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Date 14-Oct-2016
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# Clinical Protocol CA209920

Phase 3b/4 Safety Trial of Nivolumab Combined with Ipilimumab in Subjects with Previously Untreated, Advanced or Metastatic RCC

**CheckMate 920: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 920**

**Revised Protocol Number: 02**
**Incorporates Administrative Letters 01, 02, and 03**

**Study Director/Medical Monitor**
Joshua Zhang

**to partners to which BMS has transferred obligations, e.g., a Contract Research Organization (CRO).**

## DOCUMENT HISTORY

| Document | Date of Issue | Summary of Change |
|---|---|---|
| Revised Protocol 02 | 18-Dec-2019 | [redacted]<br>Medical Monitor Change<br>Incorporates Administrative Letter 03 |
| Administrative Letter 03 | 04-Sep-2018 | [redacted] |
| Administrative Letter 02 | 13-Feb-2018 | Medical Monitor Change |
| Administrative Letter 01 | 03-Nov-2017 | Medical Monitor change |
| Revised Protocol 01 | 24-Feb-2017 | Incorporates Amendment 01 |
| Amendment 01 | 24-Feb-2017 | • To modify the criteria for eligible patients with brain metastases and to clarify the assessment of target/non-target brain lesions.<br>• To align protocol with most recent program standards for nivolumab<br>• To correct inconsistences and minor grammatical errors |
| Original Protocol | 14-Oct-2016 | Not Applicable |

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# 1 SYNOPSIS

**Protocol Title: Phase 3b/4 Safety Trial of Nivolumab Combined with Ipilimumab in Subjects with Previously Untreated, Advanced or Metastatic RCC**

**Study Phase:** 3b/4

[redacted]

**Key Exclusion Criteria**

- Prior systemic treatment in the metastatic setting with VEGF or VEGF receptor targeted therapy (including, but not limited to, sunitinib, pazopanib, axitinib, tivozanib, bevacizumab, cabozantinib, and lenvantinib).
- Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti CTLA 4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways. This includes the utilization of these agents in the neo-adjuvant or adjuvant setting.
- Any active or recent history of a known or suspected autoimmune disease or recent history of a syndrome that required systemic corticosteroids (> 10 mg daily prednisone equivalent) or immunosuppressive medications except for syndromes which would not be expected to recur in the absence of an external trigger. Participants with vitiligo or type I diabetes mellitus or residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement are permitted to enroll.
- 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 > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
- Uncontrolled adrenal insufficiency
- 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.
- Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS) as per local requirements.

- Any positive test for hepatitis B or hepatitis C virus indicating acute or chronic infection.
- Known medical condition (eg, a condition associated with diarrhea or acute diverticulitis) that, in the investigator's opinion, would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results.
- Major surgery (eg, nephrectomy) less than 28 days prior to the first dose of study drug.
- Anti-cancer therapy less than 28 days prior to the first dose of study drug or palliative, focal radiation therapy less than 14 days prior to the first dose of study drug.
- Presence of any toxicities attributed to prior anti-cancer therapy, other than alopecia, that have not resolved to Grade 1 (NCI CTCAE v4) or baseline before administration of study drug.
- Any of the following laboratory test findings:
  i) WBC < 2,000/$mm^3$

  ii) Neutrophils < 1,500/$mm^3$

  iii) Platelets < 100,000/$mm^3$

  iv) AST or ALT > 3 x ULN (> 5 x ULN if liver metastases are present)

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

  vi) Serum creatinine > 1.5 x upper limit of normal (ULN) or creatinine clearance < 40 mL/min (measured or calculated by Cockroft-Gault formula)

**Objectives and Endpoints:**

**Table 1.-1: Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To assess the incidence of high grade (CTCAE v4 Grade 3-4 and Grade 5) IMAEs in participants with advanced or metastatic RCC who are treated with combination therapy of nivolumab 6 mg/kg + ipilimumab 1 mg/kg every 8 weeks alternating with nivolumab 480 mg flat dose every 8 weeks, staggered every 4 weeks (**Cohort 1**)<br>• To assess the incidence of high grade (CTCAE v4 Grade 3-4 and Grade 5) IMAEs in participants with advanced or metastatic RCC who are treated with combination nivolumab (3 mg/kg) and ipilimumab (1 mg/kg) every 3 weeks for four doses, followed by maintenance nivolumab (480 mg every 4 weeks), in the select subgroups of mRCC participants (nccRCC, asymptomatic brains metastasis, or any histology with KPS 50-60% (**Cohorts 2, 3, 4**) | • Incidence of high grade (CTCAE v4 Grade 3-4 and Grade 5) IMAEs |

**Table 1.-1: Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| **Secondary** | |
| • To characterize the outcome of all high grade (CTCAE v4 Grade 3-4 and Grade 5) IMAEs in participants with advanced or metastatic RCC who are treated with combination therapy in different cohorts. | • Characterization of outcome of all high grade (CTCAE v4 Grade 3-4 and Grade 5) IMAEs (eg, time to onset, time to resolution, percentage of patients who received immune modulating medication) |
| • To assess efficacy of nivolumab in combination with ipilimumab by measuring, progression-free survival (PFS 1 at time of initial progression; objective response rate (ORR), time to response (TTR), and duration of response (DOR), in all treated participants in different cohorts using RECIST 1.1. | • PFS 1, ORR, TTR, DOR, |
| [redacted] | [redacted] |

**Overall Design:**

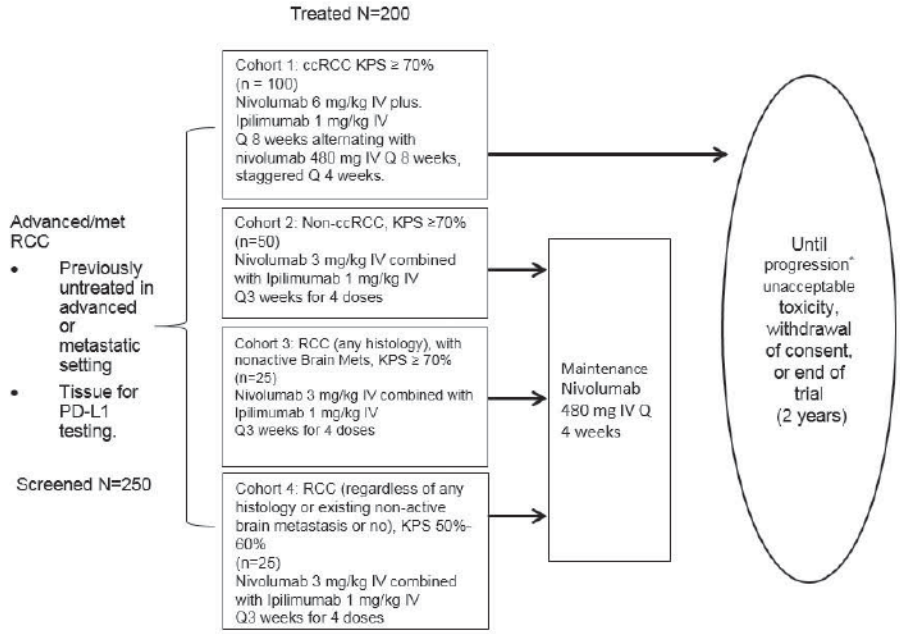
This will be a Phase 3b/4, open-label, study of first-line combination therapy (nivolumab/ipilimumab) in participants with previously untreated, advanced or metastatic RCC. Participants will be assigned to 1 of the 4 cohorts (Figure 1).

Treatment in all cohorts will continue until progression, unacceptable toxicity, withdrawal of consent, or end of trial. Treatment period will last for up to 2 years. The study will continue until

the last enrolled participant completes 5 years of survival follow up from LPFT. Participants will be permitted to continue treatment beyond progressive disease (PD) (RECIST 1.1) under protocol-defined circumstances (See Section 7.9). No dose increases or reductions will be allowed for nivolumab or ipilimumab.

The study design schematic is presented in Figure 1.

**Figure 1: Study Design Schematic**




Abbreviations: ccRCC, clear-cell renal cell carcinoma, KPS, Karnofsky performance score; RCC, renal cell carcinoma; Q, every.

Note: All participant numbers above are approximate. Enrollment of participants with a favorable risk score per IMDC Prognostic Criteria will be capped at 25% of Cohort 1. If the number of participants in Cohorts 3 and 4 cannot be reached, the number of patients enrolled in the clear-cell or non-clear cell cohorts may be increased.

Nivolumab maintenance in Cohort 2-4 to begin 6 weeks after last combination dose.

*The study will continue until the last enrolled participant completes 5 years of follow up from LPFT. The treatment period duration is a maximum of 2 years. Participants will be permitted to continue treatment beyond PD (RECIST 1.1) under protocol defined circumstances (if investigator-assessed clinical benefit is achieved, treatment is well-tolerated, and participant has stable PS, etc.)

### Number of Participants:

The sample size of the study is mainly determined by feasibility. The study plans to enroll approximately 250 participants, 200 will plan to get treatment, Approximate participant numbers are: 100 in Cohort 1, 50 in Cohort 2, 25 in Cohort 3, and 25 in Cohort 4 (100 in Cohort 1 and 100 in Cohorts 2-4 combined). The number of participants in Cohort 1 with a favorable risk score per IMDC prognostic criteria (no adverse prognostic factor present) will be capped at 25%.

### Treatment Arms and Duration:

- **Cohort 1:** Participants in Cohort 1 will receive nivolumab 6 mg/kg plus ipilimumab 1 mg/kg every 8 weeks. Beginning on Day 1 Week 5, participants will receive nivolumab (480 mg) as

a flat dose every 8 weeks. Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent, or end of trial (2 years), whichever comes first.

- **Cohorts 2, 3, and 4**: Participants in Cohorts 2, 3, and 4 will receive nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks, for up to 4 doses. Beginning Cycle 3, 6 weeks following last dose of combination therapy participants will then begin treatment with nivolumab (480 mg) every 4 weeks (± 3 days) as maintenance therapy until disease progression, unacceptable toxicity, withdrawal of consent, or end of trial (2 years). whichever comes first.

