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Clinical Protocol CA209714

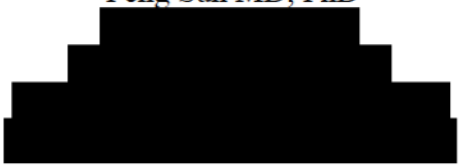
A Double-Blind, Randomized, Two Arm Phase 2 Study of Nivolumab in Combination with Ipilimumab versus Nivolumab in Combination with Ipilimumab Placebo In Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)

(CheckMate 714: **CHECK**point pathway and nivolu**MA**b clinical **T**rial **E**valuation **714**)

Revised Protocol No.: 04

Medical Monitor

Peng Sun MD, PhD



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

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 04	25-May-2018	This revision has the following purposes: 1. Incorporate Administrative Letter 04 2. Identify Tumor Mutational Burden as a secondary rather than exploratory objective and clarify exploratory objectives language 3. Clarify timing of the planned interim analysis and final analysis and update statistical analysis plan 4. Other minor edits and clarifications
Administrative Letter 04	21-Feb-2018	Change in study personnel
Revised Protocol 03	14-Nov-2017	To correct mistakes introduced by Revised Protocol 02 and to add a potential interim analysis.
Revised Protocol 02	27-Jun-2017	Incorporates Amendment 05 and Administrative Letter 02
Amendment 05	27-Jun-2017	This protocol amendment has the following purposes: 1. Increase in the size of the platinum eligible population in order to provide greater statistical precision 2. Alignment of protocol with responses to regulatory authorities 3. Minor changes to eligibility criteria and study processes 4. Clarification of outstanding issues and correction of typographical errors
Administrative Letter 02	13-Sep-2016	Change to Additional Research language
Revised Protocol 01	19-Jul-2016	Incorporates Amendment 01
Amendment 01	19-Jul-2016	PK and IMG Follow up visit samples no longer required to be collected; Updated Biomarker sample collection schedule; Updated Contraceptive language: [redacted]
Administrative Letter 01	20-Jun-2016	Protocol Title corrected and address for Medical monitor contact information updated.
Original Protocol	11-May-2016	Not applicable

[redacted]

SYNOPSIS

Clinical Protocol CA209714

Protocol Title: A Double-Blind, Randomized, Two Arm Phase 2 Study of Nivolumab in Combination with Ipilimumab versus Nivolumab in Combination with Ipilimumab Placebo In Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN) **(CheckMate 714**: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation **714**)

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):

Nivo and Ipi combo Arm A:

- Nivolumab 3 mg/kg IV will be administered every 2 weeks (± 3days)
- Ipilimumab 1 mg/kg IV will be administered every 6 weeks (± 3days) following the administration of nivolumab.

(1 Cycle =6 Weeks)

Nivo and Ipi-placebo Arm B:

- Nivolumab 3 mg/kg IV will be administered every 2 weeks (± 3days).
- Ipi-Placebo IV will be administered every 6 weeks (± 3days) following the administration of nivolumab.

(1 Cycle = 6 Weeks)

Study Phase: II

Study Population:

Subjects must have metastatic or recurrent disease that is not amenable to therapy with curative intent (surgery or radiation therapy with or without chemotherapy). Subjects that refuse potentially curative salvage surgery for recurrent disease are ineligible.

Two subgroups will be enrolled into this study. Subjects will be classified as platinum refractory or platinum eligible:

- Platinum refractory subgroup (n = approximately 216): subjects with histologically confirmed SCCHN that has recurred during or less than 6 months after completion of previous platinum-based chemotherapy, given as adjuvant or neoadjuvant treatment or as part of multimodal treatment (chemotherapy, surgery, radiotherapy) for locally advanced disease. Subjects should have not received systemic anti-cancer therapy in the recurrent or metastatic setting.
- Platinum eligible subgroup (n = approximately 180): subjects with histologically confirmed SCCHN who are platinum naive, or have recurred 6 months or more after completion of previous platinum-based chemotherapy, given as adjuvant or neoadjuvant treatment or as part of multimodal treatment (chemotherapy, surgery, radiotherapy) for locally advanced disease. Subjects should have not received systemic anti-cancer therapy in the recurrent or metastatic setting.

Research Hypothesis:

- In patients with recurrent or metastatic SCCHN, the administration of nivolumab in combination with ipilimumab as first-line therapy in the platinum refractory setting will improve objective response rate (ORR) and duration of response (DOR) compared to nivolumab in combination with ipilimumab placebo.

Objectives:

Primary Objective

- To compare the ORR and assess the DOR of the treatment of nivolumab in combination with ipilimumab vs nivolumab in combination with ipilimumab placebo, as determined by a blinded independent central review (BICR) using Response Evaluation Criteria In Solid Tumors (RECIST 1.1) criteria, for first-line treatment of recurrent or metastatic SCCHN in the platinum refractory setting.

Secondary Objectives

- To estimate the ORR and assess DOR of the treatment of nivolumab in combination with ipilimumab vs nivolumab in combination with ipilimumab placebo, as determined by BICR using RECIST 1.1 criteria, for first-line treatment of recurrent or metastatic SCCHN in the platinum eligible setting
- To assess progression-free survival (PFS), as determined by BICR, overall, of nivolumab in combination with ipilimumab vs nivolumab in combination with ipilimumab placebo for first-line treatment of recurrent or metastatic SCCHN in the platinum eligible and platinum refractory settings, separately and overall.
- To assess overall survival (OS) of nivolumab combined with ipilimumab vs nivolumab in combination with ipilimumab placebo for first-line treatment of recurrent or metastatic SCCHN in the platinum eligible and platinum refractory settings, separately and overall.
- To assess efficacy (ORR, DOR, PFS and OS) by PD-L1 expression of nivolumab in combination with ipilimumab compared to nivolumab in combination with ipilimumab placebo for first-line treatment of recurrent or metastatic SCCHN in the platinum eligible and platinum refractory settings, separately and overall.
- To assess efficacy (ORR, DOR, PFS and OS) by HPV p-16 status of nivolumab in combination with ipilimumab compared to nivolumab in combination with ipilimumab placebo for first-line treatment of recurrent or metastatic SCCHN in the platinum eligible and platinum refractory settings, separately and overall.
- To evaluate tumor mutational burden, as a potential predictive biomarker of efficacy (such as ORR, DOR, PFS and OS) of nivolumab in combination with ipilimumab or ipilimumab placebo for first-line treatment of recurrent or metastatic SCCHN in the platinum eligible and platinum refractory settings, separately and overall.

[redacted]

- [redacted]

Study Design:

Protocol CA209714 is a randomized (2:1), double-blinded, Phase 2 trial in subjects ≥ 18 years old with untreated metastatic SCCHN or recurrent SCCHN that is not amenable to curative therapy, comparing nivolumab combined with ipilimumab vs. nivolumab in combination with ipilimumab placebo as first-line treatment in subjects with recurrent or metastatic disease.

HPV p-16 status, PD-L1 status (expressing vs non-expressing or non-evaluable or indeterminate test results) and platinum-refractory subgroup (yes or no) will be needed prior to randomization. Subjects will undergo screening evaluations to determine eligibility prior to randomization.

Approximately 396 subjects will be randomized to the two treatment arms in a 2:1 ratio and stratified by the following factors:

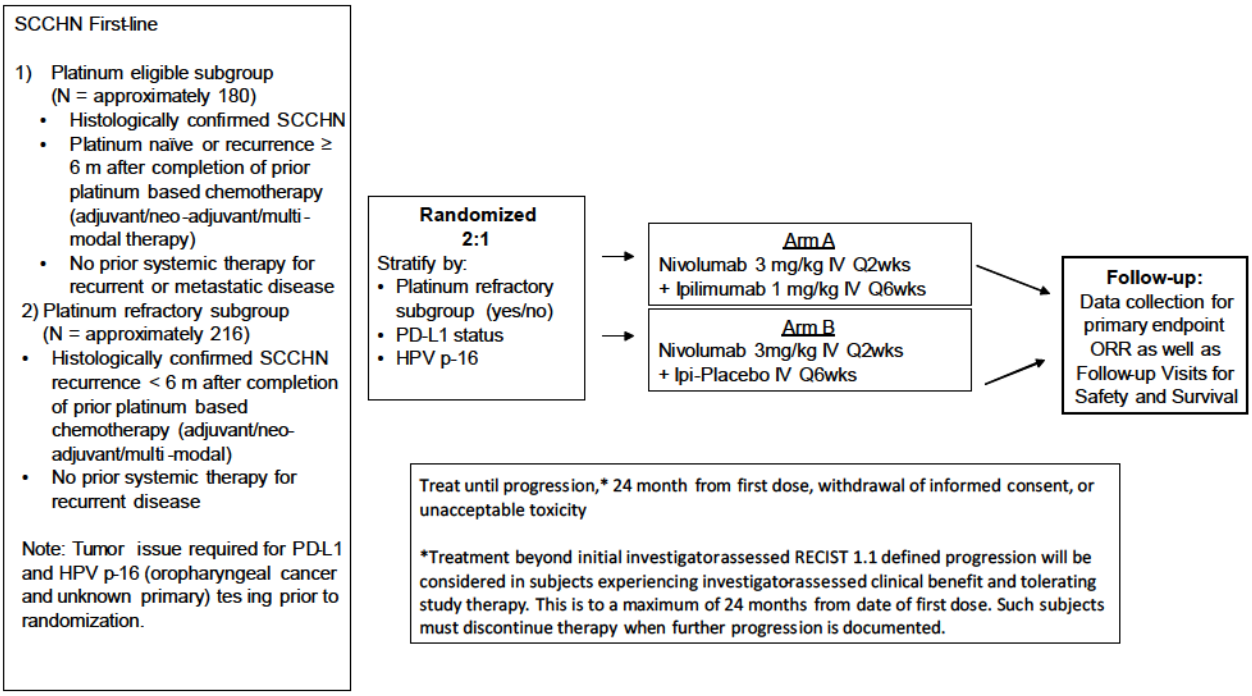
- Platinum refractory subgroup (yes/no)
- PD-L1 status (expressing/non-expressing or non-evaluable or indeterminate). PD-L1 status is set to expressing when tumor cell PD-L1 expression ≥ 1%. Up to 20% of randomized subjects can be included into the study as "non-evaluable" or "indeterminate." After this point, subjects with non-evaluable/indeterminate results will not be permitted to be randomized; the site would need to submit an additional tumor tissue for testing with either a result of "expressing" or "non-expressing" in order to randomize the subject
- HPV p-16 status (oropharyngeal cancer HPV Positive vs oropharyngeal cancer HPV negative/non-oropharyngeal cancer). For subjects with oropharyngeal cancer, sites defined in Appendix 5, and unknown primary localization.

Tumor progression and response endpoints will be assessed using RECIST 1.1 criteria. Treatment with study medication will continue until RECIST 1.1 defined progression, unacceptable toxicity, 24 months of treatment, or withdrawal of consent. See Section 3.6 for full details of discontinuation of study drug treatment.

Dose reductions will be not be allowed for nivolumab, ipilimumab or ipilimumab placebo. Treatment beyond initial investigator-assessed progression (either clinical or radiographical) is permitted for nivolumab and ipilimumab or ipilimumab placebo up to a maximum of 24 months from date of first dose if the subject has an investigator-assessed clinical benefit and is tolerating study drug (see section 4.5.7).

A Data Monitoring Committee (DMC) will be established and meet regularly during the study to ensure that subject safety is carefully monitored and to provide oversight regarding safety and efficacy considerations in protocol CA209714, see Section 7.

The analysis of ORR for each of the platinum eligible and platinum refractory subgroups will be conducted after the sufficient number of randomized subjects in the subgroup have been followed for at least 9 months. Survival follow-up may continue for up to 5 years from the time of this analysis. The study will end once survival follow-up has concluded.



Study Population:

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

Key Inclusion Criteria (See Protocol Section 3.4.1 for full list of criteria)

a) Histologically confirmed head and neck squamous cell carcinoma (SCCHN), from any of the following primary sites only: oral cavity, oropharynx, hypopharynx and larynx or unknown primary location (if p-16 positive).

b) Subjects must have metastatic or recurrent disease that is not amenable to therapy with curative intent (surgery or radiation therapy with or without chemotherapy). Subjects that refuse potentially curative salvage surgery for recurrent disease are ineligible.

c) Subjects will be classified as platinum refractory (n = approximately 216) or platinum eligible (n = approximately 180). Definitions of the subgroups are found above.

d) Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 1 (See Appendix 1).

e) Measurable disease by computed tomography (CT) or magnetic resonance imaging (MRI) per RECIST 1.1 criteria.

f) Documentation of HPV p-16 status is required for SCCHN tumor of the oropharynx. Subjects with unknown primary location must have documented positive p-16 status.

g) Documentation of PD-L1 status by IHC performed by the central lab at randomization.

h) Screening laboratory values must meet the following criteria (using CTCAE v4):

i) WBC ≥ 2000/uL

ii) Neutrophils ≥ 1500/uL

iii) Platelets ≥ $100x10^3$/uL

iv) - Hemoglobin ≥ 9.0 g/dL

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

$$\text{Female CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/ dL}}$$

$$\text{Male CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/ dL}}$$

vi) AST ≤ 3.0 x ULN

vii) ALT ≤ 3.0 x ULN

Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome who must have a total bilirubin level of < 3.0x ULN).

i) Subjects must have an estimated life expectancy of at least 3 months.

