Statistical Analysis Plan for

Official Title of Study

Safety Study of Nivolumab for Selected Advanced Malignancies in India

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STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

SAFETY STUDY OF NIVOLUMAB FOR SELECTED ADVANCED MALIGNANCIES IN INDIA

PROTOCOL CA209887

VERSION # 1.0

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LIST OF ABBREVIATIONS

AE	adverse event(s)
AEOSI	other events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	Aspartate aminotransferase
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
CR	Complete response
CRF	Case Report Form, paper or electronic
CSR	Clinical Study Report
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for AEs
ECOG	Eastern Cooperative Oncology Group
HB	hemoglobin
HR	heart rate
IMAEs	Immune-mediated AEs
IMP	investigational medicinal products
IP	investigational product
IV	intravenous
IVRS	interactive voice recognition system
LDH	lactate dehydrogenase
LFT	liver function tests
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
NSQ	non-squamous
PD	Progressive disease
PR	Partial response
PS	Performance status
PT	Preferred Term
RCC	renal cell carcinoma
RR	respiratory rate
SAE	serious adverse event(s)

SAP	statistical analysis plan
SAS	Statistical Analysis System software
SD	Stable disease
SI	standard international unit
SOC	System Organ Class
SQ	squamous
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
WHO	World Health Organization
WOCBP	women of childbearing potential

[redacted]

Research Hypothesis:

This study will describe the adverse reactions that occur during 6 months of treatment with nivolumab in patients with advanced NSCLC or RCC in India. No test of the statistical hypothesis is planned in this study.

Schedule of Analyses:

Data analyses will be conducted only on the safety data collected within the maximum of the 26 week study period, which will include safety collected during the follow-up of patients who discontinue treatment before 24 weeks.

Final analysis will be done once the study will be completed on the date on which safety data (primary endpoint) are collected for the last participant on study.

2 STUDY DESCRIPTION

2.1 Study Design

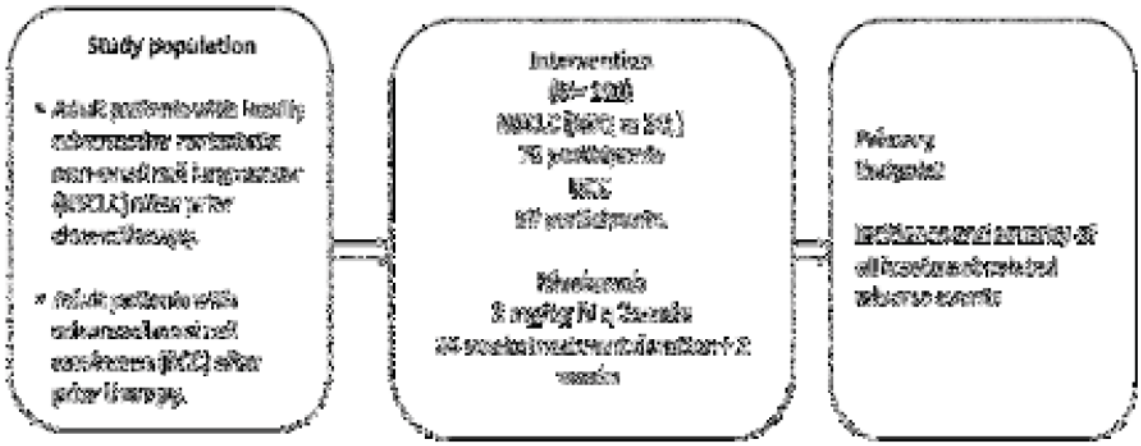
This is a Phase 4, open-label, single arm, multi-center, prospective safety study to be conducted in India with patients with either locally advanced or metastatic NSCLC (Stage IIIb/IV NSCLC) with squamous histology or non-squamous histology who have progressed during or after at least 1 prior chemotherapy (N= 70) or advanced RCC who have progressed during or after at least 1 prior therapy (N= 30). Potential patients will undergo screening evaluations to determine eligibility within 28 days prior to first dose. Patients who meet the protocol defined inclusion/exclusion criteria will be prospectively enrolled in a sequential manner. All enrolled patients will be treated with nivolumab administered intravenously over 60 minutes at 3 mg/kg every 2 weeks. Each 14 day dosing period will constitute a cycle. Treatment will continue as long as clinical benefit is observed for a maximum of 24 weeks or until treatment is no longer tolerated by the participant or withdrawal of consent. The treatment period for this study is 26 weeks, which corresponds to 24 weeks of treatment and 2 weeks of follow-up after the final on-study dose of nivolumab. Patients who are observed to continue to receive clinical benefit from nivolumab at 26 weeks will continue treatment via commercial supply (provided by BMS) as long as clinical benefit is observed or until treatment is no longer tolerated by the participant. Any participant who discontinues treatment with nivolumab before 24 weeks on study will be followed for 100 days after discontinuation of study drug or for a total of 26 weeks from first on-study treatment with nivolumab, whichever is earliest.