**Study treatment:**

| Study Drug for CA209920 | | |
|---|---|---|
| **Medication** | **Potency** | **IP/Non-IP** |
| BMS-936558-01 (Nivolumab) Solution for Injection | 100 mg (10 mg/mL) | IP |
| Ipilimumab Solution for Injection | 200 mg (5 mg/mL) | IP |

# 2 SCHEDULE OF ACTIVITIES

**Table 2-1: Screening Assessments (All Participants)**

| Procedure | Screening Visit[a] | Notes |
|---|---|---|
| **Eligibility Assessments** | | |
| Informed Consent | X | Obtain consent prior to performing any testing for eligibility |
| IWRS | X | An IWRS will be used to assign participant numbers |
| Inclusion/Exclusion Criteria | X | |
| Medical History | X | |
| Tumor Tissue Samples | X | Sufficient tumor tissue, archival or recent acquisition, (block or minimum of 10 slides; obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen) available to be received at Central Laboratory. |
| **Safety Assessments** | | |
| Physical Examination | X | |
| Vital Signs | X | Including BP, HR, and temperature. Obtain at the screening visit and within 72 hours prior to first dose |
| Physical Measurements (including performance status) | X | Height and weight and Karnofsky Performance Status. |
| ECG | X | Within 28 days prior to first dose |
| Serious Adverse Event Assessment | X | SAE assessment from the time of consent. |
| Assessment of Signs and Symptoms | X | Within 14 days prior to first dose |
| Concomitant Medication Collection | X | Within 14 days prior to first dose |
| Laboratory Tests | X | CBC with differential, Chemistry panel including LDH, AST, ALT, ALB, ALP, T Bili, BUN or serum urea level, creatinine, Mg, Ca, Na, K, Cl, Glucose, amylase, lipase, TSH, Free T4, Free T3, hepatitis B surface antigen (HBVsAg), and hepatitis C antibody (HCV Ab) or hepatitis C RNA (HCV RNA), within 14 days of first dose. |
| Pregnancy Test (WOCBP Only) | X | Within 24 hours prior to first dose (serum or urine at the site). |

**Table 2-1: Screening Assessments (All Participants)**

| Procedure | Screening Visit[a] | Notes |
|---|---|---|
| **Efficacy Assessment** | | |
| Screening/Baseline Tumor Assessments | X | CT/MRI of the chest, abdomen, pelvis and all known sites of disease and MRI (preferred) or CT contrast-enhanced scan of the Brain within 28 days prior to first dose.<br>CT with oral and intravenous contrast or contrast-enhanced MRI are the preferred imaging modalities.<br>If CT iodinated contrast is contraindicated, a non-contrast CT of the chest, and contrast enhanced MRI abdomen, pelvis and all other known or suspected sites of disease should be imaged. (See Section 7.7.2.3). |

[a] Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

**Table 2-2: On-study Assessments[a] (Cohort 1)**

| Procedure | 1 Cycle = 8 weeks<br>If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs. | | | | | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|
| | Day 1 Week 1 | Day 1 Week 2 | Day 1 Week 3 | Day 1 Week 4 | Day 1 Week 5 | Day 1 Week 6 | Day 1 Week 7 | Day 1 Week 8 | |
| **Safety Assessments** | | | | | | | | | |
| Targeted Physical Examination | X | | | | X | | | | To be performed only as clinically indicated within 72 hours prior to dosing. |
| Vital Signs | X | | | | X | | | | Including BP, HR, and temperature, |
| Physical Measurements (including performance status) | X | | | | X | | | | Weight and KPS within 72 hours prior to dosing |
| Adverse Events Assessment | Continuously | | | | | | | | |
| Review of Concomitant Medications | X | | | | X | | | | |
| Laboratory Tests | X | | | | X | | | | Within 72 hours prior to dosing to include CBC w/ differential, ALB, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH (with reflexive Free T4 and Free T3). Note: C1W1D1 labs do not need to be repeated if they were performed within 14 days of dosing. |

**Table 2-2: On-study Assessments[a] (Cohort 1)**

| Procedure | 1 Cycle = 8 weeks<br>If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs. | | | | | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|
| | Day 1 Week 1 | Day 1 Week 2 | Day 1 Week 3 | Day 1 Week 4 | Day 1 Week 5 | Day 1 Week 6 | Day 1 Week 7 | Day 1 Week 8 | |
| Pregnancy Test (WOCBP Only) | X | | | | X | | | | Within 24 hours prior to administration of first dose of study drug and thereafter Every 4 weeks independent of study drug dosing. Serum or Urine |
| Immunogenicity blood samples | See Table 9.5-1 for a detailed schedule of PK and immunogenicity evaluations for nivolumab and ipilimumab (**Cohort 1 Only**) | | | | | | | | |
| [redacted] | | | | | | | | | |
| [redacted] | [redacted] | | | | | | | | |
| [redacted] | [redacted] | | | | | | | | |
| [redacted] | [redacted] | | | | [redacted] | | | | [redacted] |
| [redacted] | [redacted] | | | | | | | | [redacted] |
| [redacted] | [redacted] | | | | [redacted] | | | | [redacted] |

**Table 2-2: On-study Assessments[a] (Cohort 1)**

| Procedure | 1 Cycle = 8 weeks<br>If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs. | | | | | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|
| | Day 1 Week 1 | Day 1 Week 2 | Day 1 Week 3 | Day 1 Week 4 | Day 1 Week 5 | Day 1 Week 6 | Day 1 Week 7 | Day 1 Week 8 | |
| [redacted] | | | | | | | | | |
| [redacted] | [redacted] | | | | | | | | |
| [redacted] | | | | | | | | | |
| [redacted] | [redacted] | | | | | | | | |
| [redacted] | | | | | | | | | |
| [redacted] | [redacted] | | | | | | | | [redacted] |

**Table 2-2: On-study Assessments[a] (Cohort 1)**

| Procedure | 1 Cycle = 8 weeks<br>If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs. | | | | | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|
| | Day 1 Week 1 | Day 1 Week 2 | Day 1 Week 3 | Day 1 Week 4 | Day 1 Week 5 | Day 1 Week 6 | Day 1 Week 7 | Day 1 Week 8 | |
| Administer Nivolumab | X (6 mg/kg) | | | | X (480 mg flat) | | | | First dose to be administered within 5 days following vial assignment. Subsequent doses may be administered within 3 days of the scheduled date if necessary. Nivolumab is 6 mg/kg when given in combination with ipilimumab. When nivolumab is given alone, a 480 mg flat dose is administered, |
| Administer Ipilimumab | X (1 mg/kg) | | | | | | | | |
| [redacted] | | | | | | | | | |
| [redacted] | [redacted] | | | | [redacted] | | | | [redacted] |
| [redacted] | [redacted] | | | | [redacted] | | | | [redacted] |
| [redacted] | [redacted] | | | | [redacted] | | | | |

[a] Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

**Table 2-3: On-study Assessments[a] Cycles 1 and 2 (Cohort 2, 3, and 4)**

| Procedure | Cycle 1 and Cycle 2 (1 Cycle = 6 weeks) If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs. | | | | | | Notes |
|---|---|---|---|---|---|---|---|
| | Day 1 Week 1 | Day 1 Week 2 | Day 1 Week 3 | Day 1 Week 4 | Day 1 Week 5 | Day 1 Week 6 | |
| **Safety Assessments** | | | | | | | |
| Targeted Physical Examination | X | | | X | | | To be performed only as clinically indicated within 72 hours prior to dosing. |
| Vital Signs | X | | | X | | | Including BP, HR, and temperature |
| Physical Measurements (including performance status) | X | | | X | | | Weight and KPS within 72 hours prior to dosing |
| Adverse Events Assessment | Continuously | | | | | | |
| Review of Concomitant Medications | X | | | X | | | |
| Laboratory Tests | X | | | X | | | Within 72 hours prior to dosing to include CBC w/ differential, ALB, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH (with reflexive Free T4 and Free T3). Note: C1W1D1 labs do not need to be repeated if they were performed within 14 days of dosing. |
| Pregnancy Test (WOCBP Only) | X | | | X | | | Within 24 hours prior to administration of first dose of study drug and thereafter every 4 weeks independent of study drug dosing. Serum or Urine |

**Table 2-3: On-study Assessments[a] Cycles 1 and 2 (Cohort 2, 3, and 4)**

| Procedure | Cycle 1 and Cycle 2 (1 Cycle = 6 weeks) If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs. | | | | | | Notes |
|---|---|---|---|---|---|---|---|
| | Day 1 Week 1 | Day 1 Week 2 | Day 1 Week 3 | Day 1 Week 4 | Day 1 Week 5 | Day 1 Week 6 | |
| [redacted] | | | | | | | |
| [redacted] | | | | | | | |
| [redacted] | | | | | | | |
| [redacted] | | | | | | | |
| [redacted] | | | | | | | |
| **Efficacy Assessments** | | | | | | | |
| Tumor Assessments | FIRST tumor assessment should be performed at Week 12 (±1 week) following first dose.<br>SUBSEQUENT tumor assessments should occur every 8 weeks (± 1 week) up to first 13 months, then every 12 weeks until disease progression or treatment discontinuation, whichever comes later.<br>CT/MRI of the chest, abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline.<br>CT with oral and intravenous contrast or contrast-enhanced MRI are the preferred imaging modalities.<br>If CT iodinated contrast is contraindicated, a non-contrast CT of the chest, and contrast enhanced MRI abdomen, pelvis and all other known or suspected sites of disease should be imaged. (See Section 7.7.2.3).<br>Participants with a history of brain metastasis perform surveillance CT/MRI approximately every 12 weeks, or sooner if clinically indicated.<br>**Tumor assessments will be performed at Weeks 12, 20, 28, 36 etc. (± 1 week) following first dose, up to first 13 months, and then every 12 weeks. These time points are independent of dosing.** | | | | | | |
| **Clinical Drug Supplies** | | | | | | | |
| IWRS- | Y | | | | | | Y=Only for cycle 1 |

**Table 2-3: On-study Assessments[a] Cycles 1 and 2 (Cohort 2, 3, and 4)**

| Procedure | Cycle 1 and Cycle 2 (1 Cycle = 6 weeks) If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs. | | | | | | Notes |
|---|---|---|---|---|---|---|---|
| | Day 1 Week 1 | Day 1 Week 2 | Day 1 Week 3 | Day 1 Week 4 | Day 1 Week 5 | Day 1 Week 6 | |
| Administer Nivolumab (3 mg) and Ipilimumab (1 mg) | X | | | X | | | First dose to be administered within 5 days following vial assignment. Subsequent doses may be administered ± 3 days of the scheduled date if necessary. |
| [redacted] | | | | | | | |
| [redacted] | [redacted] | | | [redacted] | | | [redacted] |
| [redacted] | [redacted] | | | [redacted] | | | [redacted] |
| [redacted] | [redacted] | | | [redacted] | | | |

[a] Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

| Table 2-4: | On-study Assessments[a] Cycle 3 and Beyond Maintenance (Cohort 2, 3 and 4) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Procedure** | **Maintenance Therapy Nivolumab 480 mg every 4 weeks<br>1 cycle = 8 weeks<br>If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs.** | | | | | | | | **Notes** |
| | **Day 1 Week 1** | **Day 1 Week 2** | **Day 1 Week 3** | **Day 1 Week 4** | **Day 1 Week 5** | **Day 1 Week 6** | **Day 1 Week 7** | **Day 1 Week 8** | |
| **Safety Assessments** | | | | | | | | | |
| Targeted Physical Examination | X | | | | X | | | | To be performed only as clinically indicated within 72 hours prior to dosing |
| Vital Signs | X | | | | X | | | | Including BP, HR, and temperature |
| Physical Measurements (including performance status) | X | | | | X | | | | Weight and KPS within 72 hours prior to dosing. |
| Adverse Events Assessment | Continuously | | | | | | | | |
| Review of Concomitant Medications | X | | | | X | | | | |
| Laboratory Tests | X | | | | X | | | | Within 72 hours prior to re-dosing to include CBC w/ differential, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine. Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH (with reflexive Free T4 and Free T3) |
| Pregnancy Test (WOCBP Only) | X | | | | X | | | | Within 24 hours prior to first dose for WOCBP only, and Q 4 weeks |

| Table 2-4: | On-study Assessments[a] Cycle 3 and Beyond Maintenance (Cohort 2, 3 and 4) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Procedure** | **Maintenance Therapy Nivolumab 480 mg every 4 weeks<br>1 cycle = 8 weeks<br>If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs.** | | | | | | | | **Notes** |
| | **Day 1 Week 1** | **Day 1 Week 2** | **Day 1 Week 3** | **Day 1 Week 4** | **Day 1 Week 5** | **Day 1 Week 6** | **Day 1 Week 7** | **Day 1 Week 8** | |
| | | | | | | | | | thereafter, independent of drug dosing (serum or urine at the site). |
| [redacted] | | | | | | | | | |
| [redacted] | | | | | | | | | |
| [redacted] | | | | | | | | | |
| [redacted] | | | | | | | | | |
| **Efficacy Assessments** | | | | | | | | | |
| Tumor Assessments | FIRST tumor assessment should be performed at Week 12 (± 1 week) following first dose.<br>SUBSEQUENT tumor assessments should occur every 8 weeks (± 1 week) up to first 13 months, then every 12 weeks until disease progression or treatment discontinuation, whichever comes later.<br>CT/MRI of the chest, abdomen, ppelvis and all known sites of disease. Use same imaging method as was used at screening/baseline.<br>CT with oral and intravenous contrast or contrast-enhanced MRI are the preferred imaging modalities.<br>If CT iodinated contrast is contraindicated, a non-contrast CT of the chest, and contrast enhanced MRI abdomen, pelvis and all other known or suspected sites of disease should be imaged. (See Section 7.7.2.3).<br>Participants with a history of brain metastasis perform surveillance CT/MRI approximately every 12 weeks, or sooner if clinically indicated.<br>**Tumor assessments will be performed at Weeks 12, 20, 28, 36 etc. (± 1 week) following first dose, up to first 13 months, and then every 12 weeks. These time points are independent of dosing.** | | | | | | | | |

| Table 2-4: | On-study Assessments[a] Cycle 3 and Beyond Maintenance (Cohort 2, 3 and 4) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Procedure** | **Maintenance Therapy Nivolumab 480 mg every 4 weeks<br>1 cycle = 8 weeks<br>If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs.** | | | | | | | | **Notes** |
| | **Day 1 Week 1** | **Day 1 Week 2** | **Day 1 Week 3** | **Day 1 Week 4** | **Day 1 Week 5** | **Day 1 Week 6** | **Day 1 Week 7** | **Day 1 Week 8** | |
| **Clinical Drug Supplie** | | | | | | | | | |
| Administer Nivolumab 480 mg | X | | | | X | | | | Cycle 3 dosing to begin 6 weeks ± 3 days after last dose in Cycle 2. Subsequent doses may be administered within 3 days of the scheduled date if necessary. |
| [redacted] | | | | | | | | | |
| [redacted] | [redacted] | | | | [redacted] | | | | [redacted] |
| [redacted] | [redacted] | | | | [redacted] | | | | [redacted] |
| [redacted] | [redacted] | | | | [redacted] | | | | |

[a] Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

**Table 2-5: Follow-up Assessments (All Participants)**

| Procedure | Follow-Up[a] Visits 1 and 2 | Survival[b], Follow-up Visits | Notes |
|---|---|---|---|
| **Safety Assessments** | | | |
| Targeted Physical Examination | X | | To assess for potential late emergent study drug related issues |
| Adverse Events Assessment | X | X* | *Beyond 100-114 days from the last dose of study therapy, participants 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 | | On site/local CBC w/differential, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine and TSH for X01, repeat at X02 if study drug related toxicity persists. |
| Pregnancy Test (WOCBP Only) | X | | Serum or urine |
| Review of Concomitant Medication | X | | |
| [redacted] | | | |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | | [redacted] |
| [redacted] | [redacted] | | [redacted] |
| **Survival Status** | | | |
| 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,, to include subsequent anti-cancer therapy |

| Table 2-5: Follow-up Assessments (All Participants) | | | |
|---|---|---|---|
| **Procedure** | **Follow-Up[a] Visits 1 and 2** | **Survival[b], Follow-up Visits** | **Notes** |
| **Efficacy Assessments** | | | |
| Tumor Assessments | FIRST tumor assessment should be performed at Week 12 (± 1 week) following first dose.<br>SUBSEQUENT tumor assessments should occur every 8 weeks (± 1 week) up to first 13 months, then every 12 weeks until disease progression or treatment discontinuation, whichever comes later.<br>CT/MRI of the chest, abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline.<br>CT with oral and intravenous contrast or contrast-enhanced MRI are the preferred imaging modalities.<br>If CT iodinated contrast is contraindicated, a non-contrast CT of the chest, and contrast enhanced MRI abdomen, pelvis and all other known or suspected sites of disease should be imaged. (See Section 7.7.2.3).<br>Participants with a history of brain metastasis perform surveillance CT/MRI approximately every 12 weeks, or sooner if clinically indicated.<br>**Tumor assessments will be performed at Weeks 12, 20, 28, 36 etc. (± 1 week) following first dose, up to first 13 months, and then every 12 weeks. These time points are independent of dosing.** | | |
| [redacted] | | | |
| [redacted] | [redacted] | | |

[a] Participants must be followed for at least 100 days after last dose of study treatment. Follow-up visit 1 (FU1) should occur 30 days from the last dose (+/- 7) days or can be performed on the date of discontinuation if that date is greater than 42 days from last dose. Follow-up visit #2 (FU2) occurs approximately 100 days (± 7 days) from last dose of study drug. Both Follow Up visits should be conducted in person.

[b] Survival Follow-up visits to occur every 3 months (+/- 14 days) from Follow-up Visit 2. Survival visit may be conducted in person or by telephone. BMS may request that survival data be collected on all treated participants outside of the 3 month specified window. At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contact.

Note: Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

[redacted]

[redacted]

# 4 OBJECTIVES AND ENDPOINTS

**Table 4-1: Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To assess the incidence of high grade (CTCAE v4 Grade 3-4 and Grade 5) IMAEs in participants with advanced or metastatic RCC who are treated with combination therapy of nivolumab 6 mg/kg + ipilimumab 1 mg/kg every 8 weeks alternating with nivolumab 480 mg flat dose every 8 weeks, staggered every 4 weeks (**Cohort 1**) | • incidence of high grade (CTCAE v4 Grade 3-4 and Grade 5) IMAEs |
| • To assess the incidence of high grade (CTCAE v4 Grade 3-4 and Grade 5) IMAEs in participants with advanced or metastatic RCC who are treated with combination nivolumab (3 mg/kg) and ipilimumab (1 mg/kg) every 3 weeks for four doses, followed by maintenance nivolumab (480 mg every 4 weeks), in the select subgroups of mRCC participants (nccRCC, asymptomatic brains metastasis, or any histology with KPS 50-60% (**Cohorts 2, 3, 4**) | |
| **Secondary** | |
| • To characterize the outcome of all high grade (CTCAE v4 Grade 3-4 and Grade 5) IMAEs in participants with advanced or metastatic RCC who are treated with combination therapy in different cohorts. | • Characterization of outcome of all high grade (CTCAE v4 Grade 3-4 and Grade 5) IMAEs (eg, time to onset, time to resolution, percentage of patients who received immune modulating medication) |
| • To assess efficacy of nivolumab in combination with ipilimumab by measuring, progression-free survival (PFS 1 at time of initial progression; objective response rate (ORR), time to response (TTR), and duration of response (DOR), in all treated participants in different cohorts using RECIST 1.1. | • PFS 1, ORR, TTR, DOR |

**Table 4-1: Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| [redacted] | [redacted] |

# 5 STUDY DESIGN

## 5.1 Overall Design

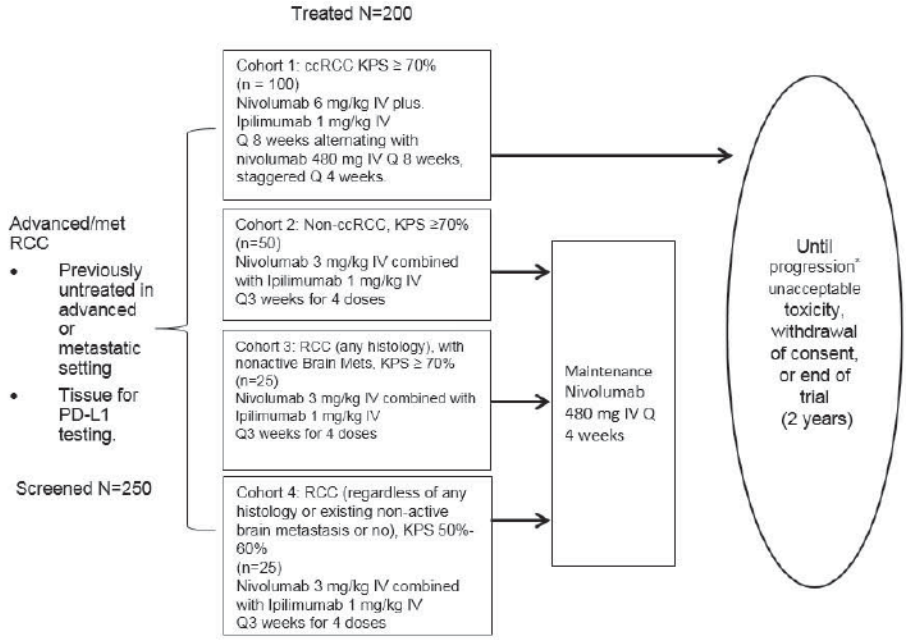
This will be a Phase 3b/4, open-label, study of first-line combination therapy (nivolumab/ipilimumab) in participants with previously untreated, advanced or metastatic RCC. Participants will be assigned to 1 of the 4 cohorts (Figure 5.1-1).

Treatment in all cohorts will continue until progression, unacceptable toxicity, withdrawal of consent, or end of trial. Treatment period will last for up to 2 years. The study will continue until the last enrolled participant completes 5 years of survival follow up from LPFT. Participants will be permitted to continue treatment beyond PD (RECIST 1.1) under protocol-defined circumstances (See Section 7.9). No dose increases or reductions will be allowed for nivolumab or ipilimumab.

Participants in any cohort, who discontinue combination therapy early due to an adverse event, may be eligible to receive nivolumab monotherapy (480 mg every 4 weeks), contingent upon discussion with, and approval by the Medical Monitor.

- The study design schematic is presented in Figure 5.1-1.

**Figure 5.1-1: Study Design Schematic**




Abbreviations: ccRCC, clear-cell renal cell carcinoma, KPS, Karnofsky performance score; RCC, renal cell carcinoma; Q, every.

Note: All participant numbers above are approximate. Enrollment of participants with a favorable risk score per IMDC Prognostic Criteria will be capped at 25% of Cohort 1. If the number of participants in Cohorts 3 and 4 cannot be reached, the number of patients enrolled in the clear-cell or non-clear cell cohorts may be increased.

Nivolumab maintenance in Cohort 2-4 to begin 6 weeks after last combination dose.

*The study will continue until the last enrolled participant completes 5 years of follow up from LPFT. The treatment period duration is a maximum of 2 years. Participants will be permitted to continue treatment beyond PD (RECIST 1.1) under protocol defined circumstances (if investigator-assessed clinical benefit is achieved, treatment is well-tolerated, and participant has stable PS, etc.)

### *5.1.1 Data Monitoring Committee and Other External Committees*

A Scientific Steering Committee (SSC) comprised of clinical experts in RCC will closely review the safety data throughout the study, especially for the special mRCC patient groups (Cohort 2, 3, and 4). The safety review plan will include, but not be limited to the following frequency. Additional reviews may be triggered on an ad hoc basis by the BMS CA209920 study team.

Safety review for all treated patients will take place, when any of the following criteria are satisfied:

- When a minimum of 5 patients with KPS of 50-60% in Cohort 4 have received at least two doses of combination therapy on study to assess safety and evaluate further enrollment into cohort 4,

  **OR**

- When a minimum of 10 patients in Cohort 2-4 have received at least two doses of combination therapy on study to assess safety and efficacy and evaluate further enrollment into the cohorts.

**OR**

- When a minimum of 25 patients in Cohort 1 have received at least two doses of combination therapy on study to assess safety and efficacy and evaluate further enrollment into Cohort 1.

According to the results of previous reviews, further monitoring and subsequent assessments and evaluation of safety and efficacy will be conducted according to the judgement of the BMS CA209920 study team, and data will be provided.

The following safety data will be provided for safety review:

- Treatment-related adverse events with focus on:
  - Drug-related SAEs in all cohorts
  - Immune-mediated adverse events all grades, in all cohorts
  - AEs leading to discontinuation
  - All treatment related deaths
- KPS over time

## 5.2 Number of Participants

This study will plan to have an -1-year enrollment period and 250 participants are expected to be screened. The approximate number of participants to be treated per cohort are 100, 50, 25, and 25 in Cohorts 1, 2, 3, and 4, respectively. The total number of participants treated on study is anticipated to be 200.

## 5.3 End of Study Definition

The start of the trial is defined as first participant first screening visit. End of trial is defined as last participant last visit. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

[redacted]

[redacted]

[redacted]

## 6 STUDY POPULATION

Males and females, age 18 years or older, with histologically confirmed, previously untreated, advanced or metastatic RCC will be eligible for the study.

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

## 6.1 Inclusion Criteria

**Inclusion**

**1) Signed Written Informed Consent**

a) Participants must have signed and dated an IRB/IEC-approved written informed consent form in accordance with regulatory and local guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal participant care.

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

**2) Type of Participant and Target Disease Characteristics**

a) Advanced (not amenable to curative surgery or radiation therapy) or metastatic (AJCC Stage IV) RCC

b) Histologically confirmed, previously untreated (treatment-naive) RCC (as defined in Appendix 3):

i) Predominant clear-cell.

ii) Non-clear cell histology including:

(1). papillary

(2). chromophobe

(3). translocation associated.

(4). collecting duct

(5). medullary

(6). any pathology unclassified.

c) No prior systemic therapy for RCC with some exceptions:

i) One prior adjuvant or neoadjuvant therapy for completely resectable RCC if such therapy did not include checkpoint inhibitors and if recurrence occurred at least 6 months after the last dose of adjuvant or neoadjuvant therapy.

d) Participants with brain metastases will be allowed if they are asymptomatic and not on systemic corticosteroids or receiving radiation treatment for at least 14 days prior to beginning protocol therapy. Brain lesion(s) that are < 10 mm or that have been previously irradiated will only be assessed as non-target lesion per RECIST 1.1. Brain lesions that are ≥ 10 mm and that have not been previously irradiated will be assessed as target lesions per RECIST 1.1.

i) Participants who are found on screening CT/MRI to have brain metastases will be enrolled to Cohort 3 or 4 (depending on the KPS level) if they do not require active treatment (radiation treatment/corticosteroids)

ii) Participants who are found on screening CT/MRI to have brain metastases that require immediate treatment (radiation treatment/corticosteroids) will be re-enrolled to Cohort 3 or 4 (depending on the KPS level) after completing active treatment

e) Measurable disease as per RECIST 1.1. Participant must have extracranial metastasis as measurable disease (Appendix 4)

f) Karnofsky Performance Status (KPS) of at least 70% for Cohort 1, 2, and 3; KPS of 50-60% for Cohort 4 (Appendix 5)

g) Participants with favorable, intermediate and poor risk categories will be eligible for the study in all cohorts per International Metastatic RCC Database Consortium (IMDC) prognostic criteria (Appendix 6). Enrollment of participants with a favorable risk score (no adverse prognostic factors present) will be capped to 25% of entire Cohort 1 population.

h) Tumor tissue (FFPE archival or recent acquisition) need be available to be received by the central vendor (block or unstained slides). (Note: Fine Needle Aspiration [FNA] and bone metastases samples are not acceptable for submission).

**3) Age and Reproductive Status**

a) Males and Females, ≥ 18 years of age

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 treatment.

c) Women must not be breastfeeding.

d) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of study treatment and 5 months after the last dose of study treatment {i.e., 30 days (duration of ovulatory cycle) plus the time required for the investigational drug to undergo approximately five half-lives.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of study treatment and 7 months after the last dose of study treatment {i.e., 90 days (duration of sperm turnover) plus the time required for the investigational drug to undergo approximately five half-lives.} -

f) Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception, (Appendix 7) which have a failure rate of < 1% when used consistently and correctly

## 6.2 Exclusion Criteria

**1) Medical Conditions**

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

b) Any active or recent history of a known or suspected autoimmune disease or recent history of a syndrome that required systemic corticosteroids (> 10 mg daily prednisone equivalent) or immunosuppressive medications except for syndromes which would not be expected to recur in the absence of an external trigger. Participants with vitiligo or type I diabetes mellitus or residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement 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 > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

d) 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) as per local requirements.

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

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

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

**2) Prior/Concomitant Therapy**

a) Prior systemic treatment in the metastatic setting with VEGF or VEGF receptor targeted therapy (including, but not limited to, sunitinib, pazopanib, axitinib, tivozanib, bevacizumab, cabozantinib, and lenvantinib)

b) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways. This includes the utilization of these agents in the neo-adjuvant or adjuvant setting.

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

**3) Physical and Laboratory Test Findings**

a) Presence of any toxicities attributed to prior anti-cancer therapy, other than alopecia, that have not resolved to Grade 1 (NCI CTCAE v4) or baseline before administration of study drug.

b) Any of the following laboratory test findings:

i) WBC < 2000/μL

ii) Neutrophils < 1500/μL

iii) Platelets < 100*103/μL

iv) Hemoglobin < 9.0 g/dL

v) Serum creatinine >1.5 x ULN or calculated creatinine clearance < 40 mL/min (using the Cockcroft-Gault formula)

vi) AST/ALT: > 3.0 x ULN

vii) Total bilirubin > 1.5 x ULN (except participants with Gilbert Syndrome who must have a total bilirubin level of < 3.0x ULN)

viii) Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, e.g. Hepatitis B surface antigen (HBsAg, Australia antigen) positive, or Hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative).

**4) Allergies and Adverse Drug Reaction**

a) History of severe hypersensitivity reactions to other monoclonal antibodies

b) History of allergy or intolerance (unacceptable AEs) to study drug components or Polysorbate-80-containing infusions

**5) Other Exclusion Criteria**

a) Prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and Bristol-Myers Squibb approval is required.

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

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

## 6.3 Lifestyle Restrictions

Not applicable. No restrictions are required

## 6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs.

### *6.4.1 Retesting During Screening or Lead-In Period*

Participant Re-enrollment: This study permits the re-enrollment of a participant that has discontinued the study as a pre-treatment failure (ie, participant has not been treated). If re-enrolled, the participant must be re-consented. Retesting of laboratory parameters and/or other assessments within any single Screening will be permitted (in addition to any parameters that require a confirmatory value).

The most current result prior to Treatment assignment is the value by which study inclusion will be assessed, as it represents the participant's most current clinical state. Laboratory parameters and/or assessments that are included in Table 2-1, Screening Procedural Outline may be repeated in an effort to find all possible well-qualified participants.

Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

# 7 TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo or medical device intended to be administered to a study participant according to the study randomization or treatment allocation.

Study treatment includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following:

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.

In this protocol, nivolumab and ipilimumab are investigational products.

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.

**Table 7-1: Study treatments for CA209920**

| Product Description / Class and Dosage Form | Potency | IP/Non-IMP | Blinded or Open Label | Packaging / Appearance | Storage Conditions (per label) |
|---|---|---|---|---|---|
| BMS-936558-01 (Nivolumab) Solution for Injection | 100 mg (10 mg/mL) | IP | Open Label | 10 mL per vial (10 vials/carton) | Store at 2° - 8 °C. Protect from light and freezing. |
| Ipilimumab Solution for Injection | 200 mg (5 mg/mL) | IP | Open Label | 40 mL per vial (4 vials/carton) | Store at 2° - 8 °C. Protect from light and freezing. |

## 7.1 Treatments Administered

The selection and timing of dose for each participant is as follows:

**Table 7.1-1: Selection and Timing of Dose**

| Study Treatment | Unit dose strength(s)/Dosage level(s) | Dosage formulation Frequency of Administration | Route of Administration |
|---|---|---|---|
| **Cohort 1** | Nivolumab 6 mg/kg<br>Ipilimumab 1 mg/kg<br><br>Nivolumab 480 mg | Combination: D1W1 and then every 8 weeks,<br>Monotherapy beginning D1W5 of C1, and then every 8 weeks | Nivolumab IV<br>Ipilimumab IV |
| **Cohort 2, 3, and 4** | Nivolumab 3 mg/kg<br>Ipilimumab 1 mg/kg<br><br>Nivolumab 480 mg | Combination therapy: every 3 weeks for 4 doses<br><br>Maintenance monotherapy every 4 weeks afterwards. | Nivolumab IV<br>Ipilimumab IV |

Participants should begin study treatment within 5 calendar days of treatment assignment.

Where dosing calculations should be based on the body weight assessed at baseline. It is not necessary to re-calculate subsequent doses if the participant weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded up or to the nearest milligram per institutional standard.

When study drugs (nivolumab and ipilimumab) are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be the ipilimumab study drug and will start after the infusion line has been flushed, filters changed and patient has been observed to ensure no infusion reaction has occurred. The time in between infusions is expected to be approximately 30 minutes but may be more or less depending on the situation.

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 1 mg/mL. Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, or pharmacy reference sheet. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent

There will be no dose escalations or reductions of nivolumab or ipilimumab allowed. For dosing cycles every 8 weeks, participants may be dosed within a ± 3 day window. Premedications are not recommended for the first dose of nivolumab.

Doses of nivolumab or ipilimumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed.

Participants should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.2.

Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

Ipilimumab injection can be used for IV administration without dilution after transferring to a PVC, non-PVC/non-DEHP or glass container and is stable for 24 hours at 2-8°C or room temperature/room light (RT/RL). For ipilimumab storage instructions, refer to ipilimumab IB and/or pharmacy reference sheets.

Separate infusion bags and filters should be used when administering nivolumab and ipilimumab on the same day.

Ipilimumab is to be administered as a 30 minute IV infusion, using a volumetric pump with a 0.2 to 1.2 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline or 5% Dextrose Injection to concentrations between 1 mg/mL and 4 mg/mL. It is not to be administered as an IV push or bolus injections. Care must be taken to assure sterility of the prepared solutions, since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents. At the end of the infusion, flush the line with a sufficient quantity of normal saline or 5% dextrose solution.

### 7.1.1 Cohort 1

Participants should receive nivolumab at a dose of 6 mg/kg as about a 60-minute IV infusion, and ipilimumab at a dose of 1 mg/kg as about an 30-minute IV infusion on Day 1 Week 1 of each cycle (every 8 weeks), until progression, unacceptable toxicity, withdrawal of consent, the study ends or up to a maximum of 24 month whichever occurs first. Participants should begin study treatment within 5 calendar days of treatment assignment. Beginning on Day 1 of Week 5 of Cycle 1, participants will receive nivolumab 480 mg flat dose, as a 60 minute infusion, and then again every 8 weeks until progression, unacceptable toxicity, withdrawal of consent, the study ends or up to a maximum of 24 month whichever occurs first.

### 7.1.2 Cohorts 2, 3, and 4

Participants in Cohorts 2, 3, and 4, will receive nivolumab at a dose of 3 mg/kg as a 60 minute infusion, and ipilimumab at a dose of 1 mg/kg as a 30 minute infusion on Day 1 Week 1 and Day 1 Week 4 of each cycle (every 6 weeks) until for up to 4 doses (2 cycles). Participants should begin study treatment within 5 calendar days of treatment assignment. Beginning with Cycle 3 (6 weeks [± 3 days] from last combo dose), participants in Cohorts 2, 3 and 4 will receive nivolumab at a dose of 480 mg as a 60 minute infusion every 4 weeks (± 3 days) until progression, unacceptable toxicity, withdrawal of consent, the study ends, or up to a maximum of 24 months, whichever occurs first.

## 7.2 Method of Treatment Assignment

After the participant's eligibility is established and informed consent has been obtained, the participant 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 participant 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 participant 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
- Performance Status

## 7.3 Blinding

This is an open-label study, blinding procedures are not applicable.

## 7.4 Dosage Modification

Dose reductions or dose escalations of nivolumab or ipilimumab are not permitted.

### *7.4.1 Study Treatment Dose Delay Criteria*

Study treatment administration should be delayed for the following:

- Grade 2 non-skin, drug-related adverse event, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related adverse event
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation (see Section8.1.1)
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Participants who require delay of study treatment should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met.

During Cycles 1 and 2, both nivolumab and ipilimumab must be delayed at the same time.

Because of the potential for clinically meaningful nivolumab or ipilimumab-related AEs requiring early recognition and prompt intervention, management algorithms have been developed for

suspected pulmonary toxicity, GI, hepatotoxicity, endocrinopathy, skin toxicity, neurological toxicity and renal toxicity.

In order to standardize the management of overlapping adverse event management algorithms present in both the BMS-936558 (nivolumab) and ipilimumab IB (**GI, hepatic, and endocrine** algorithms), the recommendations are to follow the BMS-936558 (nivolumab) IB adverse event algorithms as opposed to the ipilimumab IB algorithms.

The algorithms recommended for utilization in are included in Appendix 8.

### *7.4.2 Treatment of Nivolumab or Ipilimumab Related Infusion Reactions*

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, each 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 BMS Study Medical Monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 4) 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 participant 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 required 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 $\leq 24$ hours):

- Stop the nivolumab or ipilimumab infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor participant 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 participant closely. If symptoms recur, then no further nivolumab or ipilimumab 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 hydrocortisone 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 or ipilimumab. Begin an IV infusion of normal saline and treat the participant 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. Participant should be monitored until the Investigator is comfortable that the symptoms will not recur. Study drug will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant 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).

### *7.4.3 Management Algorithms for Immuno-Oncology Agents*

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab and ipilimumab are considered immuno-oncology agents 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 both the nivolumab and ipilimumab Investigator Brochures, as well as in Appendix 8.

## 7.5 Preparation/Handling/Storage/Accountability

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 Participants. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

The product storage manager should ensure that the study treatment 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 treatment arise, the study treatment should not be dispensed and contact BMS immediately.

Study treatment 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 (e.g., required diluents, administration sets).

Further guidance and information for final disposition of unused study treatment are provided in CA209920 Pharmacy Reference Manual.

### *7.5.1 Retained Samples for Bioavailability / Bioequivalence*

Not Applicable.

## 7.6 Treatment Compliance

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

[redacted]

[redacted]

## 7.8 Treatment After the End of the Study

At the conclusion of the study, participants who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study treatment **for the maximum treatment duration specified in Sections 7.1.1** and **7.1.2.**

Study treatment will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS.

## 7.9 Treatment Beyond Progression

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of PD. Participants will be permitted to continue study treatment beyond initial RECIST 1.1 defined 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) Participant provides written informed consent prior to receiving additional study 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 participant is clinically deteriorating and unlikely to receive any benefit from continued study treatment.

If the investigator feels that the participant continues to achieve clinical benefit by continuing treatment, the participant should remain on the trial and continue to receive monitoring according to the Time and Events Schedule (Section 2).

For the participants who continue 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-measureable 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).

Participants 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.

# 8 DISCONTINUATION CRITERIA

## 8.1 Discontinuation from Study Treatment

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

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information
- 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 participant
- 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
- Additional protocol specified criteria for discontinuation (see Section 8.1.1)

Refer to the Schedule of Activities for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed

In the case of pregnancy, the investigator must immediately notify the Sponsor or designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please contact the Sponsor or designee within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the Sponsor or designee must occur.

All participants who discontinue study treatment should comply with protocol specified follow-up procedures as outlined in Section 2. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

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

The assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of ipilimumab. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for ipilimumab but not for nivolumab, treatment with nivolumab may continue if ipilimumab is discontinued.

If a participant in any of the nivolumab/ipilimumab combination cohorts meets criteria for discontinuation and investigator is unable to determine whether the event is related to both or one study drug, the participant should discontinue both nivolumab and ipilimumab and be taken off the treatment phase of the study.

### *8.1.1 Dose Discontinuation*

Study 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 re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, or recurs with the following exceptions for laboratory abnormalities, diarrhea, colitis, neurologic toxicity, drug-related

uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:

- Grade 3 drug-related diarrhea, colitis, neurologic toxicity, uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
- Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
- Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
  - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
  - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
    - Grade ≥ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation*
    - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN

* In most cases of Grade 3 AST or ALT elevation, study drug(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug(s), a discussion between the investigator and the BMS Medical Monitor/designee must occur.

- Any Grade 4 drug-related adverse event or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin), except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
  - 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
  - Grade 4 drug-related endocrinopathy adverse events, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.

- Any event that leads to delay in dosing lasting > 8 weeks during Cycle 1- 2, and >10 weeks in cycle 3 or later for Cohorts 2-4, and >10 weeks for Cohort 1, from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
  - Dosing delays lasting longer than the number of weeks allowed for the respective cohorts that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks for Cohorts 2 through 4, or >10 weeks for Cohort 1, the BMS medical monitor must be consulted and provide written approval for participants with expected clinical benefit as per investigator assessment. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

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

### *8.1.2 Criteria to Resume Treatment*

Missed doses of nivolumab and/or ipilimumab should be administered as soon as the participant meets criteria to resume treatment. If a dose has been missed, the participant should not wait until the next scheduled dosing date.

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

- Participants may resume treatment in the presence of Grade 2 fatigue
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- For participants with Grade 2 AST, ALT and/or Total Bilirubin Abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Participants with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 8.1.1) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by BMS Medical Monitor.
- Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor.
- Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

If treatment is delayed > 8weeks for Cohorts 2 through 4, or >10 weeks for Cohort 1, the participant must be permanently discontinued from study therapy, except as specified in Section 8.1.1.

For participants in Cohort 1, during Cycles 1 and 2, both nivolumab and ipilimumab must be resumed on the same day. For participants in Cohort 2 to 4, all four doses of nivolumab combined with ipilimumab must be given prior to beginning nivolumab monotherapy (Cycle 3 and beyond). Participants in any cohort, who discontinue combination therapy early due to an adverse event, may be eligible to receive nivolumab monotherapy (480 mg every 4 weeks), contingent upon discussion with, and approval by the Medical Monitor.

If the participant is unable to receive either combination therapy or nivolumab monotherapy permanent discontinuation is required.

### *8.1.3 Post-Study Treatment Study Follow-up*

BMS may request that survival data be collected on all treated participants outside of the protocol defined window (Schedule of Activities, Section 2). At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contacts or is lost to follow-up.

## 8.2 Discontinuation from the Study

Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.

- Participants 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 treatment 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 participant 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.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

## 8.3 Lost to Follow-Up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **three** documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records.

- If it is determined that the participant has died, the site will use permissible local methods to obtain 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 participant's informed consent, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining participant'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 participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

# 9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities.
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before treatment allocation. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.

## 9.1 Efficacy Assessments

Study evaluations will take place in accordance with the Schedule of Assessment (Section 2). Baseline assessments should be performed within 28 days prior to first dose utilizing CT or MRI. In addition to chest, abdomen, pelvis, and brain, all known sites of disease should be assessed at baseline. Participants who cannot receive IV contrast for CT at the start of study should be imaged by MRI of abdomen/pelvis with IV contrast and CT of chest without contrast. Subsequent assessments should include chest, abdomen, and pelvis, and all known sites of disease and should use the same imaging method as was used at baseline. Participants initially imaged with CT of chest, abdomen, and pelvis with IV contrast who can no longer receive contrast can be monitored by CT of chest, abdomen, and pelvis without IV contrast. Please refer to additional precautions

regarding IV contrast in Section 7.7.2.3. Participants in all cohorts will be evaluated for tumor response at the following intervals and time points:

- First tumor assessment should be performed at 12 weeks (± 1 week) following first dose. Subsequent tumor assessments should occur every 8 weeks (± 1week) up to first 13 months, then every 12 weeks until disease progression or treatment discontinuation, whichever is later

For Cohorts 3 and 4: Brain lesion(s) that are < 10 mm or that have been previously irradiated will only be assessed as non-target lesion per RECIST 1.1. Brain lesions that are ≥ 10 mm and that have not been previously irradiated will be assessed as target lesions per RECIST 1.1.

Participants will be permitted to continue treatment beyond PD (RECIST 1.1) under protocol-defined circumstances (See Section 7.9).Tumor assessments for ongoing study treatment decisions will be completed by the investigator using RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 criteria.

### *9.1.1 Imaging Assessment for the Study*

Images will be submitted to the local lab, and read locally by the site Radiologist.

**Table 9.1.1-1: Imaging Assessment Schedule (Cohort 1)**

| Study Day | Event Relative to Dosing | CT/MRI |
|---|---|---|
| Screening | Pre-dose | X |
| Week 12 (± 1 week) | Post-dose | X |
| Every 8 weeks (± 1 week) | Post-dose | X |
| Every 12 weeks (± 1 week), after Month 13 of treatment | Post-dose | X |

**Table 9.1.1-2: Imaging Assessment Schedule (Cohorts 2, 3 and 4)**

| Study Day | Event Relative to Dosing | CT/MRI |
|---|---|---|
| Screening | Pre-dose | X |
| Week 12 (± 1 week) | Post-dose | X |
| Every 8 weeks (± 1 week) | Post-dose | X |
| Every 12 weeks (± 1 week), after Month 13 of treatment | Post-dose | X |

[redacted]

## 9.2 Adverse Events

The definitions of an AE or serious adverse event (SAE) can be found in Appendix 9.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue before completing the study.

Immune-mediated adverse events are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the participant's case report form.

**Contacts for SAE reporting specified in Appendix 9.**

### *9.2.1 Time Period and Frequency for Collecting AE and SAE Information*

The collection of non-serious AE information should begin at initiation of study treatment until the follow-up contact, at the time points specified in the Schedule of Activities (Section 2). 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 participants.

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 participant'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 (e.g., a follow-up skin biopsy).

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

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the eCRF section.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 9.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of this being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

The method of evaluating, and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 9.

#### *9.2.1.1 Adverse Events of Special Interest – Immune-mediated AEs*

Immune-mediated AEs (IMAEs) are specific events (or groups of PTs describing specific events) that include pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, endocrine (adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis), and other specific events, considered as potential immune-mediated events by investigator, that meet the definition summarized below:

- those occurring within 100 days of the last dose
- regardless of causality
- with no clear alternate etiology based on investigator assessment, or with an immune-mediated component
- treated with immune-modulating medication (Of note, adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis are considered IMAEs regardless of immune-modulating medication use, since endocrine drug reactions are often managed without immune-modulating medication).

Table 9.2.1.1-1 below provides a summary of the IMAEs category and their respective preferred terms.

**Table 9.2.1.1-1: 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<br>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 |

### 9.2.2 Method of Detecting AEs and SAEs

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

### 9.2.3 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 9).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment 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). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 9.2 will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

Further information on follow-up procedures is given in Appendix 9.

### 9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Sponsor or designee will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

All SAEs must be collected that occur during the screening period and within 100 days of the last dose of study treatment. For participants assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of treatment assignment.

### 9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant 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 of awareness of the event and in accordance with SAE reporting procedures described in Appendix 9.

In most cases, the study treatment will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for participant safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy. Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

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 Sponsor or designee. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

### 9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form electronic, as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

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

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

### 9.2.7 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 9.2 and Appendix 9 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.

### 9.2.8 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.

## 9.3 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 9.2).

In the event of an overdose the investigator should:

1) Contact the Medical Monitor immediately
2) Closely monitor the participant for AEs/SAEs and laboratory abnormalities
3) Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

## 9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities.

### *9.4.1 Physical Examinations*

Refer to Schedule of Activities.

### *9.4.2 Vital signs*

Refer to Schedule of Activities.

### *9.4.3 Electrocardiograms*

Refer to Schedule of Activities.

### *9.4.4 Clinical Safety Laboratory Assessments*

Investigators must document their review of each laboratory safety report. Please refer to the Schedule of Activities in Section 2 for details related to the required laboratory assessment.

### *9.4.5 Imaging Safety Assessment*

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.

[redacted]

[redacted]

# 10 STATISTICAL CONSIDERATIONS

## 10.1 Sample Size Determination

The sample size of the study is mainly determined by the feasibility concern. The study plans to enroll 200 participants, 100 in Cohort 1, 50 in Cohort 2, 25 in Cohort 3, and 25 in Cohort 4 (100 in Cohort 1 and 100 in Cohorts 2-4 combined). Enrollment in Cohort 1 for participants with a favorable risk score will be capped at 25% of the total population to be enrolled in that cohort.

In general, the combination of nivolumab and ipilimumab has higher rates in IMAE of high grade (Grade 3-4) than nivolumab monotherapy. Study CA209016 reports that both combination treatment arms have approximately 40-60% high grade IMAEs (34.0% in N3+I1 arm and 63.8% in N1+I3 arm); study CA209012 (for NSCLC) reports approximately 35% high grade IMAEs in both combined therapy arms. Given these reported values, the precision of half width of 95% confidence interval of AE rates is between 9.3% and 9.8% for 100 participants and between 6.6% and 6.9% for 200 participants pooled together. These precisions are deemed as acceptable in evaluating the research hypotheses with respect to study cohorts in terms of AE rates in the range reported by previous studies.

## 10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

| Population | Description |
|---|---|
| Enrolled | All enrolled participants: all participants who signed an informed consent form and were registered into the IVRS. |
| Treated | All treated participants: all participants who received any nivolumab. This is the primary population for safety and efficacy analyses. . |
| Response Evaluable | All response evaluable participants: all treated participants who have baseline and at least one on-study evaluable tumor measurement. |

## 10.3 Statistical Analyses

Detailed analyses will be specified in the statistical analysis plan separately. In general, unless expressly stated otherwise, all analyses will be performed by Cohort 1, and Cohorts 2-4 combined.

Demographics, baseline disease characteristics and baseline laboratory results will be summarized using descriptive statistics for all treated participants.

### *10.3.1 Efficacy Analyses*

| Endpoint | Statistical Analysis Methods |
|---|---|
| Primary | Not applicable |

| Endpoint | Statistical Analysis Methods |
|---|---|
| Secondary | PFS will be summarized by KM product-limit method for all treated participants and all response evaluable participants, respectively. Median values of PFS, along with two-sided 95% CI using Brookmeyer and Crowley method, will be calculated. Associated two-sided 95% CIs will be calculated using the Greenwood formula. This analysis will be performed for all treated participants and for all response evaluable participants for both PFS 1 as secondary endpoint and PFS 2 as exploratory endpoint.<br>The ORR will be summarized by binomial response rates and their corresponding two-sided 95% exact CIs using the Clopper-Pearson method. This analysis will be performed for all response evaluable participants.<br>Time to response (TTR) is analyzed using the KM methodology, for all evaluable participants. KM curve was to represent the cumulative rate of response over time. For the non-responders, time to response was censored at the maximum time of response + 1 day of all participants in their respective treatment group.<br>The assessed DOR will be summarized for all response evaluable participants who achieve confirmed PR or CR using the Kaplan-Meier (KM) product-limit method. Median values of DOR, along with two-sided 95% CI using Brookmeyer and Crowley method, will also be calculated. In addition, the percentage of responders still in response at different time points (3, 6, 12, 18, and 24 months and at end of study) will be presented based on the DOR KM plot. This analysis will be performed for all response evaluable participants who achieve confirmed PR or CR. |
| [redacted] | [redacted] |

### 10.3.2 Safety Analyses

All safety analyses will be performed on the Treated Population.

| Endpoint | Statistical Analysis Methods |
|---|---|
| Primary | 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. |
| Secondary | Additional descriptive statistics of 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 method of time to onset and time to resolution, and will be presented for all treated participants. Time to onset is calculated from first dosing date to the event onset date. The IMAEs of interest are the following: skin, endocrinopathy, gastrointestinal, hepatic, renal, pulmonary, and neurological adverse events. If a participant never experienced the given AE, the participant 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. |

| Endpoint | Statistical Analysis Methods |
|---|---|
| | Management of high-grade (CTCAE v4 Grade 3-4 and Grade 5) IMAEs will be characterized by measuring percentage of participants who received immune modulating medication (or hormonal replacement therapy), percentage of participants who received ≥ 40 mg prednisone equivalents, and total duration of all immune modulating medications given for the event, in all treated participants who have experience high-grade (CTCAE v4 Grade 3-4 and Grade 5) IMAEs. |
| [redacted] | [redacted] |

[redacted]

[redacted]

### 10.3.4 Interim Analyses

Not applicable.

### 10.3.5 Final Analyses

The final analysis will be performed when all participants have completed the study treatment. Data cuts for publication purposes earlier than all participants complete the study are possible.

The Statistical Analysis Plan will further describe the planned analyses.

# 12 APPENDICES

## APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

| Term | Definition |
|---|---|
| AE | adverse event |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| AST | aspartate aminotransferase |
| AT | aminotransaminases |
| BMI | body mass index |
| BMS | Bristol-Myers Squibb |
| BP | blood pressure |
| BUN | blood urea nitrogen |
| C | Celsius |
| $Ca^{++}$ | calcium |
| Cavg | average concentration |
| CBC | complete blood count |
| ccRCC | Clear-cell renal cell carcinoma |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| CLcr | creatinine clearance |
| Cmax, CMAX | maximum observed concentration |
| Cmin, CMIN | minimum observed concentration |
| CNS | Central nervous system |
| CRF | Case Report Form, paper or electronic |
| CR | Complete response |
| C1W1D1 | Cycle 1 Week 1 Day 1 |
| DMC | Data monitoring committee |
| DOR | Duration of response |
| ECG | electrocardiogram |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| EEG | electroencephalogram |

| Term | Definition |
|---|---|
| eg | exempli gratia (for example) |
| [redacted] | [redacted] |
| FDA | Food and Drug Administration |
| [redacted] | [redacted] |
| FSH | follicle stimulating hormone |
| g | gram |
| GCP | Good Clinical Practice |
| GFR | glomerular filtration rate |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HIV | Human Immunodeficiency Virus |
| HR | heart rate |
| HRQoL | Health Related Quality of Life |
| 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 |
| IMDC | International metastatic RCC database consortium (IMDC) Prognostic Criteria |
| IMP | investigational medicinal products |
| IND | Investigational New Drug Exemption |
| I-O | Immuno-oncology |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| IU | International Unit |
| IV | intravenous |
| K | slope of the terminal phase of the log concentration-time curve |

| Term | Definition |
|---|---|
| $K^+$ | potassium |
| kg | kilogram |
| KPS | Karnofsky Performance Status |
| L | liter |
| LAM | Lactation amenorrhea method |
| LC | liquid chromatography |
| LDH | lactate dehydrogenase |
| mg | milligram |
| $Mg^{++}$ | magnesium |
| min | minute |
| mL | milliliter |
| mmHg | millimeters of mercury |
| MR | medical research |
| mRCC | Metastatic Renal Cell Carcinoma |
| MSKCC | Memorial Sloan Kettering Cancer Center |
| MTD | maximum tolerated dose |
| mWHO | Modified World Health Organization |
| µg | microgram |
| N | number of subjects or observations |
| $Na^+$ | sodium |
| N/A | not applicable |
| ng | nanogram |
| NSAID | nonsteroidal anti-inflammatory drug |
| NSCLC | Non-small cell lung cancer |
| ORR | Objective response rate |
| PBMC | Peripheral blood mononuclear cell |
| PD | Progressive diseases |
| PFS | Progression-free survival |
| PK | pharmacokinetics |

| Term | Definition |
|---|---|
| PR | Partial response |
| RBC | red blood cell |
| SAE | serious adverse event |
| SD | standard deviation |
| SOP | Standard Operating Procedures |
| TTR | Time to Response |
| ULN | Upper limit of normal |
| VEGF | Vascular epithelial growth factor |
| WBC | white blood cell |
| WHO | World Health Organization |
| WOCBP | women of childbearing potential |

# APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The term 'Participant' is used in the protocol to refer to a person who has consented to participate in the clinical research study. The term 'Subject' used in the eCRF is intended to refer to a person (Participant) who has consented to participate in the clinical research study.

## REGULATORY AND ETHICAL CONSIDERATIONS

## GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Good Clinical Practice (GCP),
- as defined by the International Council on Harmonisation (ICH)
- in accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- applicable local requirements.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the participant informed consent will receive approval/favorable opinion by Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable local regulations prior to initiation of the study.

All potential serious breaches must be reported to Sponsor or designee 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 (e.g., loss of medical licensure, debarment).

## INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, participant recruitment materials (e.g., 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, Sponsor or designee should provide the IRB/IEC with reports, updates and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

## COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if

applicable, also by local health authority) 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 relevant approval/favorable opinion(s) the deviation or change will be submitted, as soon as possible to:

- IRB/IEC for
- Regulatory Authority(ies), if applicable by local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the participant: (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).

## FINANCIAL DISCLOSURE

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

## INFORMED CONSENT PROCESS

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 participant volunteers to participate.

Sponsor or designee will provide the investigator with an appropriate (i.e., 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:

- Provide a copy of the consent form and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The language must be non-technical and easily understood.

- Allow time necessary for participant or participant's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the participant or the participant's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.

If informed consent is initially given by a participant's legally acceptable representative or legal guardian, and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

Revise the informed consent whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or the participant's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the participant'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 participant records.

Subjects unable to give their written consent (e.g., stroke or subjects with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The participant must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this participant become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a participant 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.

## SOURCE DOCUMENTS

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.

## STUDY TREATMENT RECORDS

Records for study treatments (whether supplied by BMS, its vendors, or the site) must substantiate study treatment integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

| If | Then |
|---|---|
| Supplied by BMS (or its vendors): | Records or logs must comply with applicable regulations and guidelines and should include:<br>• amount received and placed in storage area<br>• amount currently in storage area<br>• label identification number or batch number<br>• amount dispensed to and returned by each participant, including unique participant identifiers<br>• amount transferred to another area/site for dispensing or storage<br>• nonstudy disposition (e.g., lost, wasted)<br>• amount destroyed at study site, if applicable<br>• amount returned to BMS<br>• retain samples for bioavailability/bioequivalence, if applicable<br>• dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form. |
| Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy) | The investigator or designee accepts responsibility for documenting traceability and study drug integrity in accordance with |

| If | Then |
|---|---|
| | requirements applicable under law and the SOPs/standards of the sourcing pharmacy.<br><br>These records should include:<br><br>• label identification number or batch number<br>• amount dispensed to and returned by each participant, including unique participant identifiers<br>• dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form. |

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

## 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 Sponsor or designee 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 electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used.

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, 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. Subinvestigators in Japan may not be delegated the CRF approval task. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet Sponsor or designee training requirements and must only access the BMS electronic data capture tool using the unique user

account provided by Sponsor or designee. User accounts are not to be shared or reassigned to other individuals

## MONITORING

Sponsor or designee 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 Sponsor or designee 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 Sponsor or designee.

## RECORDS RETENTION

The investigator (or head of the study site in Japan) 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 or designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

BMS or designee will notify the investigator (or head of the study site in Japan) when the study records are no longer needed.

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

## RETURN OF STUDY TREATMENT

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

| If.. | Then |
|---|---|
| Study treatments supplied by BMS (including its vendors | Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for |

| If.. | Then |
|---|---|
| | safety, or to meet local regulations (e.g., cytotoxics or biologics).<br><br>If study treatments will be returned, the return will be arranged by the responsible Study Monitor. |
| Study treatments sourced by site, not supplied by BMS (or its vendors) (examples include study treatments sourced from the sites stock or commercial supply, or a specialty pharmacy) | It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures. |

It is the investigator's or designee's responsibility to arrange for disposal, 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. The following minimal standards must be 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, i.e., 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.

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study treatments provided by BMS (or its vendors). Destruction of non- study treatments sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

## 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:

- External Principal Investigator designated at protocol development

- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Participant recruitment (e.g., among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (e.g., among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

## APPENDIX 3 RENAL CELL CARCINOMA: HISTOLOGY DEFINITIONS

# Clear Cell Renal Cell Carcinoma

**1) Definition**

- **Carcinoma of the kidney composed predominantly of nests and sheets of clear cells**

**2) Alternate/Historical Names**

- Conventional type renal cell carcinoma
- One of several different neoplasms previously diagnosed as granular cell renal cell carcinoma (some cases)

**3) Diagnostic Criteria**

- Grossly circumscribed mass
  - Frequently hemorrhagic and necrotic
  - Soft yellow areas frequent, alternating with fibrous to mucoid areas
    - May appear necrotic but frequently are viable
  - Multifocal in about 5% of cases
    - More frequent in familial cases
- **Sheets and nests of cells surrounded by extensive capillary network**
  - Frequently forms alveolar lumens
    - No lumenal border differentiation
    - Frequently dilates to form micro- and macrocystic pattern
  - If exclusively cystic, see multilocular cystic renal cell carcinoma
    - Lumens may contain eosinophilic proteinaceous fluid or RBCs
  - Tubular and papillary foci rare
    - Consider clear cell tubulopapillary carcinoma if present
- **Predominantly composed of clear cells**
  - Higher grade tumors often lose clear cell cytoplasm but may still have underlying recognizable low grade clear cell areas
  - Frequent granular eosinophilic areas
    - Rarely predominant
    - If extensively granular and eosinophilic, consider oncocytoma
  - Sharp cell borders
  - Cytoplasm contains lipid and glycogen
  - Features reported in rare cases
    - Rhabdoid cells in 5% of cases
      - Abundant eccentric cytoplasm containing large eosinophilic inclusions
      - Eccentric large round nuclei, may be multinucleate
      - Keratin, EMA, vimentin positive
      - 25% of cases with rhabdoid areas have sarcomatoid areas
    - Eosinophilic 5-7 mm hyaline globules
    - Basophilic inclusions
    - Myospherulosis
    - Coarse brown granular pigment
    - Melanin

- Nuclei range from round and regular at low grade to pleomorphic at high grade
  - Nuclear features and nucleolar size incorporated into grading
- Dysplasia of adjacent non-carcinomatous tubules has been reported
- Multiple and/or familial clear cell carcinomas may be seen in von Hippel Lindau syndrome

# Xp11 / TFE3 Translocation Carcinoma of the Kidney

**1) Definition**

- **Renal carcinoma comprising a large fraction of renal carcinomas occurring in young patients and associated with translocations involving the TFE3 gene at chromosome Xp11.2**

**2) Alternate/Historical Names**

- Juvenile renal cell carcinoma

**3) Diagnostic Criteria**

- **Most cases reported in children and young adults, mean age 25 years**
  - Under-recognized in adults
    - Two studies find an incidence of 1-5% in adults
    - If possible, fresh tumor tissue should be sent for cytogenetics in all renal tumor patients under 40 years of age and in older patients in which an unusual tumor is discovered at frozen section
- **Composed of cells with abundant to voluminous cytoplasm**
  - Clear to granular eosinophilic cytoplasm
  - Sharp cell borders
- Pleomorphic and polymorphic growth patterns
  - **Frequent papillary, pseudopapillary, alveolar and nested patterns**
  - Clusters of small cells centered on hyaline cores may be seen
    - Collections of small cells should suggest a t(6;11) carcinoma
  - Patterns and cells may vary according to the precise translocation involved
- Large vesicular nuclei
  - Prominent round nucleoli
  - Mitotic figures frequent
- Features frequently present
  - **Psammoma bodies** may be abundant
  - Intracytoplasmic hyaline droplets
- Melanocytic variant has been reported
- **Presence of Xp11 translocation by classical cytogenetics, PCR or FISH**
  - Demonstration may not be required in every case
  - TFE3 immunohistochemistry may be less reliable than reported in the literature with numerous false positives
  - **Lack of, or minimal, cytokeratin and EMA expression** may be the most helpful immunophenotypic findings

# Chromophobe Renal Cell Carcinoma

## 1) Definition

- **Carcinoma of the kidney composed predominantly of distinctive cells with prominent cell membranes and cleared cytoplasm**

## 1) Alternate/Historical Names

- Conventional type renal cell carcinoma (some cases)
- Granular cell renal cell carcinoma (some cases)

## 2) Diagnostic Criteria

- Generally sheet-like or broad alveolar patterns
  - Less frequently tubular or cystic
  - Vessels frequently thick walled and/or eccentrically hyalinized
- **Composed of cells with cytoplasm ranging from clear to eosinophilic**
  - Clear cells (classical) have abundant clear cytoplasm
    - May be flocculent or "soap bubble"
    - Prominent, distinct cell membrane
  - Eosinophilic (variant) cells have moderate amount of finely granular eosinophilic cytoplasm
    - **Prominent perinuclear clearing**
      - Peripheral condensation of cytoplasm accentuates cell membrane
  - **Nuclei vary from round, regular to koilocytoid**
    - Koilocytoid nuclei have wrinkled nuclear membrane, coarse chromatin
    - Frequently binucleate
  - Most often mixed but may be pure of either type
    - **Mixed cases frequently have a distinctive pattern**
      - Eosinophilic cells occupy the center of the nest, merging with
      - Peripheral clear cells with abundant cytoplasm adjacent to the fibrovascular stromal border
- **Prominent cell borders with centrally located nuclei with perinuclear clearing result in a "plant cell appearance"**
  - Reminiscent of the rigid cell walls of plant cells
- **Hale colloidal iron stain positive**
  - A temperamental stain
  - Other colloidal iron stains are not equivalent
- Chromophobe and hybrid chromophobe/oncocytoma cases may be seen in Birt Hogg Dubé syndrome
  - Sporadic hybrid chromophobe/oncocytoma cases have been described (Petersson)
- Sarcomatoid cases may have a variety of patterns (Viswanathan; Quiroga-Garza)
  - Poor prognosis
- One case reported with neuroendocrine differentiation (Parada)
  - Not clear from the report that this was not a collision tumor

# Papillary Renal Cell Carcinoma

## 1) Definition

- **Carcinoma of the kidney with a predominantly papillary growth pattern**

**Covered separately (as discrete entities)**

- Clear cell tubulopapillary carcinoma
- Papillary oncocytoma
- Xp11 translocation carcinoma

## 2) Diagnostic Criteria

**Predominantly papillary pattern**

- May have tubular areas
- Papillae have fibrovascular cores
- May be intracystic
- Rare cases of apparent solid pattern
  - Formed by collapsed tubules and papillae

**Two types, have been defined by the types of cells lining papillae and tubules**

- We do not routinely classify papillary carcinomas according to type
  - In our experience, many cases show a mixed pattern or do not clearly conform to either of these types
- Nevertheless, familial cases associated with MET mutations tend to show a type 1 morphology whereas those associated with fumarate hydratase mutations tend to show a type 2 morphology

**Type 1 is lined by small cells with clear to basophilic cytoplasm**

- Single layer of small oval nuclei
  - Inconspicuous nucleoli
- Frequent findings
  - Foamy macrophages and/or edema in papillary cores
  - Psammoma bodies and calcium oxalate crystals
  - Glomeruloid papillae
    - Most cases low grade (1 or 2)and low stage

**Type 2 is lined by large cells with abundant eosinophilic cytoplasm**

- If cytoplasm is extensively granular, consider papillary oncocytoma, see Differential Diagnosis
- Nuclei frequently pseudostratified or apical
- Large spherical nuclei
  - Prominent nucleoli
- Macrophages, edema, psammoma bodies, glomeruloid papillae infrequent
- Most cases high grade (3), many higher stage

**Papillary carcinoma with low grade spindle cell features has been described (Argani)**

- Predominantly solid
  - 4 of 5 reported cases had papillary areas
  - All appear to be Type 1
- Nuclear grade 2
- Lacks mucinous stroma of mucinous tubular and spindle cell carcinoma
  - May be distinguishable only by FISH for trisomy 7 or 17
- If under 0.5 cm and grade 1 or 2, designate as papillary adenoma

# Carcinoma of the Collecting Ducts of Bellini

## 1) Definition

- **High grade renal adenocarcinoma arising in medulla of the kidney, with a predominantly invasive tubular growth pattern**
- **Clearly overlaps morphologically and immunophenotypically with medullary carcinoma but the latter has a distinctive clinicopathologic setting**

## 2) Alternate/Historical Names

- Bellini duct carcinoma
- Collecting duct carcinoma

## 3) Diagnostic Criteria

- **Metastatic adenocarcinoma must be ruled out in every case**
  - Collecting duct carcinoma should be considered a diagnosis of exclusion
- **Firm mass centered on the renal medulla**
  - Frequently extends into renal cortex and/or pelvis
- **Infiltrating tubular or tubulopapillary pattern**
  - Occasionally solid or microcystic
  - Usually single layer of lining cells with hobnail nuclei
  - Extra-renal and vascular invasion frequent
  - Cytoplasmic mucin may be present
    - Signet ring cells seen in rare cases
  - Rare sarcomatoid cases
    - Defined by presence of a distinct spindle cell component occupying at least one microscopic low-power field (×40)
- **Prominent stromal desmoplasia**
  - Frequent mixed acute and chronic inflammation
- **High grade nuclear atypia**
  - Equivalent to Fuhrman 3 or 4
  - Frequent mitotic figures
  - Dysplastic epithelial lining frequently seen in adjacent collecting duct
- Cases described as low grade collecting duct carcinomas in the past are better classified as one of the following
  - Mucinous tubular and spindle cell carcinoma
  - Tubulocystic carcinoma
- Renal medullary carcinoma is considered a separate entity
  - Considered by some reports to be a variant of collecting duct carcinoma
  - Overlaps histopathologically with collecting duct carcinoma but is separated based on the following features
    - Occurrence in young patients
    - Association with sickle cell trait
    - Lack of INI1 expression (Cheng 2008) vs retention in 85% of collecting duct carcinoma (Elwood 2011)

# Renal Medullary Carcinoma

## 4) Definition

- **High grade renal adenocarcinoma arising in medulla of the kidney, associated with sickle cell trait**

## 5) Alternate/Historical Names

- In the past, some were included in collecting duct carcinoma
  - Distinction may be largely clinical

## 6) Diagnostic Criteria

- **Essentially every case associated with sickle cell trait or sickle cell disease**
  - Sickled cells may be seen in adjacent vessels
  - Nearly all of African ancestry
- **Firm mass centered on the renal medulla**
  - Frequently extends into renal cortex and/or pelvis
- **Infiltrating sheets or cords of cells**
  - **Frequent reticular/microcystic pattern**
    - **Spaces of varying size**
    - **Reminiscent of yolk sac tumor**
    - **May also have tubular and papillary patterns**
  - Dark eosinophilic granular cytoplasm
  - Intralumenal mucin frequent
  - Extra-renal and vascular invasion frequent
- **Rhabdoid pattern may be seen**
  - INI1 negative (all patterns)
- **Prominent stromal desmoplasia**
  - May be collagenous or myxoid
- **High grade nuclear atypia**
  - Pleomorphic vesicular nuclei with large nucleoli
  - Frequent mitotic figures
  - Frequent necrosis and hemorrhage
    - May form microabscesses
- Renal medullary carcinoma is considered a separate entity from collecting duct carcinoma
  - Considered by some reports to be a variant of collecting duct carcinoma
  - Overlaps histopathologically with collecting duct carcinoma but is separated based on the following features
    - Occurrence in young patients
    - Association with sickle cell trait
    - Lack of INI1 expression (Cheng 2008) vs retention in 85% of collecting duct carcinoma (Elwood 2011)

http://surgpathcriteria.stanford.edu/kidney

# APPENDIX 4 RECIST 1.1 GUIDELINES

## 1 EVALUATION OF LESIONS

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

### 1.1 Measurable

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

1. 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
2. 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
3. 20 mm by chest x-ray

*Malignant lymph nodes:* To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

### 1.2 Non-Measurable

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

# 2 BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

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

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

# 3 RESPONSE CRITERIA

## 3.1 Evaluation of Target Lesions

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

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

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

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

### 3.1.1 Special Notes on the Assessment of Target Lesions

#### 3.1.1.1 Lymph nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

#### 3.1.1.2 Target lesions that become 'too small to measure'

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

#### 3.1.1.3 Lesions that split or coalesce on treatment

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

### 3.2 Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need

not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

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

**Non-CR/Non-PD:** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

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

### *3.2.1 Special Notes on Assessment of Progression of Non-Target Disease*

The concept of progression of non-target disease requires additional explanation as follows:

#### *3.2.1.1 When the patient also has measurable disease*

In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy (see examples in Appendix 2 and further details below). A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

#### *3.2.1.2 When the patient has only non-measurable disease*

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

### 3.2.2 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

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

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
2. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

## 3.3 Response Assessment

### 3.3.1 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement.

### 3.3.2 Time Point Response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 3.3.2-1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 3.3.2-2 is to be used.

**Table 3.3.2-1: Time Point Response: Patients With Target (+/- Non-Target) Disease**

| Target Lesions | Non-Target Lesions | New Lesions | Overall Response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Non-CR/non-PD | No | PR |
| CR | Not evaluated | No | PR |
| PR | Non-PD or not all evaluated | No | PR |
| SD | Non-PD or not all evaluated | No | SD |
| Not all evaluated | Non-PD | No | NE |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease and NE = inevaluable

**Table 3.3.2-2: Time Point Response: Patients with Non-target Disease Only**

| Non-Target Lesions | New Lesions | Overall Response |
|---|---|---|
| CR | No | CR |
| Non-CR/non-PD | No | Non-CR/non-PD[a] |
| Not all evaluated | No | NE |
| Unequivocal PD | Yes or No | PD |
| Any | Yes | PD |

CR = complete response, PD = progressive disease and NE = inevaluable

[a] Non-CR/non-PD is preferred over SD for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

### 3.3.3 Best Overall Response

Best response determination of complete or partial response requires confirmation: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of

≥ 4 weeks later. In this circumstance, the best overall response can be interpreted as in Table 3.3.3-1.

**Special note on response assessment:** When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

**Table 3.3.3-1: Best Overall Response (Confirmation of CR&PR Required)**

| Overall Response First Time Point | Overall Response Subsequent Time Point | BEST Overall Response |
|---|---|---|
| CR | CR | CR |
| CR | PR | SD, PD OR PR[a] |
| CR | SD | SD provided minimum criteria for SD duration[b] met, otherwise, PD |
| CR | PD | SD provided minimum criteria for SD duration[b] met, otherwise, PD |
| CR | NE | SD provided minimum criteria for SD duration[b] met, otherwise, NE |
| PR | CR | PR |
| PR | PR | PR |
| PR | SD | SD |
| PR | PD | SD provided minimum criteria for SD duration[b] met, otherwise, PD |
| PR | NE | SD provided minimum criteria for SD duration [b]met, otherwise, NE |
| NE | NE | NE |

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

[b] Minimum criteria for SD duration is 6 weeks.

### *3.3.4 Confirmation Scans*

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive repeat assessments that should be performed no less than

28 days after the criteria for response are first met. For this study, the next scheduled tumor assessment can meet this requirement.

Verification of Progression: Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered to not have progressive disease.

[redacted]

# APPENDIX 7 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

## DEFINITIONS

## WOMAN OF CHILDBEARING POTENTIAL (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

**Women in the following categories are not considered WOCBP**

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state 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 > 40 mIU/mL to confirm menopause.

## CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 5 months after the end of study treatment.

Local laws and regulations may require use of alternative and/or additional contraception methods.

| **Highly Effective Contraceptive Methods That Are User Dependent**<br>*Failure rate of <1% per year when used consistently and correctly.*[a] |
|---|
| • Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b]<br>– oral<br>– intravaginal<br>– transdermal |

| |
|---|
| • Progestogen-only hormonal contraception associated with inhibition of ovulation[b]<br>– oral<br>– injectable |
| **Highly Effective Methods That Are User Independent** |
| • Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b]<br>• Intrauterine device (IUD)[c]<br>• Intrauterine hormone-releasing system (IUS)[c]<br>• Bilateral tubal occlusion |
| • Vasectomized partner<br>*A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.* |
| • Sexual abstinence<br>*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*<br>• It is not necessary to use any other method of contraception when complete abstinence is elected.<br>• WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2.<br>• Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence |
| NOTES:<br>[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.<br>[b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.<br>[c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness |

| **Unacceptable Methods of Contraception** |
|---|
| • Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously |

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal Sponge with spermicide
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus).
- Spermicide only
- Lactation amenorrhea method (LAM)

## CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until end of relevant systemic exposure defined as 7 months after the end of study treatment.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of study treatment.

## COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting

## APPENDIX 8 MANAGEMENT ALGORITHIMS

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

# APPENDIX 9 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW UP AND REPORTING

## ADVERSE EVENTS

| **Adverse Event Definition:** |
|---|
| An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant 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. |

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 discontinuation of study treatment.

Every adverse event must be assessed by the investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the participant's case report form.

## SERIOUS ADVERSE EVENTS

| **Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:** |
|---|
| Results in death |
| Is life-threatening (defined as an event in which the participant 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)<br><br>NOTE:<br><br>The following hospitalizations are not considered SAEs in BMS clinical studies:<br><br>○ 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)<br>○ elective surgery, planned prior to signing consent<br>○ admissions as per protocol for a planned medical/surgical procedure<br>○ routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)<br>○ medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases<br>○ admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)<br>○ admission for administration of anticancer therapy in the absence of any other SAEs |
| 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 participant or may require intervention [e.g., 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 9.2.7 for the definition of potential DILI.) |

Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study treatment 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 9.2.5 for reporting pregnancies).

All SAEs must be collected that occur during the screening period and within 100 days of the last dose of study treatment. For participants randomized/assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of treatment assigment.

## EVALUATING AES AND SAES

| **Assessment of Causality** |
|---|
| 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:<br><br>Related: There is a reasonable causal relationship between study drug administration and the AE.<br><br>Not related: There is not a reasonable causal relationship between study drug administration and the AE.<br><br>The term "reasonable causal relationship" means there is evidence to suggest a causal relationship. |

| **Follow-up of AEs and SAEs** |
|---|
| If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term(s) initially reported.)<br><br>If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.<br><br>All SAEs must be followed to resolution or stabilization. |

## REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms).
- 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. In the event the electronic system is unavailable for transmission, paper forms must be used and submitted immediately. 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