Statistical Analysis Plan for

Official Title of Study

PHASE 3B/4 SAFETY TRIAL OF NIVOLUMAB COMBINED WITH IPILIMUMAB IN SUBJECTS WITH PREVIOUSLY UNTREATED, ADVANCED OR METASTATIC RCC

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STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

PHASE 3B/4 SAFETY TRIAL OF NIVOLUMAB COMBINED WITH IPILIMUMAB IN SUBJECTS WITH PREVIOUSLY UNTREATED, ADVANCED OR METASTATIC RCC

PROTOCOL CA209-920

VERSION # 2.4, 26MAY2020

DOCUMENT HISTORY

Document	Date of Issues	Summary of Changes
Version 1	16-Mar-2017	Original Issue
Version 2.0	09-Aug-2018	• updated statistical analyses general method to state that all analyses will be performed by separated Cohort 1, Cohort 2, Cohort 3 and Cohort 4. • added additional populations - All Intermediate/Poor Risk Subjects, All Favorable Risk Subjects and PD-L1 treated subjects • updated IMDC prognostic criteria to <80% as per protocol and also replaced randomization with treatment. • added additional baseline characteristics - IMDC prognostic score, KPS, time from diagnosis to date of first dose, Hemoglobin, Corrected calcium, absolute neutrophils count, platelet count, histological subtypes • updated Efficacy section 7.5 to add additional analyses for All Intermediate/Poor Risk Subjects, All Favorable Risk Subjects • added section for Subset Analyses of Progression-Free Survival, OS and ORR • included Subject follow-up section. • included Follow-up Therapy section • updated section 7.7 to include only Cohort 1 [redacted]
Version 2.1	26-Oct-2018	• CBR added to BOR analysis • updated overall survival to include KM plot for responders Vs non-responders. • updated Baseline KPS score to remove < 80 and include 70 and < 70 • added additional population for BOR analysis

Document	Date of Issues	Summary of Changes
Version 2.2	13-Dec-2018	• added additional population for BOR analysis
Version 2.3	21-Oct-2019	[redacted]
Version 2.3	08-Jan-2020	• Updated Efficacy section for including or removing the populations. • Updated IP and F population definitions to consider Treated subjects rather than enrolled subjects. [redacted]
Version 2.3	02-Feb-2020	[redacted]
Version 2.4	14Apr2020	• Revise section 1.0 (schedule of analyses) per client request (added 'treatment' to end of first sentence.)
Version 2.4	15May2020	• Added Landmark Analysis for OS from 6 ,12 Months. • Removed Not qualified IMAE listing description.
Version 2.4	23May2020	• Removed Lab SI units summary. • Removed Clopper- Pearson CI from primary endpoint analysis.

Document	Date of Issues	Summary of Changes
Version 2.4	26May2020	• Added phrase in section 7.1: "Analyses based on the combination of Cohorts 2-4 are considered not necessary for CSR as Cohort 4 has low KPS and tolerability may not be the same with other groups." • Added phrase in landmark analyses: "These Landmark Analyses will not display hazard ratios, CI, median and p values." • Added phrase in section 7.5.2.6:" (population for this factor is All Treated Subjects with Intracranial Progression in Cohort 3)"

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2 STUDY DESCRIPTION

2.1 Study Design

This is 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.

Participants in Cohort 1 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.

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 week (± 3 days) until progression, unacceptable toxicity, withdrawal of consent, the study ends, or up to a maximum of 24 months, whichever occurs first.