Safety will be evaluated throughout the treatment period and during the follow up of patients who discontinue treatment before 24 weeks by physical exams including vital signs, AE/SAE monitoring, laboratory evaluations and recording of concomitant medications.

All SAEs after 26 weeks of study duration for patients on commercial nivolumab supply will be reported to India Health Authority as part of spontaneous reporting.

The study design schematic is presented in Figure 2.1.

Figure 2-1: Study Design Schematic



- Participants who discontinue on-study treatment before 24 weeks will be followed for 100 days after last on-study dose of nivolumab or for 26 weeks after first on-study dose, whichever is earliest.
- Participants who continue to benefit clinically from nivolumab at 26 weeks will continue treatment via commercial supply (provided by BMS) as long as clinical benefit is observed or until treatment is no longer tolerated by the participant. All SAEs after 26 weeks of study duration for patients on commercial nivolumab supply will be reported to India Health Authority as part of spontaneous reporting.

Physical examinations, vital sign measurements, and clinical laboratory evaluations will be performed at selected times throughout the dosing interval and during follow-up for those patients who discontinue treatment before the end of the treatment period (24 weeks). Patients will be closely monitored for AEs throughout the study.

2.2 Treatment Assignment

After informed consent has been obtained and the subject's eligibility is established, the subject will be enrolled and a number will be assigned through an interactive voice response system (IVRS). All patients will receive treatment with nivolumab in an open-label fashion. Study treatment will be dispensed at the study visits as listed in Schedule of Activities (Appendix 1).

2.3 Blinding and Unblinding

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

2.4 Protocol Amendments

Not applicable.

2.5 Data Monitoring and Other External Committees

Not applicable.

3 OBJECTIVES

3.1 Primary

- To assess the safety and tolerability of nivolumab for the treatment of locally advanced or metastatic NSCLC after prior chemotherapy or advanced RCC after prior therapy.

3.2 Secondary

- To estimate the incidence and severity of treatment-related select AEs in all treated patients.
- To estimate the incidence of all treatment-related SAEs
- To estimate the incidence of AEs that lead to discontinuation of treatment with nivolumab.

4 ENDPOINTS

4.1 Primary Endpoint

- Incidence and severity of all treatment-related AEs

4.2 Secondary Endpoints

- Incidence and severity of all treatment-related select AEs which are as follows
    - Pulmonary toxicity
    - Gastrointestinal toxicity (diarrhea or colitis)
    - Endocrinopathies
    - Hepatotoxicity (including asymptomatic liver function tests (LFT) elevations)
    - Renal toxicity
    - Skin toxicity
    - Neurological toxicity
    - Hypersensitivity/infusion reactions
- Incidence of all treatment-related SAEs
- Incidence of AEs that lead to discontinuation from treatment with nivolumab

5 SAMPLE SIZE AND POWER

The study is projected to enroll a minimum of 100 patients (70 NSCLC patients and 30 RCC patients). The total sample size for this study is based on logistical considerations. The sample size meets regulatory requirement for safety update submission.

In global clinical studies, treatment-related AEs of any grade occurred approximately 65% and of Grade 3-4 occurred approximately 10% in nivolumab users with NSCLC; treatment-related AEs

of any grade occurred approximately 80% and of grade 3-4 occurred approximately 20% in nivolumab users with RCC. Assuming these event rates, there is approximately 99% probability to observe at least 37 treatment-related AEs of any grade and approximately 84% probability to observe at least 5 treatment-related AEs of grade 3-4 in the 70 NSCLC patients; there is approximately 97% probability to observe at least 20 treatment-related AEs of any grade and approximately 88% probability to observe at least 4 treatment-related AEs of grade 3-4 in the 30 RCC patients.

Given the proposed sample size, the 95% confidence intervals for relevant AE rates are presented in Table 5-1.

Table 5-1 CA209887: Estimated Incidence Rates and 95 % CIs

Incidence Rate (%)	Sample Size	Lower 95% CI (%)	Upper 95% CI (%)
5	30	0.36	19.71
	70	1.22	13.01
	100	1.64	11.28
10	30	2.11	26.53
	70	4.12	19.52
	100	4.90	17.62
20	30	7.71	38.57
	70	11.39	31.27
	100	12.67	29.18
30	30	14.73	49.40
	70	19.62	42.13
	100	21.24	39.98
40	30	22.66	59.40
	70	28.47	52.41
	100	30.33	50.28
50	30	31.30	68.70
	70	37.80	62.20
	100	39.83	60.17
60	30	40.60	77.34

	70	47.59	71.53
	100	49.72	69.67
70	30	50.60	85.27
	70	57.87	80.38
	100	60.02	78.76

Exact confidence interval based on Clopper-Pearson method

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

6.1.1 Baseline Period

Baseline evaluations or events will be defined as evaluations or events that occur before the date and time of the first dose of study treatment. Evaluations on the same date and time of the first dose of study treatment will be considered as baseline evaluations.