Key Exclusion Criteria (See Protocol Section 3.4.2 for full list of criteria)

1. **Target Disease Exceptions**
   a) Recurrent or metastatic carcinoma of the nasopharynx, paranasal sinus, squamous cell carcinoma that originated from the skin and salivary gland or non-squamous histologies (eg, mucosal melanoma).
   b) Subjects with untreated central nervous system (CNS) metastases.

      Subjects are eligible if CNS metastases have been adequately treated and have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to randomization. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to randomization.
   c) Subjects with carcinomatous meningitis.
   d) Any prior treatment with any non-platinum containing systemic therapy regimen for SCCHN (adjuvant, neoadjuvant, or multi-modal treatment).
2. **Medical History and Concurrent Diseases**
   a) Prior treatment with an anti-PD-1, anti-PD-L1, anti-programmed death ligand 2 (PD-L2), anti-cytotoxic T-lymphocyte associated protein 4 (anti-CTLA-4) antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.
3. **Physical and Laboratory Test Findings**
   a) Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, eg, Hepatitis B surface antigen (HBsAg, Australia antigen) positive, or Hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative).
   b) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

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

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
BMS-936558-01 (Nivolumab) Solution for Injection	100 mg (10 mg/mL)	IP	Open-label[a]	10 mL/vial (5 or 10 vials/carton)	Store at 2° - 8°C. Protect from light and freezing.
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	IP	Open-label[a]	40 mL/vial (4 vials/carton)	Store at 2°- 8°C. Protect from light and freezing.
0.9% Sodium Chloride for Injection	N/A	IP	Open-label[a]	Various (local commercial product)	As per package insert
5% Dextrose for Injection	N/A	IP	Open-label[a]	Various (local commercial product)	As per package insert

[a] The term "open label" refers to the medication as it is upon receipt at the pharmacy. The trial will be conducted in a double-blinded fashion

Study Assessments The primary objective is to compare the ORR of nivolumab in combination with ipilimumab vs nivolumab in combination with ipilimumab placebo, as determined by BICR using RECIST 1.1 criteria in platinum refractory subjects with recurrent or metastatic SCCHN. Subjects will be assessed for response by CT or MRI beginning 6 weeks (± 7days) after first dose and continuing every 6 weeks (± 7days) until Week 48 and then every 12 weeks (± 7days) until progression. Tumor assessments must continue per protocol until RECIST 1.1 progression has occurred. For the best response determination, confirmation of complete or partial response is required. Subjects with clinical progression must continue to be scanned per protocol schedule until radiographic PD is documented. Subjects will be followed for Survival every 3 months via in person or telephone contact after the subject has discontinued study drug treatment. All randomized subjects will be followed

Statistical Considerations:

Sample Size:

Approximately 396 subjects (approximately 216 platinum refractory subjects and approximately 180 platinum eligible subjects) will be randomized to either nivolumab in combination with ipilimumab or nivolumab in combination with ipilimumab placebo in a 2:1 ratio.

A sample size of 216 randomized platinum refractory subjects (144 and 72, respectively) will provide 84% power for testing the odds ratio of nivolumab in combination with ipilimumab or over nivolumab in combination with ipilimumab placebo, with a 0.050 two-sided significance level, assuming ORR of 35% and 15% (odds ratio of 3.051) in the nivolumab in combination with ipilimumab or and nivolumab in combination with ipilimumab placebo treatment groups respectively (odds ratio of proportions test using EAST v6).

Approximately 180 subjects (120 and 60, respectively) will be randomized in the platinum eligible subgroup. For a sample size of 120 subjects randomized to nivolumab plus ipilimumab, the maximum width of the exact two-sided 95% confidence interval (CI) is 18.6% when the ORR is expected to be in the 10% to 55% range. About 60 subjects will be randomized into nivolumab and ipilimumab placebo arm.

Endpoints:

Primary Endpoint

The primary objective in the study is to compare the ORR and assess DoR of the treatment of nivolumab in combination with ipilimumab vs. nivolumab in combination with ipilimumab placebo, as determined by a blinded independent central review (BICR) using RECIST 1.1 criteria, for first-line treatment of recurrent or metastatic SCCHN in the platinum refractory setting. ORR is defined as the number of subjects with a BOR of a CR or PR divided by the number of randomized subjects for each treatment group The BOR is defined as the best response designation, as determined by BICR, recorded between the date of randomization and the date of progression, as assessed by BICR per RECIST 1.1 or the date of subsequent anticancer therapy (including tumor-directed radiotherapy and tumor-directed surgery), whichever occurs first. For subjects without evidence of RECIST 1.1 progression or subsequent anticancer therapy, all available response designations will contribute to the BOR assessment. For subjects who continue treatment beyond progression, the BOR will be determined based on response designations up to the time of initial RECIST 1.1 progression.

ORR will be further characterized by DOR and Time to Response (TTR). DOR is defined as the time between the date of first confirmed response to the date of the first documented tumor progression (per RECIST 1.1), or death due to any cause, whichever occurs first. TTR is defined as the time from randomization to the date of the first confirmed CR or PR. DOR and TTR will be evaluated for responders (confirmed CR or PR) only.

Subjects who neither progress nor die are censored on the date of their last evaluable tumor assessment. Subjects who start subsequent anti-cancer therapy without a prior reported progression are censored at the last evaluable tumor assessments prior to or on initiation of the subsequent anti-cancer therapy.

Secondary Endpoints:

The secondary objective of this study is to estimate the ORR and assess DoR of the treatment of nivolumab in combination with ipilimumab vs nivolumab in combination with ipilimumab placebo, as determined by BICR using RECIST 1.1 criteria, for first line treatment of recurrent or metastatic SCCHN in the platinum eligible setting.

The BICR-assessed PFS is defined as the time from randomization to the date of first documented disease progression, as assessed by the BICR using RECIST 1.1 criteria, or death due to any cause, whichever occurs first. Subjects who died without a reported progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on the date they were randomized. Subjects who started any subsequent anti-cancer therapy, including tumor-directed radiotherapy and tumor-directed surgery, without a prior reported progression will be censored at the last evaluable tumor assessment prior to/on initiation of the subsequent anti-cancer therapy.

OS is defined as the time between the date of randomization and the date of death. For subjects without documentation of death, OS will be censored on the last date the subject was known to be alive.

PD-L1 expression is defined as the percent of tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 IHC assay. Analysis of the secondary endpoints will be performed at the same time as the primary endpoint analysis.

Analyses:

Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment arm as randomized using descriptive statistics using all randomized population.

Efficacy Analyses

Efficacy analyses will be performed using all randomized subjects by treatment group as randomized.

Safety Analyses

The safety analysis will be performed in all treated subjects. Descriptive statistics of safety will be presented using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by treatment arm.

Pharmacokinetic Analyses

The nivolumab and ipilimumab concentration data obtained in this study may be combined with data from other studies in the clinical development program to develop or refine a population PK model.

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Interim Analysis

One interim analysis will be performed when around 70% of platinum-refractory subjects have been followed for at least 6 months after randomization. The comparison of ORR between nivolumab in combination with ipilimumab vs nivolumab in combination with ipilimumab placebo in platinum refractory randomized subjects will be carried out using a two-sided Cochran Mantel Haenszel (CMH) test stratified by the stratification factors as recorded in the IVRS. Using Lan DeMets alpha spending function with O'Brien-Fleming boundaries, the significance level for this comparison will be determined by the fraction of subjects included in the interim analysis. If the analysis is performed when exactly 70% of platinum refractory subjects have reached 6 months follow up after randomization, the alpha level is 0.015. Point estimate of ORR, and its corresponding two-sided 98.5% exact CI will be provided for each treatment group. The difference in ORRs between the two treatment groups and its corresponding 98.5% CI will be calculated using CMH methodology and adjusted by the stratification factors as recorded in the IVRS. The DOR, PFS and OS distribution will be estimated using Kaplan-Meier technique. Median survival time along with 95% CI will be provided for each treatment group. Similar descriptive analyses will also be performed for the platinum-eligible subgroups and both groups combined. Similar descriptive analyses may also be performed by HPV status, PD-L1, TMB, gene expression profiling, and other biomarkers in each subgroup alone or combined.

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1.3 Study Population:

Subjects must have metastatic or recurrent disease that is not amenable to therapy with curative intent (surgery or radiation therapy with or without chemotherapy). Subjects that refuse potentially curative salvage surgery for recurrent disease are ineligible.

Two subgroups will be enrolled into this study. Subjects will be classified as platinum refractory or platinum eligible:

- Platinum refractory subgroup (n = approximately 216): subjects with histologically confirmed SCCHN that has recurred during or less than 6 months after completion of previous platinum-based chemotherapy, given as adjuvant or neoadjuvant treatment or as part of multimodal treatment (chemotherapy, surgery, radiotherapy) for locally advanced disease. Subjects should have not received systemic anti-cancer therapy in the recurrent or metastatic setting.
- Platinum eligible subgroup (n = approximately 180): subjects with histologically confirmed SCCHN who are platinum naive, or have recurred 6 months or more after completion of previous platinum-based chemotherapy, given as adjuvant or neoadjuvant treatment or as part of multimodal treatment (chemotherapy, surgery, radiotherapy) for locally advanced disease. Subjects should have not received systemic anti-cancer therapy in the recurrent or metastatic setting.

1.4 Research Hypothesis

- In patients with recurrent or metastatic SCCHN, the administration of nivolumab in combination with ipilimumab as first-line therapy in the platinum refractory setting will improve objective response rate (ORR) and duration of response (DOR) compared to nivolumab in combination with ipilimumab placebo.

1.5 Objectives(s)

1.5.1 Primary Objectives

- To compare the ORR and assess DOR of the treatment of nivolumab in combination with ipilimumab vs nivolumab in combination with ipilimumab placebo, as determined by a blinded independent central review (BICR) using RECIST 1.1 criteria, for first-line treatment of recurrent or metastatic SCCHN in the platinum refractory setting

1.5.2 Secondary Objectives

- To estimate the ORR and assess DOR of the treatment of nivolumab in combination with ipilimumab vs nivolumab in combination with ipilimumab placebo, as determined by BICR using RECIST 1.1 criteria, for first-line treatment of recurrent or metastatic SCCHN in the platinum eligible setting
- To assess progression-free survival (PFS), as determined by BICR, of nivolumab in combination with ipilimumab vs nivolumab in combination with ipilimumab placebo for first-line treatment of recurrent or metastatic SCCHN in the platinum eligible and platinum refractory settings, separately and overall

- To assess overall survival (OS), of nivolumab in combination with ipilimumab vs. nivolumab in combination with ipilimumab placebo for first-line treatment of recurrent or metastatic SCCHN in the platinum eligible and platinum refractory settings, separately and overall
- To assess efficacy (ORR, DOR, PFS and OS) by PD-L1 expression of nivolumab in combination with ipilimumab compared to nivolumab in combination with ipilimumab placebo for first-line treatment of recurrent or metastatic SCCHN in the platinum eligible and platinum refractory settings, separately and overall
- To assess efficacy (ORR, DOR, PFS and OS) by HPV p-16 status of nivolumab in combination with ipilimumab compared to nivolumab in combination with ipilimumab placebo for first-line treatment of recurrent or metastatic SCCHN in the platinum eligible and platinum refractory settings, separately and overall
- To evaluate tumor mutation burden, as a potential predictive biomarker of efficacy (such as ORR, DOR, PFS, and OS) of nivolumab in combination with ipilimumab or ipilimumab placebo for first-line treatment of recurrent or metastatic SCCHN in the platinum eligible and platinum refractory settings, separately and overall

2. ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) in accordance with the ethical principles underlying European Union Directive 2001/20/EC, United States Code of Federal Regulations, Title 21, Part 50 (21CFR50), and applicable local requirements.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to Sponsor or designee immediately. A serious breach is a breach of the conditions and principles of GCP (occurring in any country) in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of 1 or more subjects of the study or the scientific value of the study.

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

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

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The investigator, Sponsor or designee should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

Sponsor or designee will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable

regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
- If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
- Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed Health Insurance Portability and Accountability Act (HIPAA) Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

Subjects unable to give their written consent (eg, stroke or subjects with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this subject become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a subject who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3. INVESTIGATIONAL PLAN

3.1 Study Subgroups

CA209714 will recruit patients with recurrent or metastatic first line SCCHN.

Subjects must have metastatic or recurrent disease that is not amenable to therapy with curative intent (surgery or radiation therapy with or without chemotherapy). Subjects that refuse potentially curative salvage surgery for recurrent disease are ineligible.

Two subgroups will be enrolled into this study. Subjects will be classified as platinum refractory or platinum eligible:

- **Platinum refractory subgroup (n = approximately 216)**: subjects with histologically confirmed SCCHN that has recurred during or less than 6 months after completion of previous platinum-based chemotherapy, given as adjuvant or neoadjuvant treatment or as part of multimodal treatment (chemotherapy, surgery, radiotherapy) for locally advanced disease. Subjects should have not received systemic anti-cancer therapy in the recurrent or metastatic setting.
- **Platinum eligible subgroup (n = approximately 180)**: subjects with histologically confirmed SCCHN who are platinum naive, or have recurred 6 months or more after completion of previous platinum-based chemotherapy, given as adjuvant or neoadjuvant treatment or as part of multimodal treatment (chemotherapy, surgery, radiotherapy) for locally advanced disease. Subjects should have not received systemic anti-cancer therapy in the recurrent or metastatic setting.

