks from Day 1 Cycle 1</b>	<b>Notes</b>
<b>Clinical Drug</b>				
Administer Study Treatment	X	X		All subjects start treatment on C1D1 and continue treatment every 2 weeks for a maximum of 24 months or until confirmed progression, unacceptable toxicity, withdrawal of informed consent or discontinuation of the study by the Sponsor. Treatment for all subjects can continue beyond initial investigator-assessed progression. Drug administration is +/- 2 days but no less than 12 days from previous dose. Study drug infusion start and stop times will be recorded.
Other				
Patient-Reported Outcome Measurements	X			Prior to any study-related procedures: FKSI-19, and EQ-5D
Health Resource Utilization	X			Prior to any study-related procedures

<b>Table 5.1-3: Follow-up Procedural Outline (CA209374)</b>			
<b>Procedure</b>	<b>Follow-up Visit 1 (X01) and Visit 2 (X02).</b>	<b>Follow-up after Visit 2 (X02)</b>	<b>Notes</b>
			<b>Follow up Visit (X01) = 30 days from last dose +/-5 days, or may be on date of discontinuation +/-5 days if the date of discontinuation is more than 35 days after last dose. Follow up Visit 2 (X02) = 100-114 days from last dose.</b>
Vital Signs	X		
Physical measurements	X		Includes performance status (Karnofsky)
Adverse Events Assessment	X	X*	*Beyond 100-114 days from the last dose of study therapy, subjects will be followed for ongoing drug-related AEs until resolved, return to baseline or deemed irreversible, or until lost to follow-up or withdrawal of study consent.
Laboratory Tests	X		CBC with differential, serum chemistry (BUN or serum urea level, serum creatinine, albumin, sodium, potassium, calcium, magnesium, phosphate, chloride, bicarbonate, glucose), liver function (AST, ALT, total bilirubin, alkaline phosphatase, LDH), thyroid function (TSH, reflex to free T3 and free T4 if abnormal result)
Review of concomitant medications	X		
Pregnancy testing	X		Serum or urine
Collection of Survival Information	X	X	Every 3 months until death, lost to follow-up, or withdrawal of study consent for 5 years following start of therapy. May be performed by phone contact or office visit.
Radiographic Tumor Assessment	X	X	For subjects who discontinue study treatment for reasons other than PD, follow up scans (or MRIs when appropriate) should be performed every 8 weeks ( $\pm$ 5 days) for the first 13 months then every 12 weeks $\pm$ 1 week until PD, death, lost to follow-up, or withdrawal of consent. Radiographic assessments should not be delayed until the X01 or X02.

<b>Table 5.1-3: Follow-up Procedural Outline (CA209374)</b>			
<b>Procedure</b>	<b>Follow-up Visit 1 (X01) and Visit 2 (X02).</b>	<b>Follow-up after Visit 2 (X02)</b>	<b>Notes</b>
Patient Reported Outcomes			
FKSI-19 and EQ-5D	X	X	At X01 and X02 and then every 3 months for the first 12 months, then every 6 months thereafter, as permitted by local IRB. Assessments can be conducted by phone or mail.
Healthcare Resource Utilization	X	X	To be collected in alignment with PRO's above (, FKSI-19 and EQ-5D). Assessments can be conducted by phone or mail.

### **5.1.1 Retesting During Screening or Lead-in Period**

Retesting of laboratory parameters and/or other assessments within any single Screening or Lead-in period will be permitted (in addition to any parameters that require a confirmatory value).

Any new result will override the previous result (i.e., the most current result prior to first dose of study drug) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

Retesting must be completed in accordance with [Table 5.1-1](#).

## **5.2 Study Materials**

The following materials will be provided at study start:

- NCI CTCAE version 4.0
- BMS-936558 (nivolumab) Investigational Brochure
- Pharmacy Binder
- Laboratory manuals for collection and handling of tissue specimens
- Site manual for operation of interactive voice response system (for study enrollment)
- Serious Adverse Event (or eSAE) case report forms
- Pregnancy Surveillance Forms
- PRO and HRU Training slides.

Each site will be provided with PRO and HRU questionnaires. Subjects will complete these at the time of the scheduled visits, prior to any study procedures and study drug infusion. During the survival follow-up period PRO and HRU questionnaires will be collected at X01 and X02. Beyond X02, the, FKSI-19, EQ-5D PRO as well as the HRU questionnaire will be administered at a frequency of every 3 months for the first 12 months, then every 6 months thereafter, as permitted by local IRB.

## **5.3 Safety Assessments**

### **5.3.1 Screening Assessments**

Screening assessments and procedures must be completed in accordance with [Table 5.1-1](#).

### **5.3.2 On-Study Safety Assessments and Procedures**

The following assessments will be monitored as specified in [Table 5.1-2](#) and [Table 5.1-3](#) and will continue at the specified frequency until discontinuation from the study.

- Assessment within 48 hours prior to dosing to include: targeted physical exam, performance status and weight. Oxygen saturation by pulse oximetry at rest and after exertion for patients who complain of dyspnea or other respiratory symptoms.
- Laboratory tests as indicated.

Concomitant medications taken throughout the study duration should be recorded within the eCRF.

For subjects who discontinue study treatment due to toxicity, please follow the procedures for follow-up visits from [Table 5.1-3](#).

### **5.3.3 Follow-up and Survival Procedures**

The Follow-Up Phase begins when the decision to discontinue a subject from study therapy is made (no further treatment with study therapy).

- Subjects who discontinue treatment for reasons other than tumor progression will continue to have tumor assessments every 8 weeks ( $\pm 1$  week) for the first 13 months from randomization, and every 12 weeks ( $\pm 1$  week) thereafter until documented tumor progression, death, lost to follow-up, or withdrawal of consent.
- Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All adverse events will be documented for a minimum of 100 days after last dose.
- After completion of the first two follow-up visits, subjects will be followed every 3 months for survival.

### **5.3.4 Imaging Assessment for the Study**

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

## **5.4 Efficacy Assessments**

### **5.4.1 Screening (Baseline visit) and On-Study Efficacy Assessments**

Study evaluations will take place in accordance with [Table 5.1-1](#) and [Table 5.1-2](#), according to RECIST 1.1 criteria.<sup>35</sup> High resolution CT with oral/intravenous contrast or contrast-enhanced MRI is the preferred imaging modalities for assessing radiographic tumor response. If a subject has a known allergy to contrast material, please use local prophylaxis standards to obtain the assessment with contrast if at all possible, or use the alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan will suffice. Screening assessments should be performed within 28 days of start of study treatment. Brain MRI is the preferred imaging method for evaluating CNS metastasis, and assessment is required during screening in all eligible subjects. All known or suspected sites of disease (including CNS) should be assessed at screening and at subsequent assessments using the same imaging method and technique. If more than one method is used at screening, then the most accurate method according to RECIST 1.1 should be used when recording data, and should again be used for all subsequent assessments. Bone scan, PET scan, or ultrasound imaging are not adequate for assessment of RECIST response. In selected circumstances where such modalities are the sole modality used to assess certain non-target organs, those 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. Previously treated CNS metastases are not considered measurable lesions for purposes of RECIST determined response. Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated.

Radiographic tumor assessments will be conducted at Week 8 ( $\pm 1$  week) and every 8 weeks ( $\pm 1$  week) for the first 13 months and then every 12 weeks ( $\pm 1$  week) until disease progression or treatment discontinuation whichever occurs later. Tumor assessments for all subjects should continue as per protocol even if dosing is interrupted. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Changes in tumor measurements and tumor responses to guide ongoing study treatment decisions will be assessed by the investigator using RECIST 1.1 (see [Appendix 1](#) for details of RECIST 1.1).

### 5.5 Pharmacokinetic Assessments

Not applicable.

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

### **5.7 Outcomes Research Assessments**

Patient reported outcomes will be captured through the use of 2 validated self-reported questionnaires: the NCCN Functional Assessment of Cancer Therapy- Kidney Symptom Index (FKSI-19) and the five dimension (EQ-5D) and visual analog scale (EQ-VAS).

The NCCN FKSI-19 is a 19-item scale that measures tumor specific HrQoL in kidney cancer patients. The FKSI-19 uses five Likert-type response categories that range from “not at all” to “very much”. Patients are asked to circle the response category that best characterizes their response over the last 7 days on 19 items that include symptoms such as lack of energy, fatigue, appetite, coughing, shortness of breath, pain, nausea and ability to work.