In cases where the time (onset time of event or evaluation time and dosing time) is missing or not collected, the following definitions will apply:

- Pre-treatment AEs will be defined as AEs with an onset date prior to but not including the day of the first dose of study treatment
- Baseline evaluations (e.g., laboratory tests and vital signs) will be defined as evaluations with a date on or prior to the day of first dose of study treatment

If there are multiple valid assessments, the assessment that is closest to day (and time if collected) of the first dose of study treatment will be used as the baseline in the analyses. If multiple assessments are collected at the same date (and time if collected), the assessment with the latest database entry date (and time if collected) will considered as baseline.

6.1.2 Post Baseline Period

- On-treatment AEs will be defined as AEs with an onset date and time on or after the date and time of the first dose of study treatment (or with an onset date on or after the day of first dose of study treatment if time is not collected or is missing). For subjects who are off study treatment, AEs will be included if event occurred within a safety window of 100 days after the last dose of study treatment or for a total of 26 weeks from first on-study treatment with nivolumab, whichever is earliest. No subtracting rule will be applied when an AE occurs both pre-treatment and post-treatment with the same preferred term and grade.

- On-treatment evaluations (laboratory tests and vital signs) will be defined as evaluations taken after the day (and time, if collected and not missing) of first dose of study treatment. For subjects who are off study treatment, evaluations should be within a safety window of 100 days after the last dose of study treatment or for a total of 26 weeks from first on-study treatment with nivolumab, whichever is earliest.
- Late emergent drug-related AEs will be defined as drug-related AEs with an onset date greater than 100 days after the last dose of study treatment in subjects who are off study treatment or for a total of 26 weeks from first on-study treatment with nivolumab, whichever is earliest.

6.2 Treatment Regimens

Patients should receive nivolumab at a dose of 3 mg/kg as a 60-minute IV infusion, on Day 1 of each treatment cycle every 2 weeks for 24 weeks or until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. Patients should begin study treatment within 3 calendar days of enrollment.

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.

6.3 Populations for Analyses

The following subject populations will be considered in this trial:

- **All Enrolled Patients:** All patients who signed an informed consent form and were registered into the IVRS.
- **All Treated Patients:** All Patients who received any nivolumab. This is the primary population for safety analyses. Subpopulation analyses will be conducted by tumor type.

7 STATISTICAL ANALYSES

7.1 General Methods

Unless otherwise noted, discrete variables will be tabulated by the frequency and proportion of subjects falling into each category, grouped by tumor type. Percentages given in these tables will be rounded to the first decimal and, therefore, may not always sum to 100%. Percentages less than 0.1 will be indicated as ‘< 0.1’. Continuous variables will be summarized by tumor type using the mean, standard deviation, median, minimum, and maximum values.

The conventions to be used for imputing partial dates for analyses requiring dates are described in Section 8.

Unless specified otherwise, all analyses will be tabulated in 3 columns: NSCLC, RCC, and the 2 cancer types pooled.

7.2 Study Conduct

Unless otherwise specified, the study conduct data will be presented on all treated subjects by tumor type.

7.2.1 Relevant Protocol Deviations

All protocol deviations identified will be summarized by protocol deviation type 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 ICOMaster.

A by-subject listing will be provided.

7.3 Study Population

Unless otherwise specified, the study population data will be presented on all treated subjects by tumor type.

7.3.1 Subject Disposition

The total number of subjects enrolled, treated and not treated will be presented along with the reason for not being treated.

In addition, the below summary will be provided.

- **Pre-Treatment Status:** The total number of subjects entered into the treatment phase and not entering the treatment phase will be presented along with the primary reason for not entering the treatment phase of this study.
- **Subject Status (End of Treatment):** Total number of subjects completed the phase of study-treatment along with the primary reason for not completing this phase of the study or not continuing in the treatment period of the study will be presented.
- **Subject Status (End of Study):** Total number of subjects continues to be followed (Yes/No) and primary reason for not continuing in the study will be presented.

Also, total number of subjects by investigational site will be provided.

A by subject listing of pre-treatment, end of treatment and end of study status will be provided separately.

7.3.2 Demographics and Baseline Characteristics

Overall summary of the following demographic and baseline characteristics will be summarized for all treated subjects and also by tumor type.

- Age
- Age Category (< 65, ≥ 65 - <75, ≥ 75years)
- Gender
- Race
- Smoking history by Status: Never/Current/Former/Unknown
- Initial disease diagnosis
  - Time from initial diagnosis to study treatment first dose
  - Tumor Type
- Current Disease Diagnosis
  - Time from diagnosis to study treatment first dose
  - Disease stage at study entry: I/II/III/IV

A by subject listing will be provided separately for demography, initial diagnosis and current disease diagnosis.

7.3.3 Physical Measurements

Descriptive statistics of the following physical measurements will be summarized for all treated subjects by tumor type and overall.

- Baseline weight (kg)
- Baseline height (cm)
- Baseline BMI (kg/m^2)
- Baseline Eastern Cooperative Oncology Group (ECOG) performance status

In addition, physical measurements will also be summarized by study visit for each tumor type and overall.

A by subject listing will be provided.

7.3.4 Medical History

General medical history will be coded and grouped into Preferred Terms (PT) by System Organ Class (SOC), using Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 or higher. Listings and summaries will be based on the SOCs and PTs. Summaries will be provided for all treated subjects by tumor type and overall.

A by subject listing of medical history will be provided. In addition, specific disease history will be displayed in listings.

7.3.5 Prior Therapy

Descriptive statistics of prior therapies will be summarized for all treated subjects by tumor type and overall.

- Prior Radiotherapy
  - Subjects received prior radiotherapy (yes/no)
  - Sites of radiotherapy
  - Time from therapy stop date to study treatment first dose
- Prior Surgery Related to Cancer
  - Subjects received any prior surgery related to cancer (yes/no)
  - Time from surgery to study treatment first dose
  - Type of surgery
- Prior Systemic Cancer Therapy
  - Subjects with systemic cancer therapy (yes/no)
  - Setting of regimen (adjuvant therapy/metastatic disease/neo-adjuvant therapy)
  - Duration of prior systemic cancer therapy
  - Best response to regimen (CR/PR/SD/PD/unable to determine/not applicable)
  - Primary reason regimen was discontinued
  - Time from therapy stop to study treatment first dose

A by subject listing of the above prior therapies will be provided separately.

7.3.6 Subsequent Systemic Cancer Therapy

A by-subject listing will be provided separately for subsequent systemic cancer therapy, radiotherapy for treatment of tumors and on-treatment\subsequent surgery for treatment of tumors.

7.3.7 Physical Examination

Subjects with abnormal baseline physical examination will be tabulated by examination criteria for all treated subjects by tumor type.

The number and percentage of patients reporting physical examination results (Normal/Abnormal) will be presented per body system/examination criteria per time-point for all treated subjects.

A by-subject listing will be provided.

7.3.8 Clinical Complaints

A by-subject listing will be provided.

7.3.9 Diagnostic and Medical Treatment Procedures

A by-subject listing will be provided separately for diagnostic and medical treatment procedures.

7.4 Extent of Exposure

Unless otherwise specified, the exposure data will be presented on all treated subjects by tumor type.

7.4.1 Administration of Study Therapy

The following parameters will be summarized (descriptive statistics):

- Relative dose intensity (%) using the following categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%.
- Number of doses received
- Cumulative dose
- Duration of treatment

A by-subject listing of dosing of study medication (record of study medication, infusion details, and dose change) and a listing of batch number will be also provided.

Below table summarizes the key parameters used to calculate dosing data.

Table 7.4-1: Administration of Study Therapy: Definition of Parameters

	Nivolumab
Dosing schedule per protocol	3 mg/kg Q2 weeks
Cumulative Dose	Cumulative dose (mg/kg) is sum of the doses (mg/kg) administered to a subject during the treatment period
Relative dose intensity (%)	[Cumulative dose (mg/kg)/((Last dose date - Start dose date + 14)*3 / 14)] x 100
Duration of treatment	Last dose date - Start dose date +1

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). The length of dose delay is defined as (duration of previous cycle in days - 14). The Dose delays will be divided into following categories: 4 - < 8 days, 8 - < 15 days, 15 - < 43, >= 43 days. Reason for dose delay will be retrieved from CRF dosing pages.

The following parameters will be summarized by tumor type and overall:

- Number of dose delayed per subject, Length of Delay, and Reason for Dose Delay
- Number of subjects with at least one dose delayed along with reason for dose delay

7.4.2.2 Dose Modifications

There will be no dose escalations or reductions of nivolumab allowed.

Nivolumab 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 by tumor type and overall:

- Number of subjects with at least one dose infusion interrupted along with the reason for the interruptions and number of infusions interrupted per subject

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

[redacted]

[redacted]

7.5 Efficacy

Not applicable.

7.6 Safety

Unless otherwise specified, the safety data will be presented by tumor type. Data analyses will be conducted only on the safety data collected within the maximum of the 26-week study period, which will include safety collected during the follow-up of participants who discontinue treatment before 24 weeks. The post study treatment follow-up is defined as participants who discontinue study treatment before 24weeks will be followed for 100 days after the last dose of nivolumab or for a total of 26 weeks from first on-study treatment with nivolumab whichever is earliest.

7.6.1 Deaths

Deaths will be summarized by tumor type:

- All deaths, reasons for death
- Deaths within 100 days of last dose received or for a total of 26 weeks from first on-study treatment with nivolumab whichever is earliest, reasons for death

By-subject listing of deaths will be provided for the all enrolled subjects population.

7.6.2 Serious Adverse Events

Unless for the safety window would be as the defined as in section 7.6. For participants assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of treatment assignment.

Serious adverse events will be summarized by tumor type:

- Overall summary of SAEs by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT
- Overall summary of drug-related SAEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.

The analysis will be conducted using the 100-day safety window or for a total of 26 weeks from first on-study treatment with nivolumab, whichever is earliest.

By-subject SAE listing will be provided for the all enrolled subjects population.

7.6.3 Adverse Events Leading to Discontinuation of Study Therapy

AEs leading to discontinuation will be summarized by tumor type:

- Overall summary of AEs leading to discontinuation by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT

The analysis will be conducted using the 100-day or for a total of 26 weeks from first on-study treatment with nivolumab whichever is earliest safety window.

By-subject AEs leading to discontinuation listing will be provided.

7.6.4 Adverse Events

Adverse events will be summarized by tumor type:

- Overall summary of any AEs by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT.
- Overall summary of drug-related AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.

By-subject AE listing will be provided.

7.6.5 Select Adverse Events

Unless otherwise specified, analyses will be performed by select AE category. Some analyses may also be repeated by subcategory of endocrine events.

Select AEs includes:

- Pulmonary toxicity
- Gastrointestinal toxicity (diarrhea or colitis)
- Endocrinopathies
- Hepatotoxicity (including asymptomatic LFT elevations)
- Renal toxicity
- Skin toxicity
- Neurological toxicity
- Hypersensitivity/infusion reactions

7.6.5.1 Incidence of Select AE

Select AEs (see Table 7.6-1) will be summarized by tumor type for each category/subcategory for all treated subjects.

- Overall summary of any select AEs by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by Category or Subcategory/PT.
- Overall summary of drug-related select AEs by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by Category or Subcategory/PT.
- Summary of frequency of unique select AEs

The analyses will be conducted using the 100-day or for a total of 26 weeks from first on-study treatment with nivolumab whichever is earliest safety window.

By-subject select AE listing will be provided.

7.6.6 Immune Modulating Medication

The percentage of subjects who received immune modulating concomitant medication for

- management of adverse event
- premedication
- other use
- any use
- management of drug-related select adverse event (any grade, grade 3-5) by select AE category/ subcategory
- management of IMAEs (any grade, grade 3-5) by IMAE category will be reported separately for each tumor group (percentages of treated subjects by medication class and generic term).

The following will be reported for each tumor group:

- The total medication treatment duration (excluding overlaps), duration of high dose of corticosteroid, initial dose of corticosteroid, and tapering duration (summary statistics)

The analysis will be conducted using the 100-day or for a total of 26 weeks from first on-study with nivolumab whichever is earliest safety window.

7.6.7 Immune Mediated Adverse Events

In order to further characterize AEs of special clinical interest analysis of immune-mediated AEs (IMAE) will be conducted. Immune-mediated AEs 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 or for a total of 26 weeks from first on-study treatment with nivolumab whichever is earliest
- regardless of causality,
- treated with immune-modulating medication (of note, endocrine Adverse events such as 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).

For the most recent studies, the data collection for IMAE was modified to also collect data on investigator assessment of potential IMAE including evidence of immune mediated etiology. For these studies (which will be clearly identified as such in the study specific SAP), an additional criteria accounting for immune mediated etiology or immune mediated component is also to be considered:

- with no clear alternate etiology based on investigator assessment, or with an immune mediated component

The list of MedDRA preferred terms used to identify Immune-Mediated adverse events is revisited quarterly and updated accordingly. The preferred terms used for the selection at the time of the database lock by categories will be provided.

IMAEs will be summarized for each immune mediated category / PT using the 100 days of the last dose or for a total of 26 weeks from first on-study treatment with nivolumab whichever is earliest:

- Overall summary of AEs by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by immune mediate Category/ PT. This summary includes all AEs that are qualified for IMAE preferred terms list, without requirement of either usage of immune modulating medications or accounting for immune mediated etiology or immune mediated component. .
- Overall summaries of IMAEs by worst CTC grade [(grade 1, 2, 3, 4, 5, unknown) and (any grade, grade 3-4, grade 5)] where immune modulating medication was initiated presented by Category / PT
- Overall summaries of endocrine IMAEs by worst CTC grade [(grade 1, 2, 3, 4, 5, unknown) and (any grade, grade 3-4, grade 5)] presented by Category / PT.
- Overall summaries of serious IMAEs by worst CTC grade [(grade1, 2, 3, 4, 5, unknown)and (any grade, grade 3-4, grade 5)] where immune modulating medication was initiated presented by Category / PT.

- Overall summaries of endocrine serious IMAEs by worst CTC grade [(grade 1, 2, 3, 4, 5, unknown) and (any grade, grade 3-4, grade 5)] presented by Category / PT.
- Overall summaries of IMAEs leading to discontinuation by worst CTC grade [(grade 1, 2, 3, 4, 5, unknown) and (any grade, grade 3-4, grade 5)] where immune modulating medication was initiated presented by Category / PT.
- Overall summaries of endocrine IMAEs leading to discontinuation by worst CTC grade [(grade 1, 2, 3, 4, 5, unknown) and (any grade, grade 3-4, grade 5)] presented by Category / PT.
- Overall summaries of IMAEs leading to dose delay or reduction by worst CTC grade [(grade 1, 2, 3, 4, 5, unknown) and (any grade, grade 3-4, grade 5)] where immune modulating medication was initiated presented by Category / PT.
- Overall summaries of endocrine IMAEs leading to dose delay or reduction by worst CTC grade [(grade 1, 2, 3, 4, 5, unknown) and (any grade, grade 3-4, grade 5)] presented by Category / PT.
- Summaries of time to onset and time to resolution of IMAEs where immune modulating medication was initiated presented by Category.
- Summaries of time to onset and time to resolution of endocrine IMAEs presented by Category.

By-subject listing of IMAEs will be provided. By-subject listings of time to resolution for longest IMAEs cluster (any grade and grade 3-5 in separate summaries) will also be provided. For new studies which collect investigator assessment of potential IMAE data, a listing of Adverse Events Considered as Immune-Mediated Events per Investigator but not Qualified for Immune-Mediated Adverse Events Definition will also be provided.

In addition, for all nivolumab treated subjects who experienced at least one immune-mediated adverse event, the following data presentation will be provided:

- Summary of subjects who were re-challenged with nivolumab by immune-mediated adverse event category, with extended follow-up
- Summary of subjects who were re-challenged with nivolumab or ipilimumab by immune mediated adverse event category with extended follow-up

For these, re-challenge is considered to have occurred when last nivolumab and/or ipilimumab infusion was administered after the onset of an IMAE.

7.6.8 Clinical Laboratory Evaluations

Clinical laboratory parameters (hematology, serum chemistry) will be evaluated.

Laboratory tests will be graded using the NCI Common Terminology Criteria, version 4.0. Clinical laboratory data will be first analyzed using International System of Units (SI). Analyses will be repeated using US conventional units.

On-study laboratory abnormalities including hematology, chemistry, liver function, thyroid function, and renal function will be summarized using worst grade per NCI CTCAE v4.0 criteria.

7.6.8.1 Hematology

The following will be summarized by tumor type as worst CTC grade on-treatment per subject and as shift table of worst on-treatment CTC grade compared to baseline CTC grade per subject: hemoglobin (HB), lymphocyte count (LYMPH), Total leukocyte count, including differential, platelet count, hematocrit and absolute neutrophil count (ANC).

The analyses will be conducted using the 100-day or for a total of 26 weeks from first on-study treatment with nivolumab whichever is earliest safety window.

A by-subject listing of these laboratory parameters will be provided.

7.6.8.2 Serum Chemistry

The following will be summarized by tumor type as worst CTC grade on-treatment per subject and as shift table of worst on-treatment CTC grade compared to baseline CTC grade per subject: Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Total bilirubin, Alkaline phosphatase (ALP), Lactate dehydrogenase (LDH), Creatinine, Blood Urea Nitrogen (BUN) or serum urea level, Uric acid and Fasting glucose.

The analyses will be conducted using the 100-day or for a total of 26 weeks from first on-study treatment with nivolumab whichever is earliest safety window.

A by-subject listing of these laboratory parameters will be provided.

7.6.9 Vital Signs

Vital signs parameters (systolic blood pressure [mmHg], diastolic blood pressure [mmHg], heart rate [bpm], respiration rate [per minute] and body temperature [°C]) will be listed. Summaries of vital signs parameters and respective changes from baseline will be provided for each vital signs parameter by tumor types and study visit for all treated subjects.

Subjects with vital signs outside of a pre-specified range will also be listed.

[redacted]

[redacted]

7.6.11 Pregnancy Testing

By-subject listing of pregnancy tests results will be provided for all treated female subjects.

[redacted]

8 CONVENTIONS

The following conventions may be used for imputing partial dates for analyses requiring dates:

For death dates, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day. The imputed date will be compared to the last known date alive and the maximum will be considered as the death date.
- If the month or the year is missing, the death date will be imputed as the last known date alive

- If the date is completely missing but the reason for death is present, then the death date will be imputed as the last known date alive

For date of progression, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day.
- If the day and month are missing or a date is completely missing, it will be considered as missing.

  In cases where the date of death is present and complete, the imputed progression date will be compared to the date of death. The minimum of the imputed progression date and date of death will be considered as the date of progression.

For missing and partial adverse event onset dates, imputation will be performed using the Adverse Event Domain Requirements Specification[3].

For missing and partial adverse event resolution dates, imputation will be performed as follows:

If only the day of the month is missing, the last day of the month will be used to replace the missing day

- If the day and month are missing or a date is completely missing, it will be considered as missing.

Missing and partial non-study medication domain dates will be imputed using the derivation algorithm described in 4.3.3 of BMS Non-Study Medication Domain Requirements Specification[4].

For other partial/missing dates, the following conventions may be used:

- If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
- If both the day and the month are missing, "July 1" will be used to replace the missing information.
- If a date is completely missing, it will be considered as missing.