Enrollment to each cohort will close when the predetermined number of patients in each cohort has been reached. If one cohort closes recruitment as it has reached the predefined number of patients in that particular subgroup (216 or 180), enrollment of patients into the other subgroup will remain open until it has completed enrollment.

3.2 Study Design and Duration

Protocol CA209714 is a randomized (2:1), double blinded, Phase 2 trial in subjects ≥ 18 years old with untreated metastatic SCCHN or recurrent SCCHN that is not amenable to curative therapy, evaluating nivolumab in combination with ipilimumab vs. nivolumab in combination with ipilimumab placebo as a first-line treatment.

HPV p-16 status (pos or neg/non-oropharyngeal), PD-L1 status (expressing or non-expressing/non evaluable/indeterminate) and platinum-refractory subgroup (yes/no) will be needed prior to randomization. Subjects will undergo screening evaluations to determine eligibility prior to randomization.

Subjects will be treated with one of the following:

Arm A: Nivo/Ipi Combo

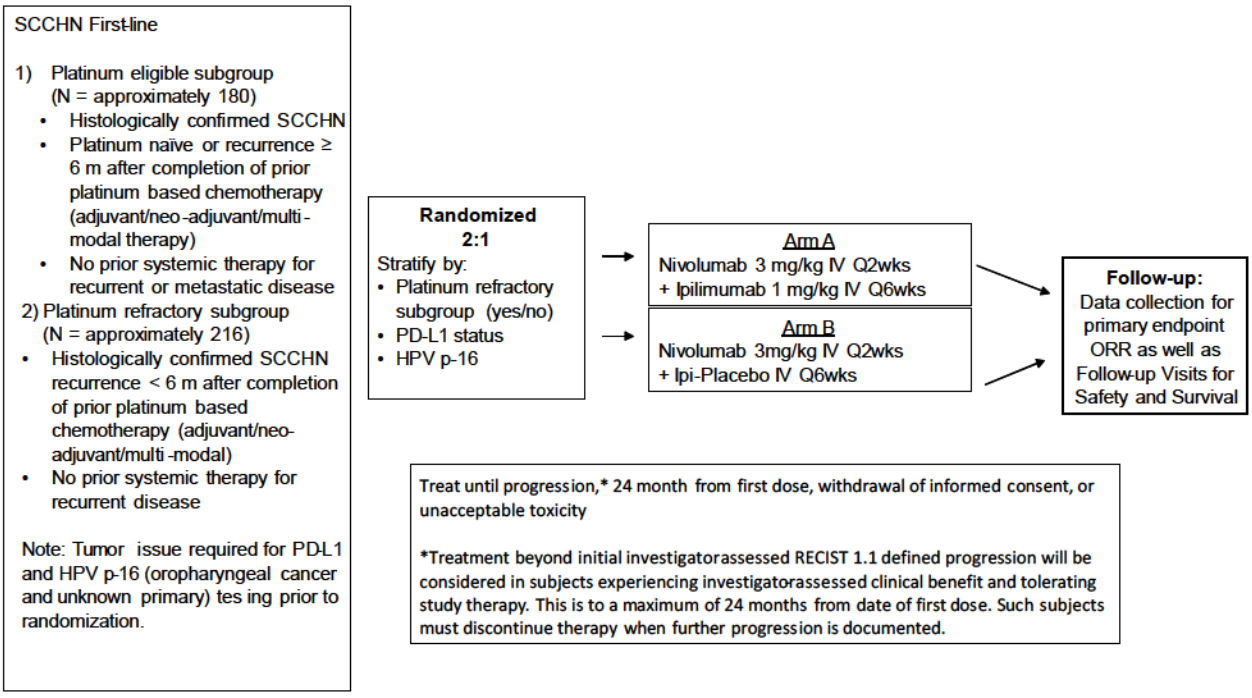
- Nivolumab 3 mg/kg IV will be administered every 2 weeks (± 3 days).
- Ipilimumab 1 mg/kg IV will be administered every 6 weeks (± 3 days) following the administration of nivolumab.

Arm B: Nivo and Ipilimumab-placebo

- Nivolumab 3 mg/kg IV will be administered every 2 weeks (± 3 days).
- Ipilimumab-Placebo IV will be administered every 6 weeks (± 3 days) following the administration of nivolumab.

The study design schematic is presented in Figure 3.2-1.

Figure 3.2-1: Study Design Schematic: A Double-Blind, Randomized, Two Arm Phase 2 Study of Nivolumab in Combination with Ipilimumab versus Nivolumab in combination with Ipilimumab placebo in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)



Approximately 396 subjects will be randomized to the two treatment arms in a 2:1 ratio and stratified by the following factors:

- Platinum refractory subgroup (yes vs no).
- PD-L1 status (expressing vs non-expressing or non-evaluable or indeterminate). PD-L1 status is set to expressing when tumor cell PD-L1 expression ≥1%. Up to 20% of randomized subjects can be included into the study as "non-evaluable" or indeterminate. After this point, subjects with non-evaluable/indeterminate results will not be permitted to be randomized; the site would need to submit an additional tumor tissue for testing with either a result of "expressing" or "non-expressing" in order to randomize the subject.

- HPV p-16 status (oropharyngeal Cancer HPV Positive vs oropharyngeal Cancer HPV Negative /non-oropharyngeal Cancer) - For subjects with oropharyngeal cancer, sites defined in Appendix 5.

Tumor progression or response endpoints will be assessed using Response Evaluation Criteria In Solid Tumors (RECIST 1.1) criteria. Treatment with study medication will continue until RECIST 1.1 defined progression, unacceptable toxicity, 24 months of treatment, or withdrawal of consent. See Section 3.6 for full details of discontinuation of study drug treatment.

Dose reductions will not be allowed for nivolumab, ipilimumab, or ipilimumab-placebo. Treatment beyond initial investigator-assessed progression (either clinical or radiographical) is permitted for nivolumab and ipilimumab or ipilimumab-placebo up to a maximum of 24 months from date of first dose if the subject has an investigator-assessed clinical benefit and is tolerating study drug (see Section 4.5.6.1).

A Data Monitoring Committee (DMC) will be established and meet regularly during the study to ensure that subject safety is carefully monitored and to provide oversight regarding safety and efficacy considerations in protocol CA209714, see Section 7.

The ORR analyses for each of the platinum eligible and platinum refractory subgroups will be conducted when the sufficient number of randomized subjects in that subgroup have been followed at least 9 months. The accrual duration will be approximately 13 months. Survival follow-up may continue for up to 5 years from the time of this analysis. The study will end once survival follow-up has concluded.

The study design schematic is presented in Figure 3.2-1.

This study will consist of three phases: screening, treatment, and follow-up.

Screening Phase

- Begins by establishing the subject's initial eligibility and signing of the Informed Consent Form (ICF).
- Subject is enrolled using the Interactive Voice Response System (IVRS).
- Tumor tissue (archival or recent tumor biopsy) must be submitted by the site to the central lab for determination of PD-L1 status. Additional tumor tissue may be required by Central Lab if initial testing is unevaluable. Subjects will be stratified on PD-L1 status (expressing/non-expressing or non-evaluable or indeterminate). Up to 20% of randomized subjects can be included into the study as "non-evaluable" or indeterminate, after this point subjects with non-evaluable results will not be permitted to be randomized; the site would need to submit an additional tumor tissue for testing with either a result of "expressing" or "non-expressing" in order to randomize the subject.
  - A patient's tumor will be classified as non-evaluable if the tumor tissue sample was not optimally collected or prepared. Some examples that would yield a non-evaluable result are: a) specimen contains <100 viable tumor cells, b) sections are folded/fragmented, c) specimen is excessively thick, or d) specimen is excessively necrotic or hemorrhagic.
  - A patient's tumor will be classified as indeterminate if the tumor cell membrane staining hampered for pre-specified reasons attributed to the biology of the tumor tissue sample,

such as high melanin content or high cytoplasmic staining, and not because of improper sample preparation or handling.
A communication will be sent to the site to inform that a PD-L1 result is available at the IVRS system.

- HPV p-16 status (in subjects with Oropharyngeal cancer) must be available prior to randomization. If it is not available locally, then this will need to be tested by central lab and resulted prior to randomization. A communication will be sent to the site to provide HPV p-16 result, if this test is being performed at the central lab.
- Subject is assessed for study eligibility.
- All screening assessments and procedures must be performed within 28 days prior to treatment.

Treatment Phase

- The treatment begins with the contact to the IVRS to randomize the subject.
- First treatment dose should occur within 3 calendar days following the randomization (after results of PD-L1 for all SCCHN and HPV p-16 status, in oropharyngeal cancer, are available).

Nivo/Ipi Combo Arm:

- Nivolumab 3 mg/kg IV will be administered every 2 weeks (± 3 days).
- Ipilimumab 1 mg/kg IV will be administered every 6 weeks (± 3 days) following the administration of nivolumab.
- On the day of infusion, nivolumab is to be administered first. The second infusion will always be ipilimumab and will start at least 30 minutes after completion of the nivolumab infusion.
- Nivolumab 3 mg/kg Q2 weeks and ipilimumab 1 mg/kg Q6 weeks will be continued until the progression of disease, discontinuation due to toxicity, withdrawal of consent, 24 months of treatment, or study closure. Subjects may discontinue only ipilimumab and continue treatment with nivolumab if certain circumstances are met.
- Treatment beyond initial investigator-assessed RECIST 1.1-defined progression is permitted if the subject has investigator-assessed clinical benefit and is tolerating treatment.
- Study assessments are to be collected as outlined in Table 5.1-2

Nivo and Ipilimumab-placebo Arm:

- Nivolumab 3 mg/kg IV will be administered every 2 weeks (± 3 days).
- Ipilimumab-Placebo IV will be administered every 6 weeks (± 3 days) following the administration of nivolumab.
- On the day of infusion, nivolumab is to be administered first. The second infusion will always be Ipilimumab-Placebo and will start at least 30 minutes after completion of the nivolumab infusion.
- Nivolumab 3 mg/kg Q2 weeks and Ipilimumab-Placebo 1 mg/kg Q6 weeks will be continued until the progression of disease, discontinuation due to toxicity, withdrawal of consent, 24 months of treatment, or study closure. Subjects may discontinue only Ipilimumab-Placebo and continue treatment with nivolumab if certain circumstances are met.

- Treatment beyond initial investigator-assessed RECIST 1.1-defined progression is permitted if the subject has investigator-assessed clinical benefit and is tolerating treatment.
- Study assessments are to be collected as outlined in Table 5.1-2:

Follow-up Phase

- The post-treatment follow-up begins when the decision to discontinue a subject from all treatment is made.
- Subjects who discontinue treatment for reasons other than disease progression will continue to have tumor assessments (if clinically feasible) according to the schedule in Table 5.1-3 until progression.
- Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All adverse events will be documented for minimum of 100 days after the last dose of study medications.
- Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data until death or the conclusion of the study.
- Survival Follow-up visits may be performed by phone contact or office visit. BMS may request that survival data be collected on all subjects outside of the protocol defined window. At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contact.

3.2.1 Duration of Treatment

The optimal duration of immunotherapy is an important question and continues to be investigated. Clinical trials across different tumor types in the nivolumab and ipilimumab development program indicate that most of the responses occur early, with a median time to response of 2 to 4 months,[44,45,46,47,48] and emerging data suggests that benefit can be maintained in the absence of continued treatment. A recent analysis in a melanoma study suggests the majority of patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment.[49] Furthermore, a limited duration of ipilimumab, including only 4 induction doses, resulted in long term survival in patients with metastatic melanoma, with a sustained plateau in survival starting around 2 years after the start of treatment.[50]

Accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long term benefit. CA209003, a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in patients with previously treated advanced solid tumors (including 129 participants with NSCLC), specified a maximum treatment duration of 2 years. Among 16 participants with NSCLC who discontinued nivolumab after completing 2 years of treatment, 12 participants were alive > 5 years and remained progression-free without any subsequent therapy. In the CA209003 NSCLC cohort, the OS curve begins to plateau after 2 years, with an OS rate of 25% at 2 years and 18% at 3 years.[51] These survival outcomes are similar to phase 3 studies in previously treated NSCLC, in which nivolumab treatment was continued until progression or unacceptable toxicity (2 year OS rates of 23% and 29%, and 3 year OS rates of 16% to18% for squamous and non-squamous NSCLC, respectively).[52]

Similar results have been reported in clinical studies of pembrolizumab, another PD-1 inhibitor. Keynote-010 was a randomized phase 3 trial of pembrolizumab (at either 2 mg/kg or 10 mg/kg every 3 weeks) versus docetaxel in participants with previously treated, PD-L1-positive, advanced NSCLC which specified a maximum treatment duration of 2 years for pembrolizumab. OS was significantly longer with both pembrolizumab 2 mg/kg (HR 0.72, P = 0.00017) and pembrolizumab 10 mg/kg (HR 0.60, P < 0.00001) compared to docetaxel, with an OS plateau developing beyond 2 years in both pembrolizumab arms. Among 690 patients who received pembrolizumab, 47 patients completed 2 years of pembrolizumab and stopped treatment. Most were able to maintain their response, including those with stable disease, with only 2 patients (4%) having confirmed progression after stopping at 2 years.[53]

Keynote-006 was a randomized phase 3 study of pembrolizumab versus ipilimumab in patients with advanced melanoma, which also specified a maximum 2 year duration of pembrolizumab treatment. 104 (19%) of 556 patients randomized to pembrolizumab completed 2 years of treatment. With a median follow-up of 9 months after completion of pembrolizumab, the estimated risk of progression or death was 9% in these patients.[54]

Taken together, these data suggest that treatment beyond 2 years is unlikely to confer additional clinically meaningful benefit and that the risk of progression after discontinuing treatment at 2 years is low.

In contrast, a shorter duration of nivolumab of only 1 year was associated with increased risk of progression in previously treated patients with NSCLC, suggesting that treatment beyond 1 year is likely needed. In CA209153, patients with previously treated advanced NSCLC who completed 1 year of nivolumab therapy were randomized to either continue or stop treatment, with the option of retreatment upon progression. Among 163 patients still on treatment at 1 year and without progression, those who were randomized to continue nivolumab had significant improvement in progression-free survival (PFS) compared to those who were randomized to stop treatment, with median PFS (post-randomization) not reached vs 10.3 months, respectively; HR = 0.42 (95% CI, 0.25 to 0.71). With a median follow-up of 14.9 months post-randomization, there also was a trend for patients on continued treatment to live longer (OS HR = 0.63 [95% CI: 0.33, 1.20]). Of note, the PFS curves in both groups plateau approximately 1 year after randomization (ie, 2 years after treatment initiation), suggesting that there may be minimal benefit in extending treatment beyond a total of 2 years.[55]

Collectively, these data suggest that there is minimal if any benefit derived from continuing I-O treatment beyond two years in advanced tumors. However, even though immunotherapy is well tolerated, patients will be at risk for additional toxicity with longer term treatment. Therefore, in this study, treatment will be given for a maximum of 2 years from the start of study treatment.

3.3 Post Study Access to Therapy

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study treatment for the maximum treatment duration specified in protocol Section 4.5.1.1. Study drug 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. BMS reserves the right to terminate access to BMS supplied study drug if any of the following occur: a) the marketing application is rejected by responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

3.4 Study population

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

3.4.1 Inclusion Criteria

1. Signed Written Informed Consent

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

b. Subjects must be willing and able to comply with scheduled visits, treatment schedule, and laboratory testing.

2. Target Population

a. Histologically confirmed head and neck squamous cell carcinoma (SCCHN) from any of the following primary sites only: oral cavity, oropharynx, hypopharynx and larynx (including squamous cell carcinoma of unknown primary arising from head and neck if HPV p-16 positive).

b. Must have metastatic or recurrent disease that is not amenable to therapy with curative intent (surgery or radiation therapy with or without chemotherapy). Subjects that refuse potentially curative salvage surgery for recurrent disease are ineligible.

c. Two subgroups will be enrolled into this study, as detailed above. Subjects will be classified as platinum refractory or platinum eligible.

No prior treatment with systemic anti-cancer therapy for recurrent or metastatic SCCHN, except if given as adjuvant or neoadjuvant chemotherapy, or chemotherapy as part of multimodal (chemo, radiation) treatment for locally advanced disease.

i. Platinum refractory subgroup (n = approximately 216): subjects with histologically confirmed SCCHN that has recurred during or less than 6 months after completion of previous platinum based chemotherapy, given as adjuvant or neoadjuvant treatment or as part of multimodal treatment (chemotherapy, surgery, radiotherapy) for locally advanced disease.

ii. Platinum eligible subgroup (n = approximately 180): subjects with histologically confirmed SCCHN who are platinum naive or have recurred 6 months or more after completion of previous platinum-based chemotherapy, given as adjuvant or neoadjuvant treatment or as part of multimodal treatment (chemotherapy, surgery, radiotherapy) for locally advanced disease.

[As of Revised Protocol 03, this criterion has been moved to 2.c] *No prior treatment with systemic anti-cancer therapy for recurrent or metastatic SCCHN, except if given as adjuvant or neoadjuvant chemotherapy, or chemotherapy as part of multimodal (chemo, radiation) treatment for locally advanced disease.*

d. Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 1
e. Measurable disease by computed tomography (CT) or magnetic resonance imaging (MRI) per RECIST 1.1 criteria; radiographic tumor assessment performed prior to randomization.
   i. Target lesions may be located in a previously irradiated field if there is documented (radiographic) disease progression in that site after the completion of radiation therapy.
f. Documentation of HPV p-16 status is required for SCCHN tumor of the oropharynx. Subjects with unknown primary location must have documented positive p-16 status

   Note: If results are not available, then a sample (tissue on microscopic slides, tissue block or a fresh tissue biopsy in formalin) should be sent to the central laboratory for analysis.
g. Documentation of PD-L1 status by IHC performed by the central lab at randomization. Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections (archival or recent: within 6 months), with an associated pathology report, must be submitted for biomarker evaluation prior to randomization. Biopsy should be excisional, incisional, or core needle. Fine needle aspiration is insufficient.
h. Prior palliative or curative radiotherapy must have been completed at least 2 weeks prior to randomization regardless of site that was irradiated.
i. If patient received prior chemotherapy, the prior chemotherapy should be completed at least 4 weeks prior to randomization.
j. All toxicities attributed to prior cancer therapy (systemic anti-cancer therapy, radiation or surgery) other than alopecia and fatigue must have resolved or returned to baseline at least 2 weeks before randomization.
k. Subject Re-enrollment: This study permits the re-enrollment of a subject who has discontinued the study as a pre-treatment failure (ie, subject has not been randomized/has not been treated). If re-enrolled, the subject must be re-consented.
l. Screening laboratory values must meet the following criteria (using CTCAE v4):

WBC	≥ 2000/uL
Neutrophils	≥ 1500/uL
Platelets	≥ $100x10^3$/uL
Hemoglobin	≥ 9.0 g/dL

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

$$\text{Female CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/ dL}}$$

$$\text{Male CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/ dL}}$$

AST	≤ 3.0 x ULN
ALT	≤ 3.0 x ULN

Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome who must have a total bilirubin level of < 3.0 x ULN).

m. Subjects must have an estimated life expectancy of at least 3 months.

3. Age and Reproductive Status

a. Males and Females, ages ≥18 years of age

b. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.

c. Women must not be breastfeeding

d. WOCBP must agree to follow instructions for method(s) of contraception for a period of 30 days (duration of ovulatory cycle) plus the time required for the investigational drug to undergo approximately five half-lives. WOCBP randomized/assigned to receive nivolumab should use an adequate method to avoid pregnancy for 5 months (30 days plus the time required for nivolumab to undergo approximately five half-lives) after the last dose of investigational drug.

e. Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for a period of 90 days (duration of sperm turnover) plus the time required for the investigational drug to undergo approximately five half-lives.

f. Males randomized to receive nivolumab who are sexually active with WOCBP must continue contraception for 7 months (90 days plus the time required for nivolumab to undergo approximately five half-lives) after the last dose of investigational drug.

g. Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in these sections.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception (see Appendix 4) which have a failure rate of < 1% when used consistently and correctly.

At a minimum, subjects must agree to use one highly effective method of contraception as listed in Appendix 4. Local laws and regulations may require use of alternative and/or additional contraception methods

3.4.2 Exclusion Criteria

1. Target Disease Exceptions

a. Recurrent or metastatic carcinoma of the nasopharynx, paranasal sinus squamous cell carcinoma that originated from the skin and salivary gland or non-squamous histologies (eg, mucosal melanoma).

b. Subjects with untreated Central Nervous system (CNS) metastases.
Subjects are eligible if CNS metastases have been adequately treated and have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to randomization. In addition, subjects must be

either off corticosteroids, or on a stable or decreasing dose of 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to randomization.

c. Subjects with carcinomatous meningitis.
d. Any prior treatment with any non-platinum containing systemic therapy regimen for SCCHN (adjuvant, neoadjuvant, or multi-modal treatment).

2. Medical History and Concurrent Diseases

a. Women who are pregnant or breastfeeding
b. Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.
c. Other active malignancy requiring concurrent intervention.
d. Subjects with previous malignancies (except non-melanoma skin cancers and the following in situ cancers: bladder, gastric, colon, esophageal endometrial, cervical/dysplasia, melanoma, or breast) unless a complete remission was achieved at least 2 years prior to study entry AND no additional therapy is required during the study period.
e. Subjects with an active, known or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
f. Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid > 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease.
g. **Not applicable per Amendment 05/Revised Protocol 02.** *Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.*
h. Known medical condition that, in the investigator's opinion, would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results.
i. Participants who have received a live / attenuated vaccine within 30 days of first treatment.

3. Physical and Laboratory Test Findings

a. Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, eg, Hepatitis B surface antigen (HBsAg, Australia antigen) positive, or Hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative).
b. Known history of positive testing for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).
c. History of allergy or hypersensitivity to study drug components. In case of history of allergy or hypersensitivity to platinum containing compounds, please discuss these individual cases with the medical monitor.

4. Other Exclusion Criteria

a. Prisoners or subjects who are involuntarily incarcerated. (Note: under specific circumstances a person who has been imprisoned may be included as a subject. Strict conditions apply and Bristol-Myers Squibb approval is required.

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

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria. Subjects not meeting the inclusion/exclusion criteria must not be enrolled into the study. There can be no exceptions to this rule.

Subject Re-enrollment: This study permits the re-enrollment of a subject who has discontinued the study as a pre-treatment failure (ie, subject has not been randomized/has not been treated). If re-enrolled, the subject must be re-consented.

3.4.3 Women of Childbearing Potential

Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause.

*Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels.

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal.

3.5 Concomitant Treatments

3.5.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study (unless utilized to treat a drug related adverse event):

- Immunosuppressive agents.
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 3.5.2)
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of cancer

- Surgical resection of tumor
- Any botanical preparation (eg herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally.

Caution should be used regarding the use of herbal medications as there may be as yet unknown interactions with nivolumab and/or ipilimumab. Discontinuation of the use of herbal medications prior to study enrollment is encouraged. Except for the permitted procedures specified as palliative local therapies (Section 3.5.3), all other radiation therapy or surgery to any tumor lesion is not permitted during study treatment. Subjects who require such non-palliative procedures must be discontinued from study treatment.

3.5.2 Other Restrictions and Precautions

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

It is the local imaging facility's responsibility to determine, based on subject attributes (eg, allergy history, diabetic history and renal status), the appropriate imaging modality and contrast regimen for each subject. Imaging contraindications and contrast risks should be considered in this assessment. Subjects with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate. If CT is contraindicated for a subject because of an iodinated contrast allergy, then a contrast enhanced MRI of the neck, chest, abdomen and pelvis will be performed.

Specific to MRI, subjects with severe renal insufficiency (ie, estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this subject population. In addition, subjects are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc. The ultimate decision to perform MRI in an individual subject in this study rests with the site radiologist, the investigator and the standard set by the local Ethics Committee.

3.5.3 Permitted Therapy

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

Regular concomitant use of bisphosphonates and receptor activator of nuclear factor kappa B ligand (RANK-L) inhibitors for prevention or reduction of skeletal-related events in subjects with

bone metastases is allowed if initiated prior to first dose of study therapy. Prior palliative radiotherapy must have been completed at least 2 weeks prior to randomization.

Prior palliative or curative radiotherapy must have been completed at least 2 weeks prior to randomization regardless of site that was irradiated. On study palliative radiotherapy is only allowed for treatment of painful bone lesions. Palliative surgical resection of tumor sites is not permitted. Subjects requiring palliative radiotherapy should be evaluated for objective evidence of disease progression prior to the initiation of such therapy, particularly if the most recent tumor assessment was more than 4 weeks prior to the start of local therapy. If progression per RECIST 1.1 is identified on any tumor assessments prior to the initiation of palliative local therapy, then subjects must either discontinue study drug treatment or they must meet criteria to continue treatment beyond progression (Section 4.5.6.1) in order to resume immunotherapy after palliative local therapy.

The potential for overlapping toxicities with radiotherapy and nivolumab/ipilimumab currently is not known; however, anecdotal data suggests that it is tolerable. As concurrent radiotherapy and nivolumab/ipilimumab have not been formally evaluated, in cases where palliative radiotherapy is required for a tumor lesion, then nivolumab and ipilimumab or ipilimumab-placebo should be withheld for at least 1 week before, during, and 1 week after radiation. Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs should resolve to Grade ≤ 1 prior to resuming nivolumab or nivolumab plus ipilimumab or ipilimumab-placebo.

3.6 Discontinuation of Subjects following any Treatment with Study Drug

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

- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)
- Pregnancy*

*In the case of pregnancy, the investigator must immediately (within 24 hours of awareness of the pregnancy) notify the BMS Medical Monitor or designee of this event. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety) (see Appendix 7). Refer to Section 6.4 Pregnancy.

All subjects who discontinue study drug should comply with protocol specified follow-up procedures as outlined in Section 5.1. The only exception to this requirement is when a subject

withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

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

3.7 Post Study Drug Study Follow up

Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5.1 until death or the conclusion of the study. Follow-Up Visit 1 to occur 30 days from the last dose (± 7 days) or Follow-Up Visit 1 can be performed on date of discontinuation if it is greater than 42 days from last dose. Follow-Up Visit 2 to occur 90 days from Follow-Up Visit 1 (± 7 days). Survival Follow-Up Visits to occur approximately every 3 months (± 7 days) from Follow-Up Visit 2. Survival Follow-up visits may be performed by phone contact or office visit.

BMS may request that survival data be collected on all subjects outside of the protocol defined window (Table 5.1-3). At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contact.

3.7.1 Withdrawal of Consent

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, if possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.7.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other

public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4. STUDY DRUG

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

Table 4-1: Study Drugs for CA209714

Product Description / Class and Dosage Form	Potency	IP/ Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
BMS-936558-01 (Nivolumab) Solution for Injection	100 mg (10 mg/mL)	IP	Open-label[a]	10 mL/vial (5 or 10 vials/carton)	Store at 2° - 8°C. Protect from light and freezing.
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	IP	Open-label[a]	40 mL/vial (4 vials/carton)	Store at 2°- 8°C. Protect from light and freezing.
0.9% Sodium Chloride for Injection	N/A	IP	Open-label[a]	Various (local commercial product)	As per package insert
5% Dextrose for Injection	N/A	IP	Open-label[a]	Various (local commercial product)	As per package insert

[a] The term "open label" refers to the medication as it is upon receipt at the pharmacy. The trial will be conducted in a double-blinded fashion

Premedications or medications used to treat infusion-related reactions should be sourced by the investigative sites if available and permitted by local regulations. Solutions used as diluent or placebo (ie, 0.9% Sodium Chloride Injection or 5% Dextrose Injection) should also be sourced by investigative sites if available and permitted by local regulations.

4.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

- Nivolumab
- Ipilimumab
- Placebo for ipilimumab (0.9% sodium chloride injection or 5% dextrose injection)

4.2 Non-investigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

4.3 Storage of Study Drug

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

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

Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

Infusion-related supplies (eg, IV bags, in-line filters, 0.9% sodium chloride injection, 5% dextrose injection) will not be supplied by the sponsor and should be purchased locally if permitted by local regulations.

Please refer to the current version of the Investigator Brochure (IB) and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information for nivolumab, ipilimumab, and matching placebo.

The unblinded pharmacist will obtain treatment assignment by interactive voice response system (IVRS) and prepare blinded drug.

Please refer to Section 9.2 for guidance on IP records and documentation.

4.4 Method of Assigning Subject Identification

After the subject's initial eligibility is established and informed consent has been obtained, the subject must be enrolled into the study by an IVRS to obtain the subject number. Every subject that signs the informed consent form must be assigned a subject number in IVRS. Specific instructions for using IVRS will be provided to the investigational site in a separate document. The

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

- Date that informed consent was obtained
- Date of birth
- Gender at birth

Once enrolled in IVRS, enrolled subjects that have met all eligibility criteria will be ready to be randomized through IVRS. PD-L1 expression data will be transferred directly from analyzing lab to IVRS. The local HPV p-16 result will be entered by the site directly into IVRS for the oropharyngeal cancer and unknown primary with p-16 positive subjects during the randomization call. The following information is required for subject randomization:

- Subject number
- Date of birth
- HPV p-16 status (oropharyngeal HPV p-16 pos vs oropharyngeal HPV p-16 neg or nonoropharyngeal)
- Oropharyngeal CA sites defined in Appendix 5
- Tumor Cell PD-L1 expression status at 1% cutoff: (expressing/non-expressing/non-evaluable/indeterminate)
- Positive (≥ 1% expressing) vs Negative (< 1% expressing)/not evaluable/indeterminate)
- Platinum refractory subgroup status (yes vs no)

Subjects meeting all eligibility criteria will be stratified by PD-L1 status (expressing vs nonexpressing/non-evaluable/indeterminate), HPV p-16 status (oropharyngeal HPV p-16 positive vs oropharyngeal HPV p-16 negative/non-oropharyngeal) and platinum refractory subgroup status (yes vs no). Subjects will be randomized in a 2:1 ratio to nivolumab + ipilimumab (Arm A) vs nivolumab + ipilimumab-placebo (Arm B).

Enrollment will stop once approximately 396 subjects have been randomized.

The exact procedures for using the IVRS will be detailed in the IVRS manual.

4.5 Selection and Timing of Dose for Each Subject

The dosing schedule is detailed below in Section 4.5.1.

All subjects will be monitored continuously for AEs while on study treatment. Treatment modifications (eg, dose delay, interruption, discontinuation) will be based on specific laboratory and adverse event criteria, as described in Sections 4.5.2, 4.5.3, 4.5.4 and 4.5.5.

4.5.1 Dosing

Table 4.5.1-1: Study Drugs for CA209714

	Cycle 1 Day 1 ± 3 Days	Cycle 1 Day 15 ± 3 Days	Cycle 1 Day 29± 3 Days
Arm A:[a] Nivolumab 3 mg/kg q 2 weeks + Ipilimumab 1 mg/kg q 6 weeks[a]	Nivolumab + Ipilimumab	Nivolumab	Nivolumab
Arm B:[b] Nivolumab 3 mg/kg q 2 weeks + Ipi-placebo 1 mg/kg q 6 weeks[b]	Nivolumab + Ipilimumab-placebo	Nivolumab	Nivolumab

[a] Arm A: Both nivolumab and ipilimumab should be administered as 30 minute infusions. nivolumab is to be administered first. The second infusion will be ipilimumab and will start at least 30 minutes after completion of the nivolumab infusion

[b] Arm B: Both nivolumab and ipilimumab-placebo should be administered as 30 minute infusions. nivolumab is to be administered first. The second infusion will be ipilimumab-placebo and will start at least 30 minutes after completion of the nivolumab infusion

4.5.1.1 Nivolumab plus Ipilimumab or ipilimumab-placebo

Subjects are randomized to receive treatment with nivolumab as a 30 minute infusion 3 mg/kg every 2 weeks (± 3 calendar days) and ipilimumab or ipilimumab-placebo as a 30 minute infusion 1 mg/kg every 6 weeks (± 3 calendar days), but no less than 12 days of the previous dose starting on Day 1, until progression, unacceptable toxicity, withdrawal of consent, 24 months from the first dose of treatment, or the study ends, whichever occurs first.

When study drugs (nivolumab and ipilimumab) are to be administered on the same day, nivolumab is to be administered first and separate infusion bags and filters should be used for each infusion. Nivolumab infusion must be promptly followed by a flush of diluent to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be the ipilimumab study drug and will start after the infusion line has been flushed, filters changed, and subject has been observed to ensure no infusion reaction has occurred. The time in between infusions is expected to be at least 30 minutes. Nivolumab and ipilimumab or ipilimumab-placebo may be diluted in 0.9% Sodium Chloride Solution or 5% Dextrose solution.

Dosing calculations should be based on the body weight. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the prior dose, the dose must be recalculated. Doses can be rounded per institutional standards. There will be no dose escalations or reductions of nivolumab and ipilimumab or ipilimumab-placebo allowed.

Subjects may be dosed with nivolumab no less than 12 days from the previous dose. There are no premedications recommended. Subjects may be dosed with Ipilimumab or Ipilimumab-placebo no less than 6 weeks from the previous dose.

Doses of nivolumab and/or ipilimumab or ipilimumab-placebo may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment. For more details, see Sections 4.5.2 (dose delays), 4.5.4 (resuming treatment), and 4.5.5 (discontinuation).

4.5.2 Dose Delays

4.5.2.1 Nivolumab and Ipilimumab/ipilimumab-placebo

Dose delay criteria apply for all drug-related AEs. Treatment delay up to 6 weeks for nivolumab and up to 12 weeks for ipilimumab or ipilimumab-placebo from the last dose are allowable (any dose delays greater than these will require approval from the medical monitor).

Tumor assessments for all subjects should continue as per protocol even if dosing is delayed. Nivolumab and ipilimumab or ipilimumab-placebo administration should be delayed for the following:

- Any Grade 2 non-skin, drug-related adverse event, except of fatigue
- Any Grade 2 drug-related creatinine, AST, ALT, and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related AE
- Any Grade 3 drug-related laboratory abnormality with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Grade ≥ 3 AST, ALT, total bilirubin will require dose discontinuation (see Section 4.5.5)
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.
- Subjects receiving ipilimumab or ipilimumab-placebo in combination with nivolumab that have drug-related toxicities that meet the criteria for dose delay, should have both drugs (ipilimumab or ipilimumab-placebo and nivolumab) delayed until retreatment criteria are met. (Exceptions apply to the retreatment criteria after dose delay of ipilimumab or ipilimumab-placebo and nivolumab for Grade ≥ 3 amylase and lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and that are attributed to ipilimumab or ipilimumab-placebo alone.)

Rescheduling:

- Nivolumab may be delayed until the next planned ipilimumab or ipilimumab-placebo dose if the next ipilimumab or ipilimumab-placebo dose is scheduled within the next 12 days. This will permit periodic ipilimumab or ipilimumab-placebo dosing to be synchronized with nivolumab dosing.
- Ipilimumab or ipilimumab-placebo should be dosed at the specified interval regardless of any delays in intervening nivolumab doses. However, in order to maintain periodic synchronized dosing of ipilimumab or ipilimumab-placebo and nivolumab, the dosing days of nivolumab and ipilimumab or ipilimumab-placebo may be adjusted within the permitted ± 3 day window, as long as consecutive nivolumab doses are given at least 12 days apart. Ipilimumab may be delayed beyond the 3 day window if needed to synchronize with the next nivolumab dose.

- If an ipilimumab or ipilimumab-placebo dose is delayed beyond 6 weeks from the prior ipilimumab or ipilimumab-placebo dose, then subsequent ipilimumab or ipilimumab-placebo doses should be rescheduled to maintain the 6 week interval between consecutive ipilimumab or ipilimumab-placebo doses.
- A dose delay of ipilimumab or ipilimumab-placebo which results in no ipilimumab or ipilimumab-placebo dosing for > 12 weeks requires ipilimumab or ipilimumab-placebo discontinuation, with exceptions as noted in Section 4.5.5.2.

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

4.5.3 Dose Reductions

4.5.3.1 Nivolumab or Ipilimumab/ipilimumab-placebo

There will be no dose reductions for nivolumab or ipilimumab or ipilimumab-placebo allowed.

4.5.4 Criteria to Resume Treatment

4.5.4.1 Criteria to Resume Nivolumab Treatment

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

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- For subjects with Grade 2 AST/ALT and/or total bilirubin values, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the BMS Medical Monitor.

Subjects with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor (or designee). Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

4.5.4.2 Criteria to Resume Ipilimumab/ipilimumab-placebo Dosing

Subjects may resume treatment with nivolumab and ipilimumab or ipilimumab-placebo when drug-related AE(s) resolve(s) to Grade 1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.

- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT or total bilirubin.
- Subjects with combined Grade 2 AST/ALT and total bilirubin values meeting discontinuation parameters (Section 4.5.5.2) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed.
- Subjects who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≤ 10 mg/day.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor.
- Dose delay of ipilimumab or ipilimumab-placebo which results in no ipilimumab or ipilimumab-placebo dosing for > 12 weeks requires ipilimumab or ipilimumab-placebo discontinuation, with exceptions as noted in Section 4.5.5.2.
- Ipilimumab may not be resumed sooner than 6 weeks (± 5days) after the prior ipilimumab or ipilimumab-placebo dose.
- In general, subjects who meet criteria to resume ipilimumab or ipilimumab-placebo will also have met criteria to resume nivolumab, so it should be feasible to synchronize dosing of both drugs when resuming ipilimumab or ipilimumab-placebo. In order to facilitate this, the dosing days of nivolumab and ipilimumab or ipilimumab-placebo may be adjusted within the permitted ± 5 day window, as long as consecutive nivolumab doses are given at least 12 days apart.
- One exception to note is when ipilimumab or ipilimumab-placebo and nivolumab doses are delayed due to drug- related Grade ≥ 3 amylase or lipase abnormalities not associated with symptoms or clinical manifestations of pancreatitis. If the investigator assesses the Grade ≥ 3 amylase or lipase abnormality to be related to ipilimumab or ipilimumab-placebo and not related to nivolumab, nivolumab may be resumed when the amylase or lipase abnormality resolves to Grade < 3 but ipilimumab or ipilimumab-placebo may only be resumed when the amylase or lipase abnormality resolves to Grade 1 or baseline. Investigator attribution of this toxicity to the ipilimumab or ipilimumab-placebo dosing must be clearly noted in the subject's medical chart. The BMS Medical Monitor should be consulted prior to resuming nivolumab in such subjects.

4.5.5 Treatment Discontinuation Criteria

For all subjects, global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time will be captured on the health outcomes questionnaires. Tumor assessments for subjects who discontinue study treatment without radiographic progression should continue as per protocol until radiographic progression is determined.

4.5.5.1 Nivolumab Dose Discontinuation

Treatment with nivolumab should be permanently discontinued for any of the following:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related AE lasting > 7 days, or recurs with the following exceptions for laboratory abnormalities, diarrhea, colitis, neurologic toxicity, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related diarrhea, colitis, neurologic toxicity, myocarditis, uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
      - Grade ≥ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation*
      - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN

        * In most cases of Grade 3 AST or ALT elevation, study treatment will be permanently discontinued. 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.
- Any Grade 4 drug-related adverse event or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin), except for the following events, which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy adverse events, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.

- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor (or designee).

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

Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks, the BMS Medical Monitor (or designee) must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

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

If a subject meets criteria for discontinuation and investigator is unable to determine whether the event is related to both or one study drug, the subject should discontinue both nivolumab and ipilimumab or ipilimumab-placebo and be taken off the treatment phase of the study. Continuation of ipilimumab or ipilimumab-placebo after discontinuation of nivolumab is not allowed on study.

4.5.5.2 Ipilimumab/ipilimumab-placebo Dose Discontinuation

Ipilimumab or ipilimumab-placebo should be permanently discontinued if any of the following criteria are met:

- Any Grade ≥ 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks OR requires systemic treatment;
- Any Grade ≥ 3 bronchospasm or other hypersensitivity reaction;
- Any other Grade 3 non-skin, drug-related adverse event with the following exceptions for laboratory abnormalities, grade 3 nausea and vomiting, grade 3 neutropenia and thrombocytopenia, and symptomatic endocrinopathies which resolved (with or without hormone substitution);
- Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
  - AST or ALT > 8 x ULN
  - Total bilirubin > 5 x ULN
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN

- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events, which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia
  - Isolated Grade 4 amylase or lipase abnormalities which are not associated with symptoms or clinical manifestations of pancreatitis. The BMS Medical Monitor should be consulted for Grade 4 amylase or lipase abnormalities.
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Any treatment delay resulting in no ipilimumab or ipilimumab-placebo dosing for > 12 weeks with the following exceptions: Dosing delays to manage drug-related adverse events, such as prolonged steroid tapers, are allowed. Prior to re-initiating treatment in a subject with a dosing delay lasting > 12 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
- Dosing delays resulting in no ipilimumab or ipilimumab-placebo dosing for > 12 weeks that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating treatment in a subject with a dosing delay lasting > 12 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued ipilimumab or ipilimumab-placebo dosing.

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

If a subject meets criteria for discontinuation and investigator is unable to determine whether the event is related to both or one study drug, the subject should discontinue both nivolumab and ipilimumab or ipilimumab-placebo and be taken off the treatment phase of the study.

4.5.6 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab and ipilimumab are considered immuno-oncology agents in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management Algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

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

- Neurological

The above algorithms are found in both the nivolumab and ipilimumab Investigator Brochures, as well as in Appendix 2.

4.5.6.1 Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of progression of disease (PD).[56]

Subjects will be permitted to continue on nivolumab + ipilimumab or ipilimumab-placebo for treatment beyond initial RECIST 1.1 defined PD, assessed by the investigator for up to a maximum of 24 months from the date of the first dose as long as they meet the following criteria:

- Investigator-assessed clinical benefit and no rapid disease progression
- Tolerance of study drug
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- Subject provides written informed consent prior to receiving additional nivolumab and ipilimumab or ipilimumab-placebo treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options. The decision to continue treatment beyond initial investigator-assessed progression should be discussed with the BMS Medical Monitor and documented in the study records.
- In cases where the subject is treated beyond investigator-assessed progression which is not confirmed by BICR, the subject should continue to be scanned following the study imaging schedule (every 6 weeks until week 48 and every 12 weeks thereafter). If the subject is treated beyond investigator-assessed progression that is confirmed by BICR a follow-up scan should be performed within six (6) weeks ± 5 days of original PD to determine whether there has been a decrease in the tumor size, or continued progression of disease. In this case, subsequent scans should be performed every twelve (12) weeks until further progression is determined.

If the investigator feels that the subject continues to achieve clinical benefit by continuing treatment, the subject should remain on the trial and continue to receive monitoring according to the Time and Events Schedule in Table 5.1-1, Table 5.1-2, and Table 5.1-3.

For the subjects who continue study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/ or the diameters of new measurable lesions compared to the time of initial PD. Nivolumab and ipilimumab or ipilimumab-placebo treatment should be discontinued permanently upon documentation of further progression.

New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measureable at the time of initial progression may become measureable and therefore included in the tumor burden if the longest diameter increases

to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm).

In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

4.5.7 Treatment of Infusion Reactions

4.5.7.1 Nivolumab or Ipilimumab Infusion Reactions

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to National Institute of cancer (NCI) common terminology criteria for adverse event (CTCAE, Version 4.0) guidelines.

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

For Grade 1 symptoms: (mild reaction; infusion interruption not indicated; intervention not indicated)

- Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab or ipilimumab or ipilimumab-placebo administrations.

For Grade 2 symptoms: (moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for $\leq$ 24 hours)

- Stop the nivolumab or ipilimumab or ipilimumab-placebo infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab or ipilimumab or ipilimumab-placebo will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF).
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg

should be administered at least 30 minutes before nivolumab or ipilimumab or ipilimumab-placebo infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

For Grade 3 or 4 symptoms: (severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]. Grade 4: Life threatening; pressor or ventilatory support indicated).

- Immediately discontinue infusion of nivolumab or ipilimumab or ipilimumab-placebo. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab or ipilimumab or ipilimumab-placebo will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

4.6 Blinding/Unblinding

The Sponsor, subjects, investigator and site staff will be blinded to the study drug administered (ipilimumab + nivolumab or nivolumab plus ipilimumab-placebo). Each investigative site must assign an unblinded pharmacist/designee, and an unblinded site monitor will be assigned by sponsor to provide oversight of drug supply and other unblinded study documentation.

Before breaking the blind of an individual subject's treatment during the blinded portion of the study, the investigator should determine that the unblinded information is necessary, ie, that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not related to the investigational product, the problem may be properly managed by assuming that the subject is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor; but, the investigator always has ultimate authority for the decision to unblind during the blinded portion of the study. The Principal Investigator should only call for emergency unblinding during the blinded portion of the study AFTER the decision to discontinue the subject has been made.

For both cohorts, the Sponsor will remain blinded until the time of planned interim analysis of the primary endpoint. However, due to the nature of the study design and corresponding data collection, the Sponsor's central protocol team (including but not limited to clinical, statistics, and data management) may have knowledge of an individual subjects' treatment assignment once subject-level unblinding occurs.

For this study, the method of unblinding is through the Interactive Response Technology (IRT).

For information on how to unblind for emergency, please consult the IRT manual.

Any request to unblind a subject for non-emergency purposes during the blinded portion of the study should be discussed with the Medical Monitor.

Subjects may not resume initial treatment once unblinded.

4.6.1 Unblinding for emergency purposes

During the blinded portion of the study, blinding of treatment assignment is critical to the integrity of clinical study. However, in the event of a medical emergency or pregnancy in an individual subject in which knowledge of the investigational product is critical to the subject's management, the blind for that subject may be broken by the investigator during the blinded portion of the study. The subject's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded during the blinded portion of the study.

4.7 Treatment Compliance

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

4.8 Destruction or Return of Investigational Product

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

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study drug.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local,

and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.9 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible Study Monitor.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

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

4.10 Retained Samples for Bioavailability / Bioequivalence

Not Applicable.

5. STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline (CA209714)

Procedure	Screening	Notes
Eligibility Assessments		
Informed Consent	X	Original IC in screening for protocol participation; Study allows for re-enrollment of a subject that has discontinued the study as a pre-treatment failure. If re-enrolled, the subject must be re-consented and assigned a new subject number from IVRS.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to first dose
Medical History	X	
Tumor Tissue Sample	X	A Tumor sample prior to therapy is mandatory for PD-L1 testing (to be shipped to Central Lab) and HPV p-16 testing for subjects with oropharyngeal CA and unknown primary location (sample either tested locally or shipped to Central Lab). If a recent tumor sample (obtained within 6 months of enrollment) is not available at screening, a fresh biopsy will be taken at any point prior to randomization. Sufficient tumor tissue should be submitted either one full block or minimum of 15 slides, obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen.
Screening/Baseline Tumor Assessment	X	Should be performed within 28 days prior to first dose. CT with IV contrast or MRI of Neck, Chest, Abdomen, Pelvis and all known or suspected sites of disease should be imaged at the screening visit. MRI with Gadolinium may be obtained if CT iodinated contrast is contraindicated. MRI of brain without and with Gadolinium is required to rule out brain metastases in cases where there is clinical suspicion of intracranial involvement. CT of the Brain (with or without contrast) can be performed if MRI is contraindicated or unavailable. TAs following RECIST 1.1 criteria.1.1 criteria.
Prior Medications	X	Dates and doses of platinum-based therapy plus prior medications subjects received to treat cancer including and radiotherapy given.

Table 5.1-1: Screening Procedural Outline (CA209714)

Procedure	Screening	Notes
ECOG Performance Status	X	Within 72 hours prior to first dose
Safety Assessments		
Physical Measurements/Physical Examination	X	Height and Weight. Within 14 days prior to first dose
Vital Signs	X	Including BP, HR, temperature. Obtain vital signs within 28 days prior to first dose.
Assessment of Signs and Symptoms	X	Within 14 days prior to first dose
Concomitant Medication Collection	X	Within 14 days prior to first dose
ECG	X	12 lead ECG required at Screening
Adverse Events Assessment	X	
Laboratory Tests	X	CBC w/differential, Chemistry panel including: Albumin , LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, phosphate, glucose, amylase, lipase, TSH, Free T4, Free T3. Within 14 days prior to first dose. Hepatitis B surface antigen (HBV sAg), and hepatitis C antibody (HCV Ab) or Hepatitis C RNA (HCV RNA). Within 28 days prior to first dose. Subjects who test positive for hepatitis C but have undetectable HCV RNA are allowed to enroll.
Pregnancy Test (WOCBP only)	X	Serum or urine within 24 hours of first dose
Biomarker Assessment		
Tumor Biopsy Sample	X	See Table 5.6-1
Study Drug		
Enrollment in IRT	X	Those supplied by BMS or sourced by the investigator

Table 5.1-2: On Treatment Procedural Outline (CA209714)

Procedure	Each Cycle Day1 ± 3	Each Cycle Day 15 ± 3	Each Cycle Day 29 ± 3	Notes
Safety Assessments				
Targeted Physical Examination	X	X	X	
Vital Signs	X	X	X	Including BP, HR, and temperature.
Physical measurements (including performance status)	X	X	X	Weight and ECOG status. The dosing calculations should be based on the body weight. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded to the nearest milligram.
Adverse Events Assessment	X	X	X	
Laboratory Tests	X	X	X	On-study local laboratory assessments should be done within 72 hours prior to each dose, CBC w/differential, (Albumin if clinically indicated), LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, phosphate, glucose, amylase, lipase, TSH with reflexive Free T4, Free T3. (Thyroid Function Testing to be evaluated every 6 weeks)
Pregnancy Test (WOCBP only)		See note		Serum or urine within 24 hours prior to first dose and then every 4 weeks (± 1 week) regardless of dosing schedule.

Table 5.1-2: On Treatment Procedural Outline (CA209714)

Procedure	Each Cycle Day1 ± 3	Each Cycle Day 15 ± 3	Each Cycle Day 29 ± 3	Notes
Efficacy Assessments				
Tumor Assessment	See note			• Tumor assessments should occur every 6 weeks (± 1 week) from first dose for the first 48 weeks, then every 12 weeks (whichever occurs later). (± 1 week) until disease progression or subsequent therapy. • CT or MRI neck, chest, abdomen, pelvis and all known/ suspected sites of disease. Use same imaging method as was used at screening/baseline. • Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks from first dose, or sooner if clinically indicated
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[redacted]				
[redacted]	[redacted]			[redacted]
[redacted]	[redacted]			[redacted]

Table 5.1-2: On Treatment Procedural Outline (CA209714)

Procedure	Each Cycle Day1 ± 3	Each Cycle Day 15 ± 3	Each Cycle Day 29 ± 3	Notes
[redacted]				
[redacted]		[redacted]		[redacted]
[redacted]		[redacted]		[redacted]
[redacted]		[redacted]		[redacted]
[redacted]	[redacted]			[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 5.1-3: Follow-Up Period (all treatment groups)

Procedure	Follow Up, Visits 1 and 2[a]	Survival Follow-Up Visits[b]	Notes
Safety Assessments			
Targeted Physical Examination	X		To assess for potential late emergent study drug related issues
Vital Signs	X		
Adverse Events Assessment	X		In survival period only to include toxicities from study therapy.
Review of Concomitant Medication	X	X	Document Subsequent Cancer Therapy
Laboratory Tests	X		CBC w/ differential, LFTs, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase, TSH (+ reflex Free T4 and Free T3) To be done at FU1, to be repeated at FU2, if study related toxicity persists.
Pregnancy Test (WOCBP only)	X		Serum or urine on the 2 the first follow up visits
Efficacy Assessments			
Tumor Assessment	X	X	Only for subjects without progression. - Tumor assessments should occur every 6 weeks (± 1 week) for the first 48 weeks, then every 12 weeks (± 1 week) until disease progression or treatment is discontinued (whichever occurs later). - CT or MRI of neck, chest, abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline. - Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks from first dose, or sooner if clinically indicated
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[redacted]	[redacted]		
[redacted]		[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]

Table 5.1-3: Follow-Up Period (all treatment groups)

Procedure	Follow Up, Visits 1 and 2[a]	Survival Follow-Up Visits[b]	Notes
Subject Status			
Survival Status	X	X	Every 3 months after FU 2; may be accomplished by visit, phone contact or email, to include assessment of subsequent anti-cancer therapy

[a] Follow-up visit 1 (FU1) = 30 days from the last dose (± 7) days or Follow up visit 1 can be performed on the date of discontinuation if it is greater than 42 days from last dose. Follow-up visit 2 (FU2) = 90 days (± 7 days) from follow-up visit 1(± 7 days).

[b] Every 3 Months (± 7 days) from FU2.

5.1.1 Retesting During Screening or Lead-in Period

Retesting of laboratory parameters and/or other assessments during the Screening or Lead-in period will be permitted (this does not include parameters that require a confirmatory result).

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

Laboratory parameters and/or assessments that are included in Table 5.1-1, Screening Procedural Outline may be repeated in an effort to find all possible well-qualified subjects. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

5.2 Study Materials

- NCI CTCAE version 4
- Nivolumab Investigator Brochure
- Ipilimumab Investigator Brochure
- Pharmacy Binder
- Laboratory manuals for collection and handling of blood (including PK, biomarker and
- immunogenicity) and tissue specimens
- Site manual for operation of IVRS, including enrollment worksheets
- Manual for entry of local laboratory data
- Pregnancy Surveillance Forms
- RECIST 1.1 pocket guide
- Study Imaging Manual

5.3 Safety Assessments

At baseline, a medical history will be obtained to capture relevant underlying conditions. The baseline examinations should include weight, height, ECOG Performance Status, blood pressure (BP), heart rate (HR), and temperature at rest, and should be performed within 28 days prior to first dose. Baseline signs and symptoms are those that are assessed within 14 days prior to first dose. Concomitant medications will be collected from within 14 days prior to the first dose through the study treatment period (see Section 5.1).

Baseline local laboratory assessments should be done within 14 days prior to first dose and are to include: complete blood count (CBC) w/differential, liver function tests (LFTs: ALT, AST, total bilirubin, alkaline phosphatase), blood urea nitrogen (BUN) or serum urea level, creatinine, albumin, calcium (Ca++), magnesium (Mg++), sodium (Na+), potassium (K+), chloride (Cl-), phosphate, lactate dehydrogenase (LDH), glucose, amylase, lipase. Thyroid function tests includes thyroid stimulating hormone (TSH), free thyroxine (T4), and free triiodothyronine (T3).

The following baseline local laboratory assessments should be done within 28 days prior to first treatment: Hepatitis B and C testing (HBV sAg and HCV Ab or HCV RNA).

Pregnancy testing for WOCBP (done locally) must be performed within 24 hours prior to the Day 1 of first dose and then every 4 weeks ± 1 week regardless of dosing Cycle.

While on-study the following local laboratory assessments are to be done within 3 days prior to each dose: CBC with differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, albumin (if clinically indicated), Ca, Mg, Na, K, Cl, phosphate, LDH, glucose, amylase, and lipase. Thyroid function testing is to be done every 6 weeks regardless of treatment arm.

Subjects will be evaluated for safety if they have received any study drug. Toxicity assessments will be continuous during the treatment phase. During the safety follow-up phase (Table 5.1-3) toxicity assessments should be done in person. Once subjects reach the survival follow-up phase either in person or documented telephone calls to assess the subject's status are acceptable.

Adverse events and laboratory values will be graded according to the NCI-CTCAE version 4.0.

On-study weight, ECOG performance status, and vital signs should be assessed at each on-study visit prior to dosing. Vital signs should also be taken as per institutional standard of care prior to, during and after infusions. The start and stop time of the study therapy infusions should be documented.

Physical examinations are to be performed as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse event page.

Additional measures, including non-study laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme evaluations) will be monitored during the follow-up phase via on site/local labs until all study drug related toxicities resolve, return to baseline, or are deemed irreversible.

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

5.3.1 ECOG Performance Status

Eastern Cooperative Oncology Group (ECOG) Performance Status will be evaluated and documented at Screening within 72 hours prior to first dose and within 72 hours prior to each dosing visit as outlined in Section 5.1. See Appendix 1 for description of ECOG status.

5.3.2 Pregnancy Testing

WOCBP are required to have pregnancy tests performed. WOCBP must exhibit a negative serum or urine pregnancy (minimum sensitivity 25 IU/L or equivalent units) of HCG within 24 hours prior to Day 1 of first dose and then every 4 weeks (± 1 week) during the treatment period and first 2 follow-up visits. Pregnancy testing will be done locally and as outlined in Section 5.1. An extension up to 72 hours prior to start of study drug may be permissible in situations where results

cannot be obtained within the standard hour window. This is subject to medical monitor/MST Chair approval.

5.3.3 Thyroid Function Testing

Local thyroid function testing will be performed as outlined in Section 5.1.

At Screening, thyroid function testing is to include TSH, free T3 and free T4. At subsequent time points, thyroid function testing consists of TSH only. However, if the TSH is abnormal, reflexive testing of free T3 and free T4 are to be performed.

Management algorithms for suspected endocrinopathy adverse events (including abnormal thyroid function) can be found in the nivolumab investigator brochure and Appendix 2 of the protocol.

5.3.4 Electrocardiogram (ECG)

All subjects who have met the eligibility criteria are required to have a 12-lead ECG performed at Screening. If clinically indicated, additional ECGs may be obtained during the study.

5.4 Efficacy Assessments

Study radiologic tumor evaluations will take place in accordance with T & E tables according to RECIST 1.1 Appendix 3.

Sites will be trained prior to scanning the first study subjects. Images will be submitted to an imaging third-party radiology vendor for central review as they are performed. Image acquisition guidelines and submission process will be outlined in the study Imaging Manual to be provided by the radiology vendor.

Screening (baseline) tumor assessments are to be performed within 28 days prior to first dose. In addition to the neck, chest, abdomen, pelvis, and all known / suspected sites of disease should be assessed at baseline. Subsequent assessments should include neck, chest, abdomen, pelvis, and all known / suspected sites of disease using the same imaging method and technique as was used at baseline.

A Screening MRI (or CT with contrast if MRI is contraindicated) of the brain without and with contrast should be done for all subjects with suspected brain involvement, including base of skull involvement, in order to rule out active metastatic disease.

Radiographic tumor response will be assessed every 6 weeks (± 1 week) after the first dose for the first 12 months (until week 48) and every 12 weeks (± 1 week) thereafter, until disease progression or subsequent therapy (whichever occurs later). Previously treated CNS metastases are not considered measurable lesions for purposes of RECIST 1.1 determined response. Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks from the date of first dose, or sooner if clinically indicated.

CT with PO/IV contrast or contrast enhanced MRI are the preferred imaging modalities for assessing radiographic tumor response. If a subject has a known allergy to contrast material, local prophylaxis standards may be used to obtain the assessment with contrast if at all possible, or use the alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan will

suffice. Should a subject have a contraindication for CT IV contrast, contrast enhanced MRI of the neck, chest, abdomen and pelvis may be obtained. Every attempt should be made to image each subject using an identical acquisition protocol on the same scanner for all imaging time points.

Use of CT component of a PET/CT scanner: Combined modality scanning such as with fluorodeoxyglucose-positron emission tomography (FDG PET)/CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined FDG-PET/CT are of limited use in anatomically based efficacy assessments, and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically based RECIST measurements. However, if a site can document that the CT performed as part of a FDG-PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the FDG-PET/CT can be used for RECIST 1.1 measurements. Note, however, that the FDG-PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Bone scan or PET scan is not adequate for assessment of RECIST 1.1 response in target lesions. In selected circumstances where such modalities are the sole modality used to assess certain non target organs, those non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

Tumor assessments for all subjects should continue as per protocol even if dosing is delayed or discontinued. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Change in tumor measurements and tumor response to guide ongoing study treatment decisions will be assessed by the Investigator using the RECIST 1.1 criteria (Appendix 3).

All radiographic assessments performed for study purposes will be submitted to the third-party radiology vendor for central review. Tumor assessments should be submitted to the third-party radiology vendor as they are performed on an ongoing basis. At the time of investigator-assessed disease progression, the site must request a Blinded Independent Central Review (BICR) from the third-party radiology vendor. For details on the timelines and associated process requirements refer to the imaging manual.

Subjects whose disease progression is not confirmed by the BICR will be required to continue tumor assessments (if clinically feasible) according to the protocol-specified schedule, in order to ensure of the primary and key secondary endpoints of the study (BICR assessed ORR and PFS) are assessed. In this situation, the decision on whether to discontinue therapy will be the responsibility of investigator. Subsequent tumor assessments must be submitted to the third party radiology vendor for BICR and may be discontinued when the investigator and BICR both assess the subject to have met RECIST 1.1 criteria for progression.

If clinically acceptable, subsequent therapy should begin only after RECIST1.1 progression has been assessed by BICR.

At the time of investigator-assessed disease progression, the site must complete the tumor assessment pages in TAO (Trial Access Online) documenting disease progression and submit a fresh biopsy sample to Central Lab for biomarker analysis as specified in Section 5.6.

If the subject is offered treatment beyond progression, the biopsy should be performed when they are taken off therapy, at the point after RECIST progression when they meet the criteria for discontinuation as defined in the protocol

In addition, subjects receiving nivolumab or ipilimumab or ipilimumab-placebo treatment beyond progression must continue tumor assessments until such treatment has been discontinued.

5.4.1 Primary Efficacy Assessment

The primary endpoint is objective response rate (ORR) in the platinum refractory subgroup (See Section 8.3.1 for the definitions of ORR). All randomized subjects will be monitored by radiographic assessment on an every 6 week schedule every 6 weeks (± 7 days) from first dose for the first 12 months (until week 48) and every 12 weeks (± 7 days) thereafter (beginning from the first on-study assessment on week 6 [± 7 days]), to determine changes in tumor size. RECIST 1.1 criteria will be used for the assessment. For details regarding the response criteria using RECIST 1.1 refer to Appendix 3.

5.4.2 Secondary Efficacy Assessment

The secondary endpoint of ORR in platinum eligible subgroup is defined similarly as described for the primary endpoint.

The BICR-assessed PFS is defined as the time from randomization to the date of first documented disease progression, as assessed by the BICR using RECIST 1.1 criteria, or death due to any cause, whichever occurs first. Subjects who died without a reported progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on the date they were randomized. Subjects who started any subsequent anti-cancer therapy, including tumor-directed radiotherapy and tumor-directed surgery, without a prior reported progression will be censored at the last evaluable tumor assessment prior to/on initiation of the subsequent anti-cancer therapy.

Every effort will be made to collect survival data on all randomized subjects including subjects withdrawn from treatment for any reason, who are eligible to participate in the study and who have not withdrawn consent for survival data collection. If the death of a subject is not reported, all dates in this study representing a date of subject contact will be used in determination of the subject's last known date alive.

PD-L1 expression is defined as the percent of tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 IHC assay.

Analysis of the secondary endpoints will be performed at the same time as the primary endpoint analysis.

To determine changes in tumor size. RECIST 1.1 criteria will be used for the assessment. .For details regarding response criteria using RECIST 1.1 refer to Appendix 3.

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6. ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all AE. The causal relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. Care should be taken not to introduce bias when collecting

AEs and/or SAEs. Inquiry about specific AEs should be guided by clinical judgement in the context of known adverse events, when appropriate for the program or protocol.

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.

6.1 Serious Adverse Events

A S***erious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

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

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

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

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)

- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures.

All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing, except in cases where a study participant has started a new anti-neoplastic therapy. However, any SAE occurring after the start of a new treatment that is suspected to be related to study treatment by the investigator will be reported. If applicable, SAEs must be collected that relate to any later protocol specified procedure (eg, a follow-up skin biopsy). For subjects randomized/assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of randomization/treatment assignment. 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.

An SAE report must be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship must be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to Sponsor or designee within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission,

paper forms must be used and submitted immediately. When paper forms are used, the original paper forms are to remain on site.

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

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

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to Sponsor or designee using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

BMS 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.

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

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

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

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

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form 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 subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy

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

6.4 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half lives after product administration, the investigator must immediately notify the Sponsor or 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 Section 6.1.1.

If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, or re-initiation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur. If, for whatever reason, the pregnancy has ended, confirmed by negative serum pregnancy test, treatment may be resumed (at least 3 weeks and not greater than 6 weeks after the pregnancy has ended), following approvals of participant /sponsor /IRB/EC, as applicable.

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 BMS 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.

6.5 Overdose

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

6.6 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

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

AND

2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

6.7.1 Adverse Events of Interest

Definition of immune-mediated adverse events (IMAEs)

Immune-mediated AEs are specific events (that include pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, and endocrine (adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis) for which subjects received immunosuppressive medication for treatment of the event, with the exception of endocrine events (hypothyroidism/thyroiditis, hyperthyroidism, hypophysitis, diabetes mellitus, adrenal insufficiency), which are included regardless of treatment since these events are often managed without immunosuppression.

IMAEs include events, regardless of causality, occurring within 100 days of the last dose. This list is subject to change based on Health Authority feedback or change of Medical Dictionary for Regulatory Activities (MedDRA) version. The final list used will be described in the clinical study report (CSR).

Table 6.7.1-1 below provides a summary of the IMAEs category and their respective preferred terms (PTs). This list is subject to change based on Health Authority feedback or change of MedDRA version. The final list used will be described in the CSR.

Table 6.7.1-1: Preferred Terms Included in Analysis of IMAEs to Support Warnings and Precautions

IMAE Category	PTs included under IMAE Category
Pneumonitis	Pneumonitis, Interstitial lung disease
Diarrhea/Colitis	Diarrhea, Colitis, Enterocolitis

Table 6.7.1-1: Preferred Terms Included in Analysis of IMAEs to Support Warnings and Precautions

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

7. DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

A Data Monitoring Committee (DMC) will be utilized to provide general oversight and safety considerations for this study. The DMC will provide advice to the Sponsor regarding actions the committee deems necessary for the continuing protection of subjects enrolled in this study. The DMC will be charged with assessing such actions in light of an acceptable risk/benefit profile for nivolumab in combination with placebo, and nivolumab in combination with ipilimumab. The DMC will act in an advisory capacity to BMS and will monitor subject safety data for the study approximately every 6 months for the duration of the trial.

The DMC will be advisory to the clinical study leadership team. The clinical study leadership will have responsibility for overall conduct of the study including managing the communication of study data. The group will be responsible for promptly reviewing the DMC recommendations, for providing guidance regarding the continuation or termination of the study, and for determining whether amendments to the protocol or changes to the study conduct are required.

Details of the DMC responsibilities and procedures will be specified in the DMC charter.

When required, adjudicated events will be submitted to the DMC and Health Authorities for review on a specified timeframe in accordance with the adjudication documentation.

8. STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The primary objective is to compare the ORR of nivolumab in combination with ipilimumab vs nivolumab in combination with ipilimumab placebo, as determined by BICR using Response Evaluation Criteria In Solid Tumors (RECIST 1.1) criteria in platinum refractory subjects with recurrent or metastatic SCCHN. The alpha level for the ORR is adjusted for one planned interim analysis using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. Given that the interim analysis for the primary endpoint is expected to be performed when 70% of platinum refractory subjects have reached 6 months follow up after randomization, the alpha level is expected to be 0.015 for the interim analysis and 0.045 for the final analysis.

Approximately 396 subjects (216 platinum refractory subjects and 180 platinum eligible subjects) will be randomized to either nivolumab plus ipilimumab or nivolumab in combination with ipilimumab placebo in a 2:1 ratio.

A sample size of 216 randomized platinum refractory subjects (144 and 72, respectively) will provide 84% power for testing the odds ratio of nivolumab plus ipilimumab over nivolumab in combination with placebo, with a 0.050 two-sided significance level, assuming ORR of 35% and 15% (odds ratio of 3.051) in the nivolumab plus ipilimumab and nivolumab in combination with ipilimumab placebo treatment group, respectively (odds ratio of proportions test using EAST v6).

The first secondary objective is to estimate the ORR of the treatment of nivolumab in combination with ipilimumab vs nivolumab in combination with ipilimumab placebo, as determined by BICR using RECIST 1.1 criteria for first-line treatment of recurrent or metastatic SCCHN in the platinum eligible setting.

Approximately 180 subjects (120 and 60, respectively) will be randomized in the platinum eligible subgroup. For a sample size of 120 subjects randomized to nivolumab plus ipilimumab, the maximum width of the exact two-sided 95% confidence interval (CI) is 18.6% when the ORR is expected to be in the 10% to 55% range. The table below summarizes the 95% exact CI when observed ORRs are between 10% and 55% respectively.

Table 8.1-1: Observed ORR with Exact 95% CI in Platinum Eligible Subjects randomized to nivolumab plus ipilimumab (N=120)

Observed ORR	95% Exact CI
10%	(5.3%, 16.8%)
20%	(13.3%, 28.3%)
30%	(22.0%, 39.0%)
40%	(31.2%, 49.3%)
50%	(40.7%, 59.3%)
55%	(45.7%, 64.1%)

About 60 subjects will be randomized to nivolumab plus ipilimumab placebo arm. The following table summarizes the 95% exact CI when observed ORRs are between 10% and 55%.

Table 8.1-2: Observed ORR with Exact 95% CI in Platinum Eligible Subjects randomized to nivolumab plus ipilimumab placebo (N=60)

Observed ORR	95% Exact CI
10%	(3.8%, 20.5%)
20%	(10.8%, 32.3%)
30%	(18.8%, 43.2%)
40%	(27.6%, 53.5%)
50%	(36.8%, 63.2%)
55%	(41.6%, 67.9%)

8.2 Populations for Analyses

- All Enrolled Subjects: All subjects who signed an informed consent form and were registered into the IRS.
- All Randomized Subjects: All subjects who were randomized to any treatment arm in the study. This is the primary dataset for analyses of study conduct, study population, and efficacy.
- All Treated Subjects: All subjects who received at least one dose of nivolumab, or ipilimumab, or nivolumab in combination with ipilimumab placebo.
- All pharmacokinetic (PK) Subjects: All subjects with available serum time-concentration data
- Immunogenicity Evaluable Subjects:
  - Nivolumab ADA Evaluable Subjects: all treated subjects with baseline and at least 1 post-baseline pre-infusion nivolumab immunogenicity assessment.
  - Ipilimumab ADA Evaluable Subjects: all treated subjects with baseline and at least 1 post-baseline pre-infusion ipilimumab immunogenicity assessment.
- All PD-L1 Tested subjects: All subjects, randomized or not, who had a tumor biopsy specimen available for PD-L1 expression testing. This includes both randomized and screen failure subjects.

A description of the participant population will be included in the statistical output reported, including subgroup of age, gender, and race.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The primary objective in the study will be measured by the primary endpoint of ORR in Platinum Refractory subgroup. ORR is defined as the number of subjects with a best overall response (BOR) of a complete response (CR) or partial response (PR) divided by the number of randomized subjects for each treatment group. The BOR is defined as the best response designation, as determined by BICR, recorded between the date of randomization and the date of progression, as

assessed by BICR per RECIST 1.1 or the date of subsequent anticancer therapy (including tumor-directed radiotherapy and tumor-directed surgery), whichever occurs first. For subjects without evidence of RECIST 1.1 progression or subsequent anticancer therapy, all available response designations will contribute to the BOR assessment. For subjects who continue treatment beyond progression, the BOR will be determined based on response designations up to the time of initial RECIST 1.1 progression.

ORR will be further characterized by Duration of Response (DOR) and Time to Response (TTR). DOR is defined as the time between the date of first confirmed response to the date of the first documented tumor progression (per RECIST 1.1), or death due to any cause, whichever occurs first. Subjects who neither progress nor die will be censored on the date of their last evaluable tumor assessment. Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to or on initiation of the subsequent anti-cancer therapy. TTR is defined as the time from randomization to the date of the first confirmed CR or PR. DOR and TTR will be evaluated for responders (confirmed CR or PR) only.

The final analysis of the primary endpoint will occur at least 9 months after the last subject in the platinum refractory subgroup has been randomized.

8.3.2 Secondary Endpoint(s)

The secondary endpoint of ORR and DOR in platinum eligible subgroup is defined similarly as described for the primary endpoint.

The BICR-assessed PFS is defined as the time from randomization to the date of first documented disease progression, as assessed by the BICR using RECIST 1.1 criteria, or death due to any cause, whichever occurs first. Subjects who died without a reported progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on the date they were randomized. Subjects who started any subsequent anti-cancer therapy, including tumor-directed radiotherapy and tumor-directed surgery, without a prior reported progression will be censored at the last evaluable tumor assessment prior to/on initiation of the subsequent anti-cancer therapy.

OS is defined as the time between the date of randomization and the date of death. For subjects without documentation of death, OS will be censored on the last date the subject was known to be alive.

PD-L1 expression is defined as the percent of tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 IHC assay.

The final analysis of the ORR in each of platinum eligible and platinum refractory subgroups will occur at least 9 months after the sufficient number of subjects in that subgroup have been randomized (approximately 180 in platinum eligible and 216 in platinum refractory subgroups). Analysis of the PFS and OS will also be performed at the same time as the ORR analysis.

[redacted]

8.4 Analyses

Safety and tolerability will be measured by the incidence of deaths, adverse events, serious adverse events, adverse events leading to discontinuation, immune-mediated adverse events, select adverse events, adverse events leading to dose delay, and specific laboratory abnormalities (worst grade) in each treatment group. Toxicities will be graded using the NCI CTCAE version 4.0.

[redacted]

8.4.1 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment arm as randomized using descriptive statistics using all randomized population.

8.4.2 Efficacy Analyses

Efficacy analyses will be performed by treatment for each of platinum eligible and platinum refractory sub-group as randomized and for all randomized subjects.

8.4.2.1 Method for primary endpoint

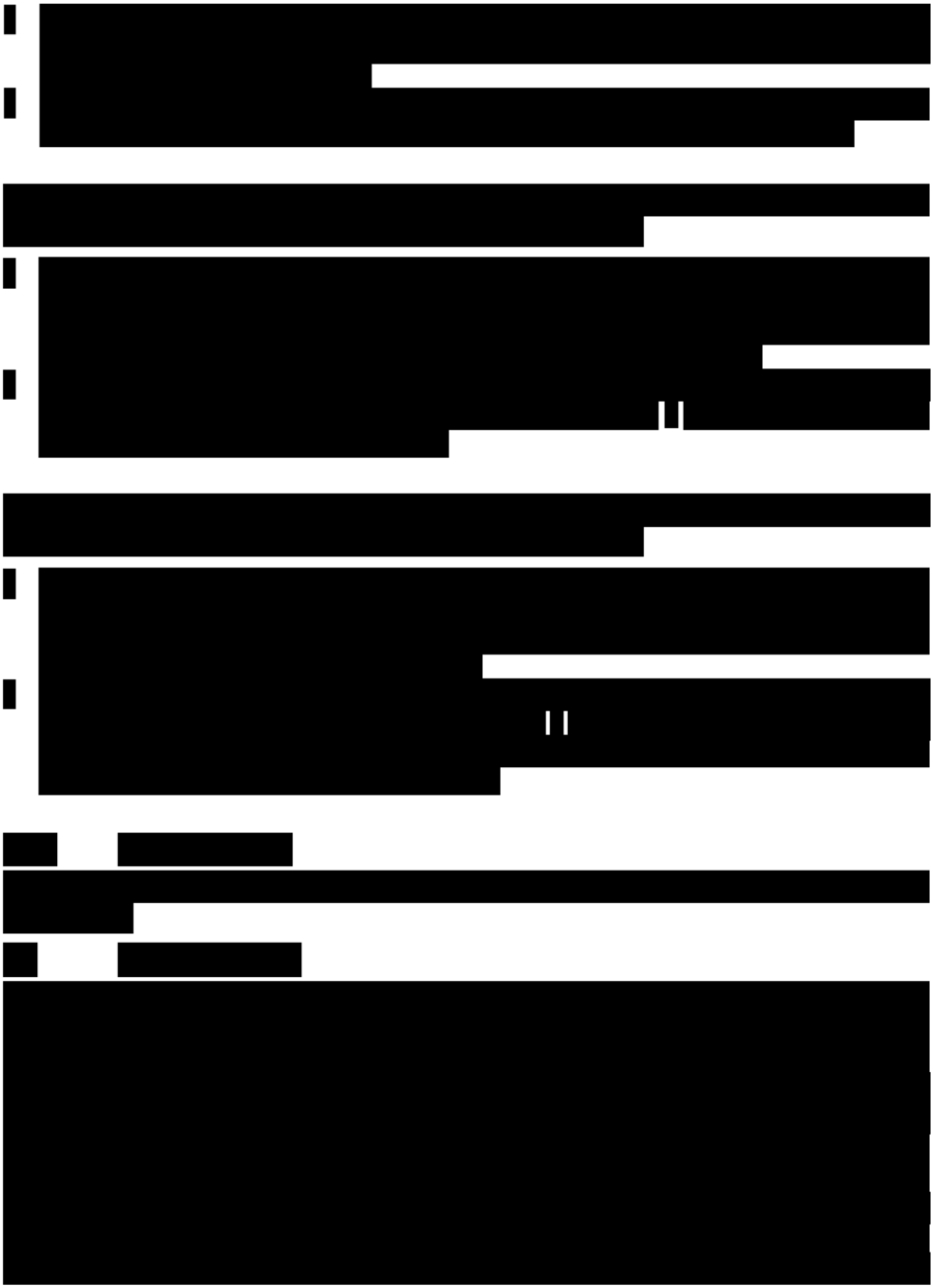
The comparison of ORR between nivolumab in combination with ipilimumab vs nivolumab in combination with ipilimumab placebo in platinum refractