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Clinical Protocol CA209887

Safety Study of Nivolumab for Selected Advanced Malignancies in India

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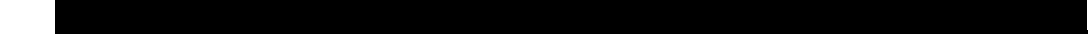
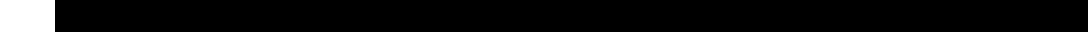
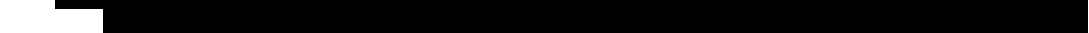
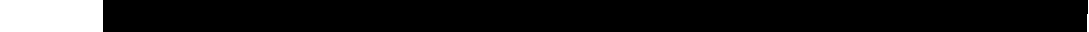
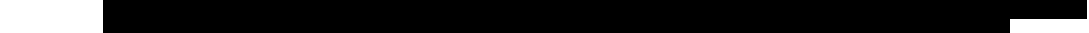
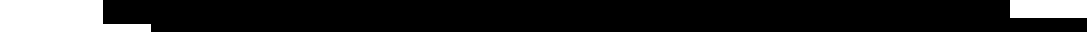
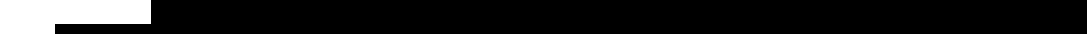
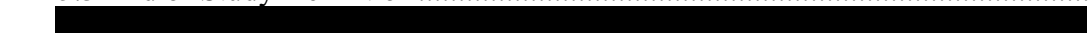
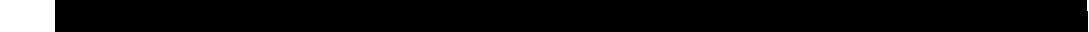

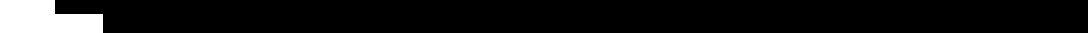
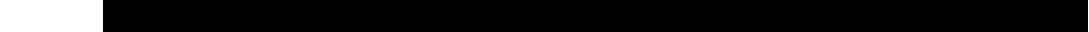
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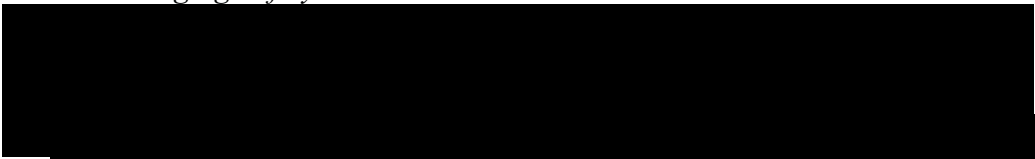
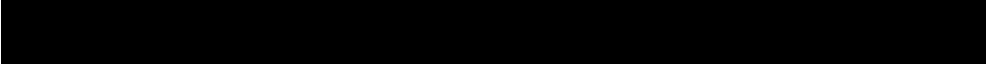
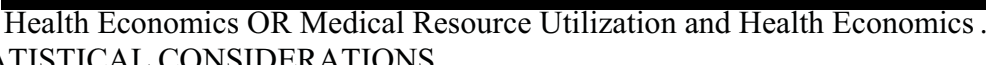



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DOCUMENT HISTORY

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1 SYNOPSIS

Protocol Title: Safety Study of Nivolumab for Selected Advanced Malignancies in India

Study Phase: Phase 4

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[REDACTED]

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Study Population:

The study population includes:

- adult patients with locally advanced or metastatic NSCLC after prior chemotherapy
- adult patients with advanced RCC after prior therapy.