The following conversion factors will be used to convert days to months or years: 1 month = 30.4375 days and 1 year = 365.25 days.

Duration (e.g. time from first diagnosis to first dosing date, duration of response, and time to response) will be calculated as follows:

Duration = (Last date - first date + 1)

All statistical analyses will be carried out using SAS (Statistical Analysis System software, SAS Institute, North Carolina, USA) unless otherwise noted.

9 CONTENT OF REPORTS

All analyses described in this SAP will be included in the Clinical Study Report except where otherwise noted. Refer to the Data Presentation Plan for mock-ups of all tables and listings.

APPENDIX 1 SCHEDULE OF ACTIVITIES

Table 2-1: CA209887 Screening procedures and assessments

Procedure	Screening Visit	Notes Screening visit will occur within 28 days before start of nivolumab
Eligibility Assessments		
Informed Consent	X	
IVRS	X	An interactive voice recognition system (IVRS) will be used to assign participant numbers.
Inclusion/Exclusion Criteria	X	
Medical History	X	Medical history will include smoking history, and comorbidities. Mutation status of EGFR and ALK will be collected if available. Additional biopsies for mutation status, if not previously tested, are not required.
Safety Assessments		
Physical Examination	X	Includes height, weight, and ECOG PS (Appendix 1). Full physical exam required at baseline.
Vital Signs	X	Temperature, BP, HR, RR. Obtain vital signs at screening visit and within 72 hours of first dose.
Assessment of Signs and Symptoms	X	After obtaining Informed Consent, assess all signs and symptoms within 14 days of first dose, prior to study treatment initiation.
Concomitant medications	X	Within 14 days of first dose.
Laboratory Tests	X	Laboratory Tests performed locally within 14 days prior to first dose (unless otherwise specified): CBC with differential, serum chemistry (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, and glucose), liver function tests (AST, ALT, total bilirubin, alkaline phosphatase, albumin, LDH). TSH, free T3, free T4 (within 28 days prior to first dose), hepatitis B surface antigen (HBsAg) and hepatitis C antibody (HCV Ab) or HCV RNA.
Pregnancy Test	X	Within 24 hours prior to first dose for WOCBP only (serum or urine at the site).

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; BUN = blood urea nitrogen; CBC = complete blood count; ECOG = Eastern Cooperative Oncology Group; HR = heart rate; LDH = lactate dehydrogenase; NCI CTCAE = National Cancer Institute Common Terminology Criteria for AEs; RR = respiratory rate; TSH = thyroid stimulating hormone; T3 = triiodothyronine; T4 = thyroxine; WOCBP = Women of Childbearing Potential

Table 2-2: CA209887: On-Study Procedures and assessments

Procedure	Each Cycle (Every 2 weeks)	Notes
Safety Assessments		
Physical Measurements (including Performance Status)	X	Collect weight and ECOG Performance Status (Appendix 1) within 72 hours prior to dosing. Targeted physical examination may be performed if clinically indicated and is recommended to include cardiovascular, gastrointestinal, pulmonary and neurological exam for participants with brain metastases.
Vital Signs	X	Within 72 hours prior to dosing, tests includes temperature, BP, HR and RR
Serious Adverse Event Assessment	X	Assessed using NCI CTCAE v 4.0 (continuously monitored throughout treatment period)
Adverse Events Assessment	X	Assessed using NCI CTCAE v 4.0(continuously monitored throughout treatment period)
Review Concomitant Medication	X	
Laboratory Tests	X [a, b, c, d]	CBCs with differential [a] Serum chemistry tests [b] and liver function tests [c] should be checked every cycle, and the results should be obtained prior to dosing. Thyroid Function Test (TFTs) [d] should be checked every 6 weeks.
Pregnancy Test	Every 4 weeks	Completed more frequently if required by local standards (serum or urine as required by standard of care at the site)
Clinical Drug Supplies		
Administration of nivolumab (3 mg/kg)	X	All enrolled participants continue treatment every 2 Weeks. Treatment should be continued as long as clinical benefit is observed for a maximum of 24 weeks or until treatment is no longer tolerated by the participant or withdrawal of consent. Record Study Drug Infusion start and stop

BP = blood pressure; CBC = complete blood count; ECOG = Eastern Cooperative Oncology Group; HR = heart rate; LDH = lactate dehydrogenase; NCI CTCAE = National Cancer Institute Common Terminology Criteria for AEs; RR = respiratory rate.

[a] CBCs with differential includes white blood cell count, lymphocyte count, absolute neutrophil count, hemoglobin, hematocrit, and platelet count. Results to be obtained prior to dosing on infusion days.

[b] Serum chemistry tests include blood urea nitrogen (BUN) or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, and glucose.

[c] Liver function tests include AST, ALT, total bilirubin, alkaline phosphatase, albumin, LDH.

[d] Thyroid function testing including TSH (reflex to free T3 and free T4 if abnormal result).

Table 2-3: CA209887: Follow-up Procedures

Procedure	Follow-up phase **Follow-up Visit 1: 30 days (+/- 5 days) after last dose or on the date of discontinuation (+/- 5 days) if date of discontinuation is greater than 35 days after last dose.** **Follow up Visit 2: 70 days (+/- 5 days) after Follow up Visit 1.**	Notes **Participants who discontinue on-study treatment with nivolumab before 24 weeks will be followed for 100 days after the last on-study dose of nivolumab or for a maximum of 26 weeks from the date of the first on-study dose of nivolumab, whichever occurs earliest.**
Safety Assessments		
Physical measurements	X	Collect weight and ECOG Performance Status. Focused physical examination may be performed if clinically indication.
Vital Signs	X	Temperature, BP, HR and RR
Adverse Events Assessment	X	All SAEs after 26 weeks of study duration for participants on commercial nivolumab supply will be reported to India Health Authority as part of spontaneous reporting.
Serious Adverse Event Assessment	X	
Review Concomitant Medication	X	
Laboratory Tests	X	Laboratory tests as listed for on treatment assessment in Table 2-2.
Pregnancy Test	X	Completed more frequently if required by local regulations (serum or blood as required by standard of care at the site).

BP = blood pressure; ECOG = Eastern Cooperative Oncology Group; HR = heart rate; RR = respiratory rate.

Table 7.6-1: Select Adverse Events

Category	Subcategory	Preferred Terms
Endocrine Adverse Events	ADRENAL DISORDER	ADRENAL INSUFFICIENCY
		ADRENAL SUPPRESSION
		BLOOD CORTICOTROPHIN DECREASED
		BLOOD CORTICOTROPHIN INCREASED
	DIABETES	DIABETES MELLITUS
		LATENT AUTOIMMUNE DIABETES IN ADULTS
	PITUITARY DISORDER	HYPOPHYSITIS
	THYROID DISORDER	AUTOIMMUNE THYROIDITIS
		BLOOD THYROID STIMULATING HORMONE DECREASED
		BLOOD THYROID STIMULATING HORMONE INCREASED
		HYPERTHYROIDISM
		HYPOTHYROIDISM
		SECONDARY ADRENOCORTICAL INSUFFICIENCY
		THYROID FUNCTION TEST ABNORMAL THYROIDITIS
		THYROXINE DECREASED
		THYROXINE FREE DECREASED

Category	Subcategory	Preferred Terms
		THYROXINE FREE INCREASED
		THYROXINE INCREASED
		TRI-IODOTHYRONINE INCREASED
Hypersensitivity/Infusion Reactions		ANAPHYLACTIC REACTION
		HYPERSENSITIVITY
		INFUSION RELATED REACTION
Gastrointestinal Adverse Events		COLITIS
		DIARRHOEA
		ENTERITIS
		ENTEROCOLITIS
		FREQUENT BOWEL MOVEMENTS
		GASTROINTESTINAL PERFORATION
Hepatic Adverse Events		ACUTE HEPATIC FAILURE
		ALANINE AMINOTRANSFERASE INCREASED
		ASPARTATE AMINOTRANSFERASE INCREASED
		BILIRUBIN CONJUGATED INCREASED
		BLOOD BILIRUBIN INCREASED
		HEPATIC ENZYME INCREASED
		HEPATIC FAILURE
		HEPATITIS
		HYPERBILIRUBINAEMIA
		LIVER DISORDER
		LIVER FUNCTION TEST ABNORMAL

Category	Subcategory	Preferred Terms
		TRANSAMINASES INCREASED
Pulmonary Adverse Events		ACUTE RESPIRATORY DISTRESS SYNDROME
		ACUTE RESPIRATORY FAILURE INTERSTITIAL
		LUNG DISEASE
		LUNG INFILTRATION
		PNEUMONITIS
Renal Adverse Events		BLOOD CREATININE INCREASED
		CREATININE RENAL CLEARANCE DECREASED
		HYPERCREATININAEMIA
		NEPHRITIS
		NEPHRITIS ALLERGIC
		RENAL FAILURE
		RENAL FAILURE ACUTE RENAL
		TUBULAR NECROSIS
		TUBULOINTERSTITIAL NEPHRITIS
Skin Adverse Events		BLISTER
		DERMATITIS
		DERMATITIS EXFOLIATIVE
		DRUG ERUPTION
		ECZEMA
		ERYTHEMA
		EXFOLIATIVE RASH
		PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME

Category	Subcategory	Preferred Terms
		PHOTOSENSITIVITY REACTION
		PRURITUS
		PRURITUS ALLERGIC
		PRURITUS GENERALISED
		PSORIASIS
		RASH
		RASH ERYTHEMATOUS
		RASH GENERALISED
		RASH MACULAR
		RASH MACULO-PAPULAR
		RASH PAPULAR
		RASH PRURITIC
		SKIN EXFOLIATION
		SKIN IRRITATION
		URTICARIA
Neurological toxicity		NEUROTOXICITY

Source: MedDRA version 16

[redacted]