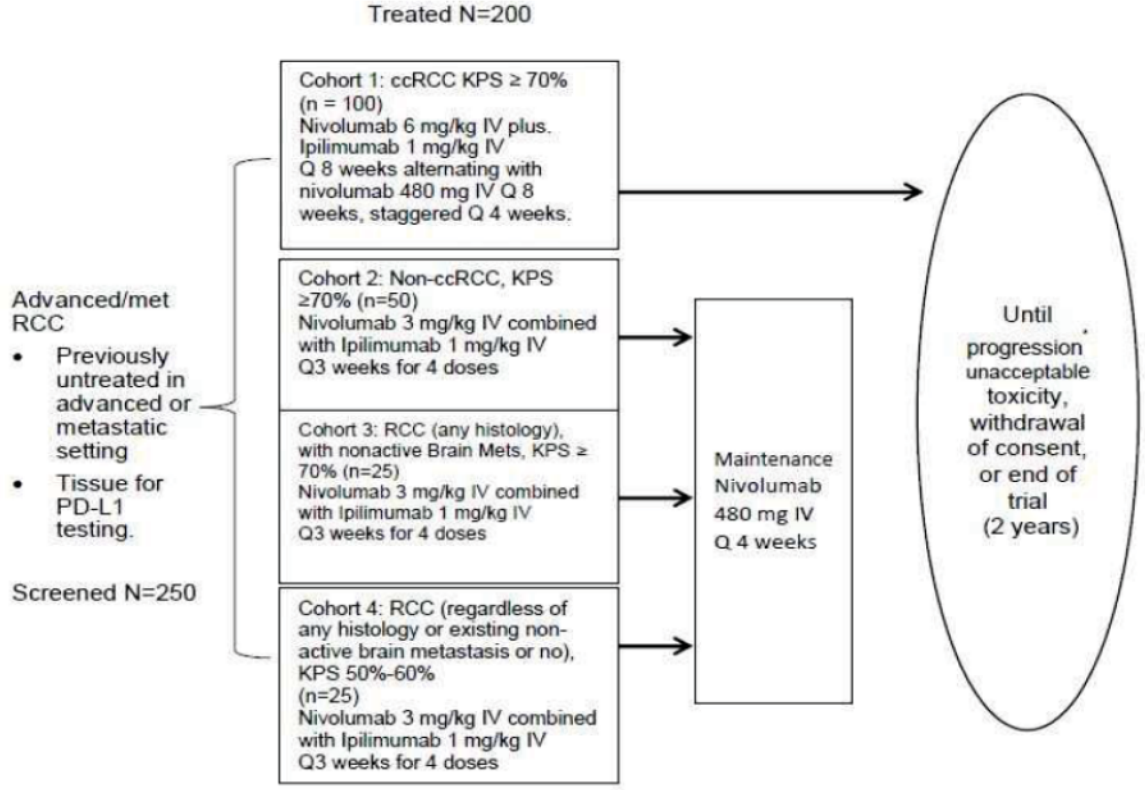
The study will continue until the last enrolled participant completes 5 years of survival follow up from last patient first treatment (LPFT). Participants will be permitted to continue treatment beyond progressive disease (PD) (Response Evaluation Criteria in Solid Tumor (RECIST) 1.1) under protocol-defined circumstances (See Protocol Section 7.9). No dose increases or reductions will be allowed for nivolumab.

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

This study will plan to have a 1-year enrollment period and approximately 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 in study is anticipated to be 200.

The start of the trial is defined as first participant first screening visit. The end of trial is defined as the 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.

Figure 2.1-1: 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.)

2.2 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
- KPS

2.3 Blinding and Unblinding

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

2.4 Protocol Amendments

Table 2.4-1: Protocol Amendments

Amendments	Date of Issue	Summary of Major Changes
01	24-Feb-2017	1. To align protocol with most recent program standards for nivolumab 2. To correct inconsistences and minor grammatical errors 3. Added language to indicate that the number of participants to be included in each cohort would be approximate. 4. If the number of participants in Cohorts 3 and 4 cannot be reached, the number of participants enrolled in the clear-cell or non-clear cell cohorts may be increased.

3 OBJECTIVES

3.1 Primary Objective

The primary objectives of this study are:

1. 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 in Cohort 1,
2. 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 4 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% in Cohorts 2, 3, and 4).

3.2 Secondary Objective

The secondary objectives of this study are:

1. 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,
2. To assess efficacy of nivolumab in combination with ipilimumab by measuring PFS 1 at time of initial progression, ORR, time to response (TTR), and duration of response (DOR), in all treated participants in different cohorts using RECIST 1.1.

4 ENDPOINTS

4.1 Primary Endpoint

The primary endpoint is the incidence of high grade (Grade 3-4 and Grade 5) IMAEs.

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:

1. Those occurring within 100 days of the last dose
2. Regardless of causality
3. With no clear alternate etiology based on investigator assessment, or with an immune-mediated component
4. 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).

The followings are the list of IMAEs in this study: skin, endocrinopathy, gastrointestinal, hepatic, renal, pulmonary, and neurologic adverse events.

4.2 Secondary Endpoints

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

1. Characterization of outcome of all high grade (Grade 3-4 and Grade 5) IMAEs: Time to onset, time to resolution and percentage of subjects who received immune modulating medication will be analyzed for high grade (Grade 3-5) IMAEs of interest. Time to onset is calculated from first dosing date to the IMAE event onset date. Time to resolution is calculated from the IMAE onset date to IMAE end date. If an IMAE is ongoing at the time of analysis, the time to resolution will be censored at the last contact date. Management of high-grade (Grade 3-5) IMAEs will be characterized according to the following for all treated subjects:
    1. Percentage of participants who received immune modulating medication (or hormonal replacement therapy),
    2. Percentage of participants who received $\geq$ 40 mg prednisone equivalents,
    3. Total duration of all immune modulating medications given for the event.
2. PFS 1: PFS 1 is defined as the time from first dose to the date of the first documented PD as determined by the investigator (per RECIST 1.1 criteria or clinical) or death due to any cause whichever occur first. Subjects who die without a reported PD and without subsequent anti-cancer therapy will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on-study tumor assessments and did not die will be censored on the date of first dose. Subjects who received any subsequent anti-cancer therapy without a prior reported progression will be censored at the

last evaluable tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy.