Objectives and Endpoints:

Objective	Endpoint
Primary	
<ul style="list-style-type: none">• 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	<ul style="list-style-type: none">• Incidence and severity of treatment related adverse events (AEs)

Objective	Endpoint
Secondary	
<ul style="list-style-type: none"> • To estimate the incidence and severity of treatment-related select AEs in all treated participants. • To estimate the incidence of all treatment-related serious adverse events (SAEs) • To estimate the incidence of AEs that lead to discontinuation of treatment with nivolumab. 	<ul style="list-style-type: none"> • Incidence and severity of treatment-related select AEs, as specified in Section 10.3.2 in all treated participants • Incidence of all treatment-related SAEs • Incidence of AEs that lead to discontinuation from treatment with nivolumab

Overall Design:

This is a Phase 4, open-label, single arm, multi-center, prospective safety study to be conducted in India with participants 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 participants will undergo screening evaluations to determine eligibility within 28 days prior to first dose. Participants who meet the protocol-defined inclusion/exclusion criteria will be prospectively enrolled in a sequential manner. All enrolled participants 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. Participants 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 participants who discontinue treatment before 24 weeks by physical exams including vital signs, AE/SAE monitoring, laboratory evaluations and recording of concomitant medications.

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.

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.

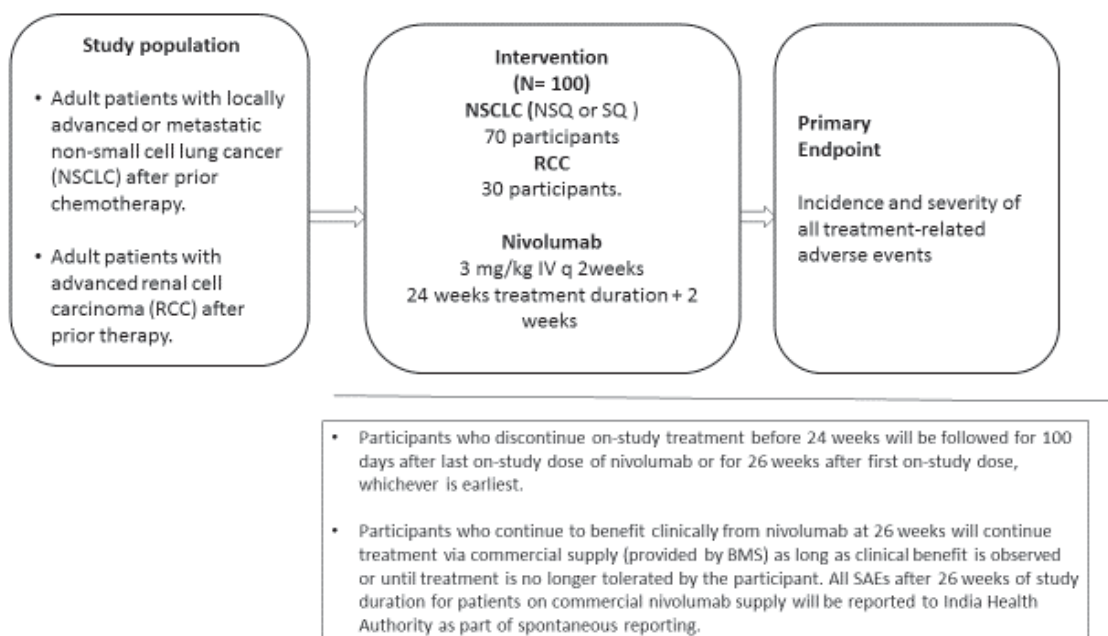
Number of Participants:

A total of 100 participants will be enrolled: 70 NSCLC and 30 RCC

Treatment Arms and Duration: All participants will be treated with nivolumab 3mg/kg IV q 2 weeks on Day 1 of each cycle. Each treatment cycle is 14 days long. The treatment period for all participants is a maximum of 26 weeks. Participants who are observed to continue to receive clinical benefit from treatment with nivolumab at 26 weeks may 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.

Study treatment:

Study Drug for CA209887		
Medication	Potency	IP/Non-IP
Nivolumab	10 mg/mL concentrate for solution for infusion	IP



2 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.

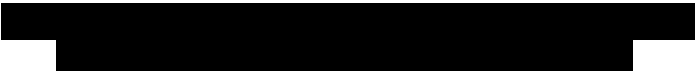
^a CBCs with differential includes white blood cell count, lymphocyte count, absolute neutrophil count, hemoglobin, hematocrit, and platelet count. Results to be obtained prior to dosing on infusion days.

^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	Notes
	<p>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.</p> <p>Follow up Visit 2: 70 days (+/- 5 days) after Follow up Visit 1.</p>	<p>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.</p>
Safety Assessments		
Physical measurements	X	
Vital Signs	X	Temperature, BP, HR and RR
Adverse Events Assessment	X	
Serious Adverse Event 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.
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.

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4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Incidence and severity of treatment related AEs
Secondary	
<ul style="list-style-type: none"> To estimate the incidence and severity of treatment-related select AEs in all treated participants. To estimate the incidence of all treatment-related SAEs To estimate the incidence of AEs that lead to discontinuation of treatment with nivolumab. 	<ul style="list-style-type: none"> Incidence and severity of treatment-related select AEs, as specified in Section 10.3.2 in all treated participants Incidence of all treatment-related SAEs Incidence of AEs that lead to discontinuation from treatment with nivolumab

5 STUDY DESIGN

5.1 Overall Design

This is a Phase 4, open-label, single arm, multi-center, prospective safety study to be conducted in India with participants 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 participants will undergo screening evaluations to determine eligibility within 28 days prior to first dose. Participants who meet the protocol defined inclusion/exclusion criteria will be prospectively enrolled in a sequential manner. All enrolled participants 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. Participants 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.

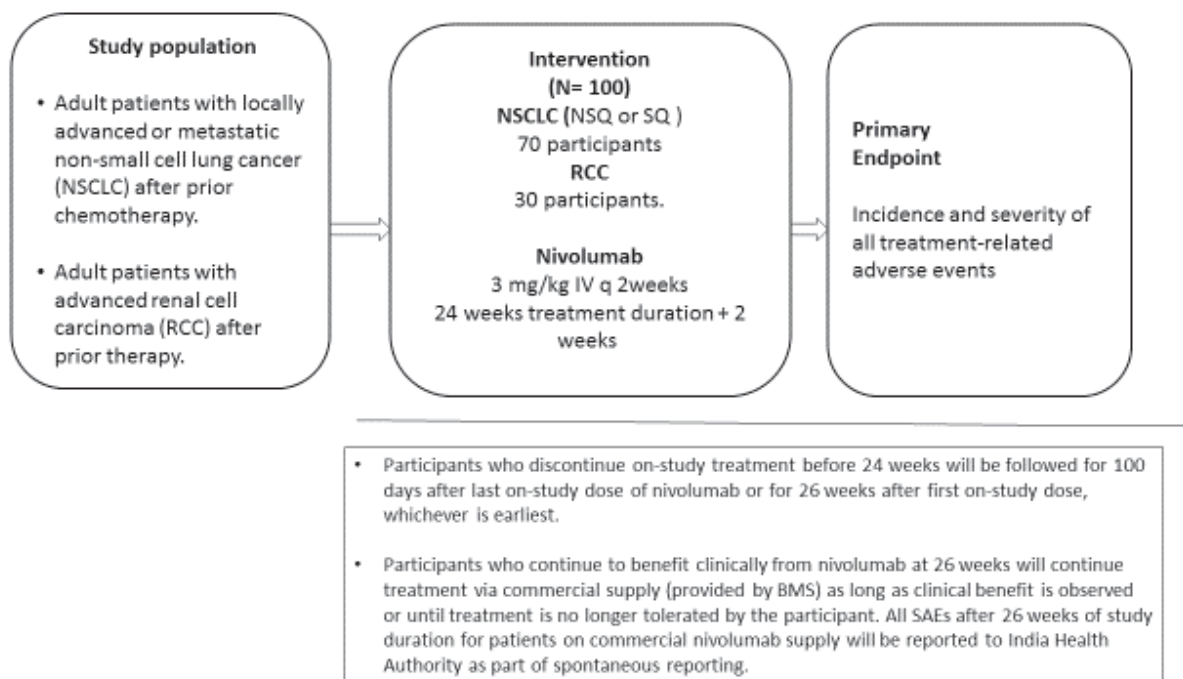
Safety will be evaluated throughout the treatment period and during the follow up of participants who discontinue treatment before 24 weeks by physical exams including vital signs, AE/SAE monitoring, laboratory evaluations and recording of concomitant medications.

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.

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.

The study design schematic is presented in [Figure 5.1-1](#).

Figure 5.1-1: Study Design Schematic



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 participants who discontinue treatment before the end of the treatment period (24 weeks). Participants will be closely monitored for AEs throughout the study.

5.1.1 Data Monitoring Committee and Other External Committees

Not applicable.

5.2 Number of Participants

A total of 100 participants will be enrolled:

- 70 participants with locally advanced or metastatic NSCLC after prior chemotherapy.
- 30 participants with advanced renal cell carcinoma (RCC) after prior therapy.

The sample size calculation is presented in [Section 10.1](#).

5.3 End of Study Definition

The start of the trial is defined as the first visit of the first person as part of screening for the trial. The end of trial is defined as the last visit of the last participant. 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.

In this trial, the study will be completed on the date on which safety data (primary endpoint) are collected for the last participant on study.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

6 STUDY POPULATION

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

6.1 Inclusion Criteria

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 institutional 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 tests and other requirements of the study.

2) Type of Participant and Target Disease Characteristics

- a) Locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy OR advanced renal cell carcinoma (RCC) after prior therapy.
- b) Eastern Cooperative Oncology Arm (ECOG) ([Appendix 1](#)) performance status of ≤ 1
- c) Prior radiotherapy or radiosurgery must have been completed at least 2 weeks prior to randomization.

3) Age and Reproductive Status

- a) Males and Females, ages ≥ 18 or age of majority
- 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 of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab 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 5 half-lives}.
- d) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of study treatment with nivolumab 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.}
- e) 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 4](#) which have a failure rate of $< 1\%$ when used consistently and correctly).

6.2 Exclusion Criteria

1) Medical Conditions

- a) Women who are pregnant or breastfeeding
- b) Women with a positive pregnancy test at enrollment or prior to administration of study medication
- c) Participants with untreated, symptomatic central nervous system (CNS) metastases.
- d) Participants with carcinomatous meningitis.
- e) Participants with active, known or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll

- f) Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of first dose of study drug. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
- g) Other active malignancy requiring concurrent intervention.
- h) Participants with previous malignancies (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, endometrial, cervical/dysplasia, melanoma, or breast) are excluded unless a complete remission was achieved at least 2 years prior to study entry AND no additional therapy are ongoing and required during the study period with the exception of anti-estrogen/androgen therapy or bisphosphonates. Participants with other active malignancy requiring concurrent intervention are excluded.
- i) All toxicities attributed to prior anti-cancer therapy other than alopecia, fatigue, or peripheral neuropathy must have resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of study drug.
- j) Participants must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study treatment.
- k) Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated locally.

2) Prior/Concomitant Therapy

- a) Ongoing or planned administration of anti-cancer therapies other than those specified in this study
- b) Use of corticosteroids or other immunosuppressive medications with exceptions detailed in the protocol consistent with nivolumab program.
- c) Treatment with any investigational agent within 14 days of first administration of study treatment

3) Physical and Laboratory Test Findings

- a) WBC < 2000/mm³
- b) Neutrophils < 1500/mm³
- c) Platelets < 100*10³/mm³
- d) Hemoglobin < 9.0 g/dL
- e) Serum creatinine > 1.5 x ULN or calculated creatinine clearance < 40 mL/min (using the Cockcroft-Gault formula)
- f) AST/ALT: > 3.0 x ULN
- g) Total bilirubin > 1.5 x ULN (except participants with Gilbert Syndrome who must have a total bilirubin level of < 3.0x ULN)
- h) 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). Any serious or uncontrolled medical disorder or active infection with hepatitis that may be reactivated.

4) Allergies and Adverse Drug Reaction

- a) History of severe hypersensitivity reactions to other monoclonal antibodies.
- b) History of allergy or intolerance (unacceptable adverse event) to study drug components, or Polysorbate-80-containing infusions.
- c) Participants with history of life-threatening toxicity related to prior immune therapy (eg. anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (eg. Hormone replacement after adrenal crisis).

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 (i.e., participant has not been randomized / 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 or Lead-in period will be permitted (in addition to any parameters that require a confirmatory value).

The most current result prior to enrollment 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](#), CA209887 Screening Procedure and Assessments 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

Participants 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. Participants 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.

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.

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 CA209887					
Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Nivolumab Solution for Injection ^a	100 mg (10 mg/mL concentrate)	IP	Open label	10 mL per vial (5 or 10 vials per carton)	Store at 2° - 8° C Protect from light and freezing

^a Nivolumab is labeled as BMS-936558-01 Solution for Injection

NOTE: Medications used to treat BMS-936558 (nivolumab)-related infusion reactions are (eg, diphenhydramine, acetaminophen/paracetamol, corticosteroids) considered NIMPs (non-investigational products) and will not be provided by the sponsor. These will be obtained by the investigational sites as marketed product, which should be stored in accordance to the package insert. For further details related to these medications and nivolumab-related infusion reactions, please see [Section 7.7.3](#)

7.1 Treatments Administered

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
nivolumab	3 mg/kg	every 2 weeks	IV

7.2 Method of Treatment Assignment

An IVRS will be used to assign participant numbers.

All participants 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 ([Section 2](#)).

7.3 Blinding

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

7.4 Dosage Modification

There will be no dose escalations or reductions of nivolumab allowed. Participants may be dosed no less than 12 days from the previous dose during q2w cycles. Premedications are not recommended for the first dose of nivolumab.

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 7.7.3](#).

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

Nivolumab Injection, 100 mg/10 mL (10 mg/mL). Nivolumab injection 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.

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

7.4.1 Dose Delay and Resumption of Treatment Criteria for Nivolumab

Dosing delay or discontinuation of nivolumab may be required based on individual safety and tolerability. Guidelines for permanent discontinuation, withholding of doses and resumption of treatment are included in the Nivolumab India Prescribing Information ([Appendix 3](#)).

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).

7.5.1 Preparation and administration

7.5.1.1 Calculating the dose

The prescribed dose for the participant is given in mg/kg. Based on this prescribed dose, calculate the total dose to be given. More than 1 vial of nivolumab concentrate may be needed to give the total dose for the participant.

- The total nivolumab dose in mg = the participant's weight in kg × the prescribed dose in mg/kg.
- The volume of nivolumab concentrate to prepare the dose (mL) = the total dose in mg, divided by 10 (the nivolumab concentrate strength is 10 mg/mL).

7.5.1.2 Preparing the infusion

Take care to ensure aseptic handling when you prepare the infusion. The infusion should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents.

Nivolumab can be used for intravenous administration either:

- without dilution, after transfer to an infusion container using an appropriate sterile syringe; or
- after diluting to concentrations as low as 1 mg/mL. The final infusion concentration should range between 1 and 10 mg/mL. Nivolumab concentrate may be diluted with either:
 - sodium chloride 9 mg/mL (0.9%) solution for injection; or
 - 50 mg/mL (5%) glucose solution for injection.

STEP 1

- Inspect the nivolumab concentrate for particulate matter or discoloration. Do not shake the vial. Nivolumab concentrate is a clear to opalescent, colorless to pale-yellow liquid.

Discard the vial if the solution is cloudy, is discolored, or contains particulate matter other than a few translucent-to-white particles.

- Withdraw the required volume of nivolumab concentrate using an appropriate sterile syringe.

STEP 2

- Transfer the concentrate into a sterile, evacuated glass bottle or intravenous container (PVC or polyolefin). If applicable, dilute with the required volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection. Gently mix the infusion by manual rotation. Do not shake.

7.5.2 Administration of Nivolumab

Nivolumab infusion must not be administered as an intravenous push or bolus injection. Administer the nivolumab infusion intravenously over a period of 60 minutes.

Nivolumab infusion should not be infused at the same time in the same intravenous line with other agents. Use a separate infusion line for the infusion.

Use an infusion set and an in-line, sterile, non-pyrogenic, low protein binding filter (pore size of 0.2 μm to 1.2 μm).

Nivolumab infusion is compatible with:

- PVC containers
- Polyolefin containers
- Glass bottles
- PVC infusion sets
- In-line filters with polyethersulfone membranes with pore sizes of 0.2 μm to 1.2 μm .

After administration of the nivolumab dose, flush the line with sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection.

7.5.2.1 Disposal

Do not store any unused portion of the infusion solution for reuse. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

- Further guidance and information for final disposition of unused study treatment are provided in [Appendix 5](#).

[REDACTED]

7.6 Treatment Compliance

Administration of nivolumab will be documented on the case report form, including start and stop time for each infusion.

[REDACTED]

7.7.2 Permitted Therapy

Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

7.7.3 Treatment of Nivolumab-Related Infusion Reactions

Severe infusion reactions have been reported in clinical trials of nivolumab as specified in the Nivolumab India Prescribing Information ([Appendix 3](#)). In case of a severe or life-threatening infusion reaction, the nivolumab infusion must be discontinued and appropriate medical therapy administered. Participants with mild or moderate infusion reaction may receive nivolumab with close monitoring and use of premedication according to local treatment guidelines for prophylaxis of infusion reactions.

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. 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. In this study, participants who are observed to continue to receive clinical benefit from treatment with nivolumab at the end of 26 weeks, may continue treatment via commercial supply, with nivolumab supplied by BMS.

BMS reserves the right to terminate access to BMS supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of nivolumab is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government sponsored or private health program. In all cases BMS will follow local regulations

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 (e.g., infectious disease) illness

Additional criteria for the discontinuation of nivolumab as recommended in the Nivolumab India Prescribing Information is presented in [Appendix 3](#).

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 BMS Medical Monitor/designee of this event. In the event a normal healthy female participant becomes pregnant during a clinical trial, the study treatment must be discontinued immediately. 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. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the BMS Medical Monitor/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.

8.1.1 Post Study Treatment Study Follow-up

Participants who discontinue study treatment before 24 weeks 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.

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. AEs/SAEs for participants receiving commercial supply will be reported via spontaneous reporting.

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 randomization. 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

This is a safety study of nivolumab, required as a post marketing commitment per condition of approval by the Indian Health Authority. Clinical benefit is not a formal assessment in this study. However, clinical benefit will be assessed by the treating physician as part of routine practice in the decision to continue or discontinue treatment with nivolumab.

9.1.1 Imaging Assessment for the Study

Imaging assessment is not included in this study due to very short duration of treatment.

At the sponsor's discretion, scans may be collected for review.

9.2 Adverse Events

The definitions of an AE or serious adverse event (SAE) can be found in [Appendix 6](#).

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.