General health status will be measured using the EQ-5D. The EQ-5D is a standardized instrument for use as a measure of self-reported general health status. The EQ-5D comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety) and a visual analog rating scale (VAS). The utility data generated from the EQ-5D is recommended for and commonly used in health economics research analysis.

### **5.8 Other Assessments**

In addition, healthcare resource utilization (HRU) data (e.g., hospitalizations, non-protocol specified medical visits, etc) will be collected for all enrolled or treated subjects. Specifically, healthcare resource utilization 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.

### **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 preexisting medical condition in a clinical investigation subject administered study drug and that

does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal 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 Adverse Event (SAE)* is any untoward medical occurrence that at any dose:

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

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) 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).



Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see Section 6.1.1 for reporting details).

**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 an important medical or life-threatening event)
- 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 other than to remedy ill health and 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, caregiver respite, family circumstances, administrative reason).
- 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**

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited 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).

The investigator should report any SAE that occurs after these time periods and 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 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. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

**SAE Email Address:** Refer to Contact Information list.

**SAE Facsimile Number:** Refer to Contact Information list.

For studies capturing SAEs 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.

**SAE Telephone Contact** (required for SAE and pregnancy reporting): Refer to Contact Information list.

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

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

All SAEs should be followed to resolution or stabilization.

## **6.2 Nonserious Adverse Events**

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

### **6.2.1 Nonserious Adverse Event Collection and Reporting**

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

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 and for those 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).

All nonserious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

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

### **6.2.2 Adverse Events of Interest**

IMAEs are specific events occurring within 100 days of the last dose of study drug (which includes pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, and endocrine abnormalities [adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis]), regardless of causality, for which subjects received immunosuppressive medication for treatment of the event. The exception to the immunosuppressive medication criteria for IMAEs is endocrine events

(hypothyroidism/thyroiditis, hyperthyroidism, hypophysitis, diabetes mellitus, adrenal insufficiency), which are included regardless of treatment since these events are often managed without immunosuppression.

Per FDA guidance, IMAE analyses included events, regardless of causality, occurring within 100 days of the last dose. These analyses are limited to subjects who received immunosuppressive medication for treatment of the event, with the exception of endocrine events (hypothyroidism/thyroiditis, hyperthyroidism, hypophysitis, diabetes mellitus, adrenal insufficiency), which were included in the analysis regardless of treatment since these events are often managed without immunosuppression.

Table 6.2.2-1 provides a summary of the IMAEs category and their respective PTs.

**Table 6.2.2-1: Preferred Terms Included in Analysis of IMAEs to Support Warnings and Precautions**

IMAE Category	PTs included under IMAE Category
Pneumonitis	Pneumonitis, Interstitial lung disease
Diarrhea/Colitis	Diarrhea, Colitis, Enterocolitis
Hepatitis	Hepatotoxicity, Hepatitis, Hepatitis acute, Autoimmune hepatitis, AST increased, ALT increased, Bilirubin increased, ALP increased
Adrenal insufficiency	Adrenal insufficiency
Hypothyroidism/Thyroiditis	Hypothyroidism, Thyroiditis Thyroiditis acute (collapsed with thyroiditis for frequency), Autoimmune thyroiditis (collapsed with thyroiditis for frequency)
Hyperthyroidism	Hyperthyroidism
Hypophysitis	Hypophysitis
Diabetes mellitus	Diabetes mellitus, Diabetic ketoacidosis
Nephritis and renal dysfunction	Nephritis, Nephritis allergic, Tubulointerstitial nephritis, Acute renal failure, Renal failure, Increased creatinine
Rash	Rash, Rash maculopapular

### 6.3 Laboratory Test Result Abnormalities

The following laboratory test result 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 test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

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

#### **6.4 Pregnancy**

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours and in accordance with SAE reporting procedures described in [Section 6.1.1](#).

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug after a thorough discussion of benefits and risk with the subject

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

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

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

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

#### **6.5 Overdose**

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

#### **6.6 Potential Drug Induced Liver Injury (DILI)**

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

Potential drug induced liver injury is defined as:

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)  
AND

2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),  
AND
3. No other immediately apparent possible causes of 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, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

## **7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES**

Not applicable

## **8 STATISTICAL CONSIDERATIONS**

### **8.1 Sample Size Determination**

In general, for nivolumab monotherapy, the safety profile to date is similar across tumor types, while IMAEs of high grade (Grade 3-4) are rather uncommon. Their overall incidence was 6% in a previous Phase 1 trial that tested nivolumab at doses between 0.1 mg/kg to 10 mg/kg in 306 subjects with different recurrent or refractory malignancies (MDX-03).<sup>36,37</sup>

In order to further characterize the frequency and outcome of such apparently infrequent safety events, the current study will treat approximately 150 subjects with nivolumab. This sample size will allow for estimating an incidence rate of 0.67% (n=1 subject with events) with a 95% CI (confidence interval) of (0.02%, 3.7%), or an incidence rate of 2% (n=3 subjects with events) with a 95% CI of (0.4%, 5.7%). Furthermore, the sample size will allow for enough events to compare incidence in large community practice with historical adverse event data.

**Table 8.1-1: Estimated Incidence Rates and 95% CIs**

Sample Size	Incidence Rate (%)	Lower 95% CI (%)	Upper 95% CI (%)
150	0.67	0.02	3.66
150	1.0	0.16	4.73
150	2.0	0.41	5.73
150	5.0	2.33	10.24
150	10.0	5.71	15.96
150	11.0	6.74	17.52
150	12.0	7.27	18.30
150	13.0	8.34	19.84
150	14.0	8.88	20.60
150	15.0	9.98	22.11
150	16.0	10.53	22.86
150	17.0	11.65	24.36
150	18.0	12.21	25.10
150	19.0	13.35	26.57
150	20.0	13.92	27.30
150	21.0	15.07	28.76
150	22.0	15.65	29.49
150	23.0	16.82	30.93
150	24.0	17.41	31.65
150	25.0	18.59	33.07

The number of subjects who are evaluable for AEs in the study will be 150. We make the conservative assumption based on Motzer<sup>29</sup> that the rate of IMAEs of grades 3-5 is 13%. The primary goal of the present study is to address whether the rate is consistent with the rate reported in the Motzer study in the sense that the final 95% confidence interval is wholly less than 20%. As indicated in Table 8.1-1, this would happen if the observed rate is less than 13.3% or less (20/150 or fewer grade 3-5 IMAEs). The trial has 61% power to demonstrate consistency of rates in the sense that the probability is 61% of showing the upper bound of the 95% confidence interval is less than 20% when the true rate is 13%. The trial has 80% power to demonstrate the consistency of rates when the true rate is 11.5%

The observed rate may be somewhat larger than 13.3% and will still be consistent with expectations regarding safety, although it may raise concerns that the present population may be different from that of the Motzer study or that the assessment of AEs is different in the two studies. Only if the 95% confidence interval extends beyond 25% would the results of the study raise

serious safety concerns. This would happen if the observed rate is at least 18% (27/150 or more grade 3-5 STRAEs), see [Table 8.1-1](#). Again assuming that the true rate is 13%, the power of the study, the probability that the 95% confidence interval is wholly less than 25% (and so the observed rate is less or equal to 18%) is 95%. Also, if the true rate in the present study is actually 15%, the probability of showing that the 95% confidence interval is wholly less than 25% is 82%.

## 8.2 Populations for Analyses

- All enrolled subjects: all subjects who signed an informed consent form and were registered into the IVRS.
- All treated subjects: all subjects who received any nivolumab. This is the primary population for safety and efficacy analyses. Subpopulation analyses will be conducted for subjects in Groups 1-3.
- All response evaluable subjects: all treated subjects who have baseline and at least one on-study evaluable tumor measurement.

## 8.3 Endpoints

### 8.3.1 Primary Endpoint(s)

The primary objective of the study will be assessed by measuring the incidence for high grade (Grade 3-4 and Grade 5) IMAEs.

The IMAEs of interest are the following: skin, endocrinopathy, gastrointestinal, hepatic, renal, pulmonary, and neurologic adverse events.

### 8.3.2 Secondary Endpoint(s)

The secondary objective of the study will be assessed by measuring the following:

- median time to onset, median time to resolution of high grade (Grade 3-4) IMAEs
- percentage of subjects who received immune modulating medication (e.g. corticosteroids, infliximab, cyclophosphamide, IVIG, and mycophenolate mofetil), or hormonal replacement therapy, the percentage of subjects who received  $\geq 40$  mg prednisone equivalents, total duration of all immune modulating medications given for the IMAE and summary of subjects with resolution of AES after initiating these therapies.

[REDACTED]

- [REDACTED]
- █ [REDACTED]
- █ [REDACTED]
- █ [REDACTED]
- █ [REDACTED]
- █ [REDACTED]

## **8.4 Analyses**

### **8.4.1 Demographics and Baseline Characteristics**

Demographics, baseline disease characteristics and baseline laboratory results will be summarized using descriptive statistics for all treated subjects and all subjects in Groups 1, 2, and 3.

### **8.4.2 Primary Analyses**

The number and percentage of subjects who report high grade (Grade 3-4 and Grade 5) IMAEs will be summarized for all treated subjects. High grade (Grade 3-4 and Grade 5) IMAEs will be tabulated using worst grade per NCI CTCAE v4.0 criteria by system organ class and Medical Dictionary for Regulatory Affairs (MedDRA) preferred term.







## **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
- BMS
- 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 done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

#### **9.1.2 Monitoring**

BMS representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

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

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.

### **9.1.2.1 Source Documentation**

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

### **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 BMS, 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 study drug (inventoried and dispensed) is maintained at the study site to include investigational product and the following non-investigational product(s). 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 identification 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 BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS 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 that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

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 BMS.

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 the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. 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 BMS. 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 as appropriate based on the following criteria:

- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS'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 BMS 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. BMS 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
Complete Abstinence	<p>If one form of contraception is required, Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.</p> <p>If two forms of contraception is required, Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.</p> <p><b>Expanded definition</b> Complete abstinence as defined as complete avoidance of heterosexual intercourse is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (e.g., calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence</p>

**11 LIST OF ABBREVIATIONS**

<b>Term</b>	<b>Definition</b>
ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AT	aminotransaminases
β-HCG	beta-human chorionic gonadotrophin
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
Ca <sup>++</sup>	calcium
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
Cl <sup>-</sup>	chloride
CLcr	creatinine clearance
CLR	renal clearance
CLT	total body clearance
cm	centimeter
CNS	Central nervous system
CRC	Clinical Research Center
CRF	Case Report Form, paper or electronic
CYP	cytochrome p-450
D/C	discontinue
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4th Edition)
ECG	electrocardiogram
eCRF	Electronic Case Report Form
eg	exempli gratia (for example)



<b>Term</b>	<b>Definition</b>
ESR	Expedited Safety Report
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
g	gram
GCP	Good Clinical Practice
GFR	glomerular filtration rate
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCO <sub>3</sub> <sup>-</sup>	bicarbonate
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IMAE	immune-mediated adverse event
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
IU	International Unit
IV	intravenous
K <sup>+</sup>	potassium
kg	kilogram
L	liter
LC	liquid chromatography
LDH	lactate dehydrogenase
MDSC	myeloid-derived suppressor cell

<b>Term</b>	<b>Definition</b>
mg	milligram
Mg <sup>++</sup>	magnesium
min	minute
mL	milliliter
mmHg	millimeters of mercury
mTOR	mechanistic target of rapamycin
MTD	maximum tolerated dose
µg	microgram
N	number of subjects or observations
Na <sup>+</sup>	sodium
N/A	not applicable
ng	nanogram
NIMP	non-investigational medicinal products
NSAID	nonsteroidal anti-inflammatory drug
PBMC	peripheral blood mononuclear cell
PO	per os (by mouth route of administration)
PRO	patient reported outcomes
QD, qd	quaque die, once daily
RBC	red blood cell
SAE	serious adverse event
SD	standard deviation
SOP	Standard Operating Procedures
Subj	subject
t	temperature
T	time
TAO	Trial Access Online, the BMS implementation of an EDC capability
TID, tid	ter in die, three times a day
UV	ultraviolet
VEGF	vascular endothelial growth factor
VHL	Von Hippel–Lindau (tumor suppressor gene)

<b>Term</b>	<b>Definition</b>
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
x g	times gravity









































