Table 4.2-1: Censoring Scheme Used in Primary Analysis of PFS 1

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments	First dose	Censored
No on study tumor assessments and no death	First dose	Censored
Progression documented between scheduled visits (per RECIST 1.1 criteria or clinical)	Date of the first documented tumor progression	Progressed
No progression, no death	Date of last tumor assessment with no documented progression	Censored
New anticancer treatment started without a prior reported progression	Date of last tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy	Censored
Death without progression and without subsequent anti-cancer therapy	Date of death	Progressed

3. ORR: ORR is defined as the number of subjects with a best overall response (BOR) of CR or PR divided by the number of response evaluable subjects. BOR is defined as the best response designation, as determined by the investigator, recorded between the date of first dose and the date of objectively documented progression (per RECIST 1.1 or Clinical) or the date of subsequent therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR determination. For subjects who continue treatment beyond progression, the BOR should be determined based on response designations recorded up to the time of the initial RECIST 1.1defined PD or clinical progression, whichever occurs first.

4. TTR: TTR is defined as time from the date of first dose to first documented CR or PR. Cohort 1 subjects who do not have a CR or PR will be censored at the maximum time of response + 1 day. Subjects who do not have a CR or PR in combined cohort 2, 3 and 4 will be censored at the maximum time of response in combined cohort +1 day.

5. DOR: DOR will be computed for subjects who achieve PR or CR only. The DOR is defined as the time between the date of first confirmed response to the date of the first documented tumor progression (per RECIST 1.1), or death due to any cause, whichever occurs first. Subjects who neither progress nor die will be censored on the date of their last evaluable tumor assessment. Subjects who received any subsequent anti-cancer therapy on or after the

date of first confirmed response will be censored at the last evaluable tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy.

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[redacted]

5 SAMPLE SIZE AND POWER

The sample size of the study is mainly determined by the feasibility concern. The study plans to enroll 200 participants; approximately100 in Cohort 1, 50 in Cohort 2, 25 in Cohort 3, and 25 in Cohort 4 (approximately 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 (CI) 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.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

The Baseline period and the Post-baseline period will be defined as detailed in Section 6.1 of the IO Core SAP.

6.2 Treatment Regimens

Refer to the Section 2.1 for treatments subject receiving in each cohort.

6.3 Populations for Analyses

The following analysis populations are defined for this study:

- Enrolled subjects: All subjects who signed an informed consent form and were registered into the IVRS.
- Treated subjects: All subjects who received any nivolumab. This is the primary population for safety and efficacy analyses.

- Response evaluable subjects: All treated subjects who have baseline and at least one on-study evaluable tumor measurement. Refer to the efficacy analysis section for the analyses conducted on this population.
- Intermediate/Poor Risk Subjects: All Treated subjects with baseline IMDC prognostic score ≥ 1 (IVRS).
- Favorable Risk Subjects: All Treated subjects with baseline IMDC prognostic score = 0 (IVRS)
- PD-L1 treated subjects: All subjects with a PD-L1 assessment at baseline who received any dose of study therapy.

7 STATISTICAL ANALYSES

SAS® version 9.2 or higher will be used for statistical analyses, tabulations and graphical presentations.

7.1 General Methods

In general, unless expressly stated otherwise, all analyses will be performed by separated Cohort 1, Cohort 2, Cohort 3 and Cohort 4. Except where otherwise stated in this SAP, all analyses and summaries will be performed for all treated subjects. Analyses based on the combination of Cohorts 2-4 are considered not necessary for CSR as Cohort 4 has low KPS and tolerability may not be the same with other groups.

Unless otherwise noted, the bulleted titles in the following subsections describe tabulations of discrete variables, by the frequency and proportion of subjects falling into each category, by cohorts (with total). Percentages given in these tables will be rounded and, therefore, may not always sum to 100%. Continuous variables will be summarized by cohort (with total) using the mean, standard deviation, median, minimum and maximum values.

Time to event distribution (i.e. progression free survival, overall survival and duration of response) will be estimated using Kaplan Meier (KM) techniques. When appropriate, the median along with 95% CI will be provided using Brookmeyer and Crowley methodology (using log-log transformation for constructing the confidence intervals). Rates at fixed timepoints (e.g. PFS 1 at 6 months) will be derived from the Kaplan Meier estimate and corresponding confidence interval will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function S(t).

The CA209 Core Safety DPP refers to several analyses that are to be performed on subjects with extended follow-up. For these summaries, AEs occurring from the time of the first dose of study therapy through 100 days after the last dose of study therapy will be summarized. Further general methods information for the safety analyses, including general methods for AEs and laboratory tests can be found in Section 7.1 of the IO core SAP.

7.2 Study Conduct

7.2.1 Accrual

The accrual pattern will be summarized per country, investigational site, and per month for all enrolled subjects. Enrollment date, first dosing date, country, investigational site will be presented in a by subject listing of accrual.

7.2.2 Relevant Protocol Deviations

The relevant protocol deviations will be summarized for all treated subjects. The following programmable deviations from inclusion and exclusion criteria will be considered as relevant protocol deviations. Non-programmable relevant eligibility and on-treatment protocol deviations, as well as significant (both programmable and non-programmable) eligibility and on-treatment protocol deviations will be reported through CTMS listings.

Eligibility at entrance:

1. Subjects having a baseline KPS less than 70% for Cohort 1, 2, and 3 or a baseline KPS no equal to 50-60% for Cohort 4

2. Subjects without extracranial metastasis as measurable disease

On-Study:

3. Subjects receiving antineoplastic therapy while on study therapy for a reason other than to treat a drug-related AE (i.e., chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of RCC)

A by-subject listing of relevant protocol deviation will also be produced.

7.3 Study Population

7.3.1 Subject Disposition

Number of subjects enrolled, treated, not treated and reasons for not treated will be summarized for all enrolled subjects. Number of subjects who discontinued treatment, discontinued study, and reasons for these discontinuations will be tabulated by cohorts.

Subject disposition will be listed for all enrolled subjects. For subjects who are treated, the subject's gender, age, race, consent date, first and last dosing date, study discontinuation date, and reason for treatment discontinuation and study discontinuation will be listed for Treated subjects. For subjects who were enrolled but not treated, the subject's gender, age, race, consent date, and reason for not being treated will be listed.

7.3.2 Demographic and Baseline Characteristics

The following baseline characteristics will be summarized for all treated subjects, according to the general methods. All baseline presentations will identify subjects with missing measurements. Listings will also be provided.

- Age (descriptive statistics)
- Age (< 65, ≥ 65 - < 75, ≥ 75, ≥ 65)

- Gender (male, female)
- Race
- Ethnicity
- Child Bearing Potential Status
- Weight (descriptive statistics)
- Height (descriptive statistics)
- Baseline ECG
- Enrollment Cohort (1, 2, 3, 4)
- Baseline KPS (100, 90, 80,70, <70)
- Baseline IMDC prognostic score (0, 1-2, 3-6) (source: CRF)
- Smoking status (Never, Current, Former, Unknown)
- Disease stage at initial diagnosis (Stage I, II, III, IV)
- Time from initial disease diagnosis to date of first dose (< 1 year, >= 1 year)
- Disease stage at study entry (Stage III, Stage IV)
- Hemoglobin (<LLN, ≥ LLN)
- Corrected Calcium (≤ 10 mg/dl, >10mg/dl)
- Absolute Neutrophil count (>ULN, <=ULN)
- Platelet count (>ULN, <=ULN)
- Cell type (Clear Cell RCC, Non-Clear Cell RCC)
- All lesions (Tumor assessments at baseline): sites of disease, number of disease sites per subject.
- Target lesions (Tumor assessments at baseline): presence of target lesions, measurement of largest target lesion, site of target lesion, sum of target lesion diameters.
- Baseline PD-L1 expression
- Brain Metastases (Yes/No)
- Sarcomatoid Features (Yes/No)
- Histological subtypes (Papillary, Chromophobe, Translocation Associated, Collecting duct, Medullary, any pathogen unclassified, only for Cohort 2)

7.3.3 Medical History

General medical history will be listed by subject and pretreatment events will be tabulated by worst CTCAE grade and by system organ class (SOC)/ preferred term (PT) for all treated subjects.

7.3.4 Prior Therapy Agents

The following will be summarized by cohorts for all treated subjects, according to the general methods:

- Prior systemic cancer regimen (yes/no)
- Prior systemic therapy regimen setting (adjuvant/ neo-adjuvant/metastatic)

- Prior radiotherapy (yes/no)
- Prior surgery related to cancer (yes/no)
- Prior systemic therapy by setting and generic name.
- Prior/current other medication classified by anatomic and therapeutic classes.

Medication will be reported using the generic name. Listings of prior systemic cancer therapy, prior radiotherapy and prior surgery related to cancer, prior/current medications by subject will also be provided.

7.3.5 Baseline Examinations

Subjects with abnormal baseline physical exam results will be tabulated by examination criteria (eg, neck, cardiovascular, lungs, etc) for all treated subjects, according to the general methods.

7.4 Extent of Exposure

7.4.1 Administration of Study Therapy

The following parameters will be summarized (descriptive statistics) for all treated subjects, according to the general methods:

- Number of combined doses received (nivolumab + ipilimumab). A subject will be considered to have received combined doses of ipilimumab and nivolumab, if both infusions are administered on the same date.
- Number of doses received (nivolumab and ipilimumab)
- Cumulative dose (nivolumab and ipilimumab) in mg or mg/kg
- Relative dose intensity (%) using the following categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%. (nivolumab and ipilimumab)

Table 7.4.1-1: 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 Ipilimumab 1 mg/kg Nivolumab 480 mg	Combination: D1W1 and then every 8 weeks. Monotherapy beginning D1W5 of C1, and then every 8 weeks	Nivolumab IV Ipilimumab IV
Cohort 2, 3, and 4	Nivolumab 3 mg/kg Ipilimumab 1 mg/kg Nivolumab 480 mg	Combination therapy: every 3 weeks for 4 doses. Maintenance monotherapy every 4 weeks afterwards.	Nivolumab IV Ipilimumab IV

Table 7.4.1-2: Study Therapy Parameter Definitions

	Cohort 1		Cohort 2, 3 and 4	
	Nivolumab	**Ipilimumab 1 mg/kg**	**Nivolumab**	**Ipilimumab 1 mg/kg**
Actual Dose (mg)	Actual dose is defined as the total dose delivered (mg) within each dosing visit.	Actual Dose (mg) is defined as the total dose delivered (mg) within each dosing visit.	Actual dose is defined as the total dose delivered (mg) within each dosing visit.	Actual Dose (mg) is defined as the total dose delivered (mg) within each dosing visit.
Actual Dose Level (mg/kg)	Actual Dose Level (mg/kg) is defined as the actual dose delivered (mg) within a dosing visit /most recent weight (kg) at the dosing visit.	Actual Dose Level (mg/kg) is defined as the actual dose delivered (mg) within a dosing visit /most recent weight (kg) at the dosing visit.	Actual Dose Level (mg/kg) is defined as the actual dose delivered (mg) within a dosing visit /most recent weight (kg) at the dosing visit.	Actual Dose Level (mg/kg) is defined as the actual dose delivered (mg) within a dosing visit /most recent weight (kg) at the dosing visit.
Cumulative Dose (mg/Kg)	Cumulative Dose (mg/kg) is the sum of the actual dose levels administered to a subject during the study.	Cumulative Dose (mg/kg) is the sum of the actual dose levels administered to a subject during the study.	Cumulative Dose (mg/kg) is the sum of the actual dose levels administered to a subject during the study.	Cumulative Dose (mg/kg) is the sum of the actual dose levels administered to a subject during the study.
Cumulative Dose (mg)	Cumulative Dose (mg) is the sum of the actual doses administered to a subject during the study.	Cumulative Dose (mg) is the sum of the actual doses administered to a subject during the study.	Cumulative Dose (mg) is the sum of the actual doses administered to a subject during the study.	Cumulative Dose (mg) is the sum of the actual doses administered to a subject during the study.
Total Expected Dose (mg)	[6 x Weight* x (Last dose date of 6mg/kg – Start dose date of 6mg/kg + 56)/56] + [480 x (Last dose date of 480 mg – Start dose date of 480 mg + 56)/56] *Average weight during 6 mg/ kg dosing is used.	[1 x Weight* x (Last dose date – Start dose date + 56)/56] *Average weight during 1 mg/ kg dosing is used.	[3 x Weight* x (Last dose date of 6mg/kg – Start dose date of 6mg/kg + 21)/21] + [480 x (Last dose date of 480 mg – Start dose date of 480 mg + 28)/28] *Average weight during 3 mg/ kg dosing is used.	[1 x Weight* x (Last dose date – Start dose date + 21)/21] *Average weight during 1 mg/ kg dosing is used.

Table 7.4.1-2: Study Therapy Parameter Definitions

	Cohort 1		Cohort 2, 3 and 4	
	Nivolumab	**Ipilimumab 1 mg/kg**	**Nivolumab**	**Ipilimumab 1 mg/kg**
Relative Dose Intensity (%)	Cumulative Dose (mg) x100/ Total Expected Dose (mg)	Cumulative Dose (mg) x100/ Total Expected Dose (mg)	Cumulative Dose (mg) x100/ Total Expected Dose (mg)	Cumulative Dose (mg) x100/ Total Expected Dose (mg)
Duration of Treatment	Last dose date - Start dose date +1. Last dose date is the last date subject received Nivolumab 6 mg/kg or 480 mg.	Last dose date - Start dose date +1	Last dose date - Start dose date +1. Last dose date is the last date subject received Nivolumab 3 mg/kg or 480 mg.	Last dose date - Start dose date +1

Duration of treatment will be presented using a Kaplan-Meier curve whereby the last dose date will be the event date for those subjects who are off study therapy. Median duration of treatment and associated 95% CI will be provided. Subjects who are still on study therapy will be censored on their last dose date.

A by-subject listing of dosing of study medication (record of study medication, infusion details, and dose changes) and a listing of drug assignment and dispensation will be also provided.

7.4.2 Modifications of Study Therapy

7.4.2.1 Dose Delays

A dose will be considered as actually delayed if the delay is exceeding 3 days (i.e., greater than or equal to 4 days from scheduled dosing date). Dose delays will be divided into following categories: 4-7 days, 8-14 days, 15-42 days, >42 days. Reason for dose delay will be retrieved from CRF dosing pages.

The following parameters will be summarized:

- Number of dose delays per subject, length of delay and reason for dose delay
- Number of subjects with at least one dose delay along with reason for dose delay.

7.4.2.2 Dose Reductions/Escalations and Infusion Interruption

There will be no dose escalations or reductions of nivolumab or ipilimumab allowed per protocol. Nivolumab or ipilimumab infusion can be interrupted and/or the IV infusion rate can be reduced. This information will be retrieved from CRF dosing pages.

The following parameters will be summarized for nivolumab and ipilimumab administration by cohorts:

- Number of subjects with at least one dose infusion interrupted along with the reason of all interruptions,
- Number of subjects with at least one infusion with IV rate reduced along with the reason of all rate reductions.

A by subject listing of study drug administered will be provided.

[redacted]

7.5 Efficacy

7.5.1 Secondary Analyses

7.5.1.1 Progression-Free Survival 1

PFS 1 will be summarized by the KM product-limit method for all treated subjects for all cohorts and all intermediate/poor risk subjects and all favorable risk subjects only for Cohort 1. Median values of PFS 1, along with two-sided 95% CI using the Brookmeyer and Crowley method, will be calculated. Standard error will be calculated using the Greenwood formula. Survival rate at different time points (at 6, 12, 18, 24 months) will be estimated based on KM method for all treated subjects for all Cohorts and all intermediate/poor risk subjects and all favorable risk subjects only for Cohort 1.

PFS 1 will be graphically displayed along with the median and 95% CI. The source of progression (death versus progression) will be summarized by cohort for all Treated subjects and all intermediate/poor risk subjects and all favorable risk subjects only for Cohort 1.

7.5.1.2 Objective Response Rate and Clinical Benefit Rate

The Objective Response Rate (ORR) and Clinical Benefit Rate (CBR) 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 subjects for all cohorts and response evaluable intermediate/poor risk subjects and all response evaluable favorable risk subjects will be presented only for Cohort 1. The BOR will be tabulated.

Listings of BOR, per time point tumor response, and lesion evaluations will be provided.

7.5.1.3 Time to Response

TTR will be summarized using the KM method for all response evaluable subjects for all cohorts, all intermediate/poor risk subjects and all favorable risk subjects only for Cohort 1. Median values

of TTR, along with two-sided 95% confidence intervals using the Brookmeyer and Crowley method, will also be calculated.

TTR will be graphically displayed using the cumulative rate of response over time.

7.5.1.4 Duration of Response

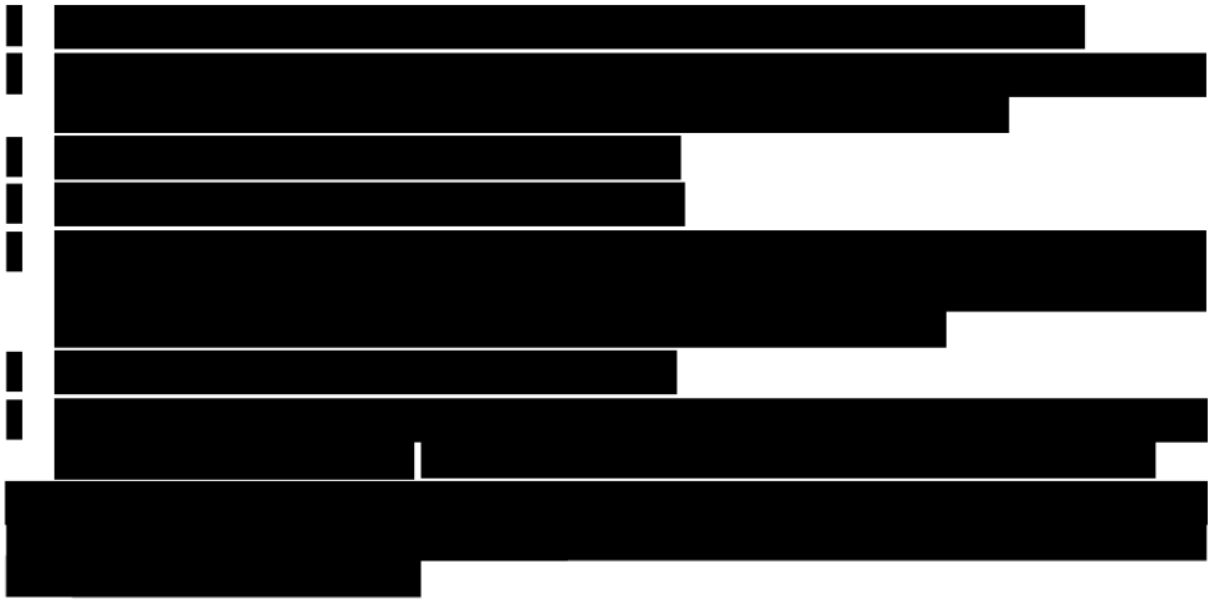
DOR will be summarized using KM product-limit method. Median values of DOR based on KM method, along with two-sided 95%CI using Brookmeyer and Crowley method, will be calculated and presented in a table.

In addition, the percentage of subjects with ongoing response at different time points (3, 6, 12, 18, and 24 months) will be presented based on the DOR KM plot.

This analysis will be performed for all response evaluable subjects for all Cohorts, all intermediate/poor risk subjects and all favorable risk subjects only for Cohort 1 who achieve confirmed PR or CR.

A by-subject listing of TTR and DOR will be provided.

[redacted]



7.6 Safety

7.6.1 Primary Analyses

7.6.1.1 Incidence of High Grade Immune-Mediated Adverse Events

The number and percentage of subjects who report high-grade (Grade 3-4 and Grade 5) IMAEs will be summarized using all treated subjects. The IMAEs of interest are the followings: skin, endocrinopathy, gastrointestinal, hepatic, renal, pulmonary, and neurologic adverse events.

High grade (Grade 3-4 and Grade 5) IMAEs will be tabulated using worst grade per CTCAE v4.0 criteria by system organ class and Medical Dictionary for Regulatory Affairs (MedDRA) preferred term.

IMAEs are identified using a custom MedDRA query that is fully defined and updated by BMS and maintained as a separate file. The most recent version will be used for the analysis.

7.6.2 Secondary Analyses

7.6.2.1 Characterization of Outcome of High Grade Immune-Mediated Adverse Events

Time to onset and time to resolution will be analyzed for high grade (Grade 3-5) IMAEs of interest. The IMAEs of interest are the followings: skin, endocrinopathy, gastrointestinal, hepatic, renal, pulmonary, and neurological adverse events. Median values using the Kaplan-Meier (KM) product limit method with 95%CI using Brookmeyer and Crowley method will be presented for all treated subjects.

Analysis of endpoints related to management of high-grade (Grade 3-5) IMAEs will be conducted based on General Methods specified in Section 7.1.

[redacted]

[redacted]

[redacted]

[redacted]

7.6.4 Laboratory Abnormalities

Laboratory abnormalities including hematology, chemistry, liver function, and thyroid function will be summarized using conventional units.

7.6.4.1 Hematology

See Section 7.6.10.1 of IO Core SAP.

7.6.4.2 Serum Chemistry

See Section 7.6.10.2 of IO Core SAP.

7.6.4.3 Electrolytes

See Section 7.6.10.3 of IO Core SAP.

7.6.4.4 Additional Analyses

See Section 7.6.10.4 of IO Core SAP.

7.6.5 Vital Signs and Pulse Oximetry

See Section 7.6.11 of CA209 Core Safety SAP.

[redacted]

[redacted]

7.6.7 Pregnancy

See Section 7.6.15 of IO Core SAP.

7.6.8 Adverse Event By Subgroup

Not applicable.

[redacted]

[redacted]

[redacted]

[redacted]

8 CONVENTIONS

Conventions are described in Section 8 of the IO Core SAP.

9 CONTENT OF REPORTS

9.1 Clinical Study Report

Statistical components for the clinical study report will be based on the content of this statistical analysis plan (SAP). Details of the tables, listings, and figures to be prepared for the final CSR will be included in a study-specific Data Presentation Plan (DPP).

9.2 Other Reports and Reviews

9.2.1 Safety Reviews

The safety review planned will include, but not be limited to the following frequency. Additional reviews may be triggered on an ad hoc basis by the BMS CA209-920 study team. Safety review for all treated subjects will take place, when any of the following criteria are satisfied:

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

OR

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

OR

- When a minimum of 25 subjects in Cohort 1 have received at least two combination doses 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 data will be provided for safety review:

- Subject disposition
- Demographic and baseline characteristics
- Exposure of study drug
- AEs 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.

APPENDIX 1 INTERNATIONAL METASTATIC RCC DATABASE CONSORTIUM (IMDC) PROGNOSTIC CRITERIA

Adverse Prognostic Factors
Clinical
KPS < 80%
Time from diagnosis to treatment < 1 year
Laboratory
Hemoglobin < LLN
Corrected calcium > ULN
Absolute neutrophil count > ULN
Platelet count > ULN

LLN = Lower limit of normal

ULN = Upper limit of normal

Corrected calcium (mg/dL) = measured total Ca (mg/dL) + 0.8 (4.0 - serum albumin [g/dL]), where 4.0 represents the average albumin level in g/dL.

Corrected calcium (mmol/L) = measured total Ca (mmol/L) + 0.02 (40 - serum albumin [g/L]), where 40 represents the average albumin level in g/L

APPENDIX 3 ADVERSE EVENTS OF INTEREST DEFINITION AND CONVENTIONS

The adverse events of interest including IMAE, select AE, and other event of special interest consist of a list of preferred terms grouped by specific category and by subcategory. These categories and subcategories are defined by the Sponsor and the list that is most current at the time of analysis will be used. Also, changes may be made to this list with each new version of MedDRA.

Time-to onset definition

Time-to onset of AE (any grade) for a specific category (e.g. pulmonary events, gastrointestinal events, ...) is defined as the time between the day of the first dose of study treatment and the onset date of the earliest AE (of any grade) in this category.

If the subject did not experience an AE (of any grade) in the category, time-to onset will be censored at the maximum follow-up time of all subjects in their respective treatment group (i.e for subjects without an event, follow-up time is defined from first dosing date up to last dosing date +30 days (or 100 days depending on the analysis) if subjects are off treatment and followed for at least 30 days (or 100 days depending on the analysis) , otherwise it is defined up to the last known alive date). The resulting Kaplan-Meier plot will represent the cumulative rate of the select AE (any grade) in the category over time.

Time-to onset of AE (grade 3-5) for a specific category is defined similarly but restricted to grade 3-5 AEs.

Time-to onset of drug-related (grade 3-5 or any grade) AE for a specific category is defined similarly but restricted to drug-related AEs.

Time-to onset for a specific subcategory is defined similarly but restricted to event of this subcategory.

Time-to resolution definition

In order to derive the time-to resolution, overlapping or contiguous AEs within a specific category will be collapsed into what will be termed "clustered" AEs. For example, if a subject (without pre-treatment AE) experienced an AE from 1st to 5th January, another AE (with different PT but within same category) from 6th to 11th January and same AE from 10th to 12th January, these will be collapsed into one clustered AE from 1st to 12th January. Table A3-1 summarizes key derivation steps for each type of clustered AEs.

Time-to resolution of AE (any grade) for a specific category is defined as the longest time from onset to complete resolution or improvement to the grade at baseline among all clustered select AEs in this category experienced by the subject. Events which worsened into grade 5 events (death) or have a resolution date equal to the date of death are considered unresolved. If a clustered AE is considered as unresolved, the resolution date will be censored to the last known date alive. Improvement to the grade at baseline implies that all different adverse events in the clustered adverse event should at least have improved to the corresponding (i.e. with same preferred term)

baseline grade. This measure is defined only for subjects who experienced at least one AE in the specific category.

The time-to resolution of AE (grade 3-5) for a specific category is defined similarly with an onset date corresponding to a grade 3-5 AE.

Time-to resolution of drug-related AE (any grade or grade 3-5) is defined similarly but restricted to drug-related AE.

The time-to resolution of AE (any grade or grade 3-5, drug-related or all) where immune modulating medication was initiated is defined similarly with the additional condition that the subject started an immune modulating medication during the longest AE resolution period.

Time-to resolution for a specific subcategory is defined similarly but restricted to event of this subcategory.

Table A3-1: Derivation of Clustered AE of Interest

Type of clustered AE of interest	Derivation
Any grade	Collapse any on-treatment AE from the same category
Drug-related of any grade	Collapse any on-treatment drug-related AE from the same category
Grade 3-5	Collapse any on-treatment AE from the same category. Resolution will be based on the onset date of the earliest grade 3-5 records (if no grade 3-5 record, clustered AE is excluded)
Drug-related of Grade 3-5	Collapse any on-treatment drug-related AE from the same category Resolution will be based on the onset date of the earliest grade 3-5 record (if no Grade 3-5 record, clustered AE is excluded)

The algorithm for collapsing adverse event of interest (IMAE, select AE, other event of special interest) records uses the following conventions:

For each subject and specified category, the corresponding adverse event records will be collapsed when:

1) Multiple adverse event records have the same onset date.
2) The onset date of an event record is either the same day or 1 day later than the resolution date of a preceding event record (contiguous events).

The onset date of an event record is after the onset date and prior to or on the resolution date of a preceding event record (overlapping events).

[redacted]

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[redacted]