Contacts for SAE reporting are specified in Appendix 6.

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.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious 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, during treatment, and within 100 days or a maximum of 26 weeks of discontinuation of dosing, whichever is earliest. 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 6](#).
- 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 6](#).

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 [Section Appendix 6](#)).
- 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 6](#).

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 during the treatment period and within 100 days or a maximum of 26 weeks of discontinuation of dosing, whichever is earliest, as specified in the study design [Section 5.1](#).

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 6](#)

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.

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 6](#) 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](#)).

9.4 Safety

Safety will be assessed from the screening period, during the treatment phase and, for those participants who discontinue treatment before 24 weeks, during the follow up period. Safety assessments include physical exam, vital signs, AE/SAE assessments, recording of concomitant medications, and laboratory assessments. For WOCBP, a pregnancy test (serum or urine) is also required 24 hours prior to the first dose and at least monthly during the treatment phase of the study.

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

9.4.1 Clinical Safety Laboratory Assessments

The schedule of laboratory assessment to be conducted at screening, during treatment, and during follow up for those participants who discontinue treatment before 24 weeks of treatment is presented in [Table 2-1](#), [Table 2-2](#), and [Table 2-3](#). Specific laboratory assessments to be performed throughout the study are listed in [Table 9.4.1-1](#).

- Investigators must document their review of each laboratory safety report.

Table 9.4.1-1: CA209887 - Laboratory Assessments

Hematology	
Complete Blood Count (CBC) includes	
Hemoglobin	Hematocrit
lymphocyte count,	absolute neutrophil count (ANC)
Total leukocyte count, including differential	
Platelet count	
Serum Chemistry	
Aspartate aminotransferase (AST)	Total Protein
Alanine aminotransferase (ALT)	Albumin
Total bilirubin	Sodium
Alkaline phosphatase	Potassium
Lactate dehydrogenase (LDH)	Chloride
Creatinine	Calcium
Blood Urea Nitrogen (BUN) or serum urea level	Phosphorus
Uric acid	Magnesium
Fasting glucose	Creatinine clearance (CLcr)- screening only
Serology	

Table 9.4.1-1: CA209887 - Laboratory Assessments

Hepatitis B surface antigen (HBsAg) and hepatitis C antibody (HCV Ab) or HCV RNA (screening only).
Other Analyses
Thyroid function testing including TSH (reflex to free T3 and free T4 if abnormal result).
Pregnancy test (WOCBP only: screening, every 4 week during treatment, and during follow up for those participants who discontinue treatment before 24 weeks as presented in Table 2-3)
Follicle stimulating hormone (FSH) (screening only for women only) <i>use as applicable</i>

9.4.2 Imaging Safety Assessment

Not Applicable.

[REDACTED]

9.9 Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters will not be evaluated in this study.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

The study is projected to enroll a minimum of 100 participants (70 NSCLC participants and 30 RCC participants). 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 participants; 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 participants.

Given the proposed sample size, the 95% confidence intervals for relevant AE rates are presented in Table 10.1-1

Table 10.1-1: 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

Table 10.1-1: CA209887: Estimated Incidence Rates and 95% CIs

Incidence Rate (%)	Sample Size	Lower 95% CI (%)	Upper 95% CI (%)
	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.

10.2 Populations for Analyses

Table 10.2-1: CA209887: Population for Analyses

Population	Description
All enrolled participants	All participants who sign informed consent and were registered into the IVRS.
All treated participants	All Participants who received any nivolumab. This is the primary population for safety analyses. Subpopulation analyses will be conducted by tumor type and tumor histology (SQ or NSQ in NSCLC).

10.3 Statistical Analyses

The study is intended to provide information regarding the safety profile for participants in India, and will contribute additional information to the overall safety profile of nivolumab. Due to the small sample size, this study should not be directly compared to the data from any other country.

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

10.3.1 Efficacy Analyses

Clinical benefit from treatment with nivolumab will not be analyzed in this study due to the very short duration of treatment.

10.3.2 Safety 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 participants who discontinue treatment before 24 weeks.

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.

10.3.2.1 Primary Endpoint(s)

The primary endpoint is the incidence and severity of all treatment-related adverse events.

10.3.2.2 Secondary Endpoint(s)

The secondary endpoints include:

1) Incidence and severity of all treatment-related select adverse events which are as follows:

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

2) Incidence of serious treatment-related adverse events

3) Incidence and severity of adverse events that lead to discontinuation.

All safety data will be summarized and listed for all treated participants. All on-study AEs, SAEs, treatment-related AEs, treatment-related SAEs and select AEs will be summarized using worst grade per NCI CTCAE v4.0 by system organ class and Medical Dictionary for Regulatory Affairs (MedDRA) preferred term. 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.

[REDACTED]

12 APPENDICES

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

APPENDIX 2 ABBREVIATIONS AND TRADEMARKS

Term	Definition
AE	adverse event
ALK	Alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	Aspartate aminotransferase
β-HCG	beta-Human Chorionic Gonadotrophin
BA/BE	bioavailability/bioequivalence
%BE	percent biliary excretion
BMS	Bristol-Myers Squibb
BP	blood pressure
BTLA	B and T lymphocyte attenuator
BUN	blood urea nitrogen
Ca ⁺⁺	calcium
CBC	complete blood count
CD28	cluster of differentiation 28
C _{expected-tau}	expected concentration in a dosing interval
CFR	Code of Federal Regulations
CI	confidence interval
Cl ⁻	chloride
CL _{cr}	creatinine clearance
cm	centimeter
C _{max} , C _{MAX}	maximum observed concentration
C _{min} , C _{MIN}	minimum observed concentration
CNS	Central nervous system
CRF	Case Report Form, paper or electronic
CTLA-4	cytotoxic T lymphocyte antigen-4
C _{trough}	Trough observed plasma concentration
CV	coefficient of variation
CYP	cytochrome p-450

Term	Definition
D/C	discontinue
dL	deciliter
ECG	electrocardiogram
EC50	half maximal effective concentration
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eg	exempli gratia (for example)
EGFR	estimated glomerular filtration rate.
F	bioavailability
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
g	gram
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
h	hour
HBsAg	hepatitis B surface antigen
HBV	Hepatitis B virus
HCO ₃ ⁻	bicarbonate
HCV ab	hepatitis C virus antibody
HCV RNA	hepatitis C virus ribonucleic acid
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
IC50	half maximal inhibitory concentration
ie	id est (that is)
IEC	Independent Ethics Committee
IL	interleukin
IMP	investigational medicinal products

Term	Definition
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
IU	International Unit
IV	intravenous
IVRS	interactive voice recognition system
kg	kilogram
L	liter
LDH	lactate dehydrogenase
mg	milligram
Mg ⁺⁺	magnesium
min	minute
mL	milliliter
mmHg	millimeters of mercury
MR	medical research
MS	mass spectrometry
MTD	maximum tolerated dose
µg	microgram
N	number of subjects or observations
Na ⁺	sodium
N/A	not applicable
ng	nanogram
NIMP	non-investigational medicinal products
NCI CTCAE	National Cancer Institute Common Terminology Criteria for AEs
NSCLC	non-small cell lung cancer
PD-1	programmed death-1
PS	Performance status
PT	prothrombin time
PTT	partial thromboplastin time
QC	quality control
RBC	red blood cell

Term	Definition
RCC	renal cell carcinoma
RR	respiration rate
SAE	serious adverse event
SD	standard deviation
SOP	Standard Operating Procedures
Subj	subject
t	temperature
T	time
T ₃	triiodothyronine
T ₄	thyroxine
TCR	T-cell receptor
TSH	thyroid stimulating hormone
UV	ultraviolet
W	washout
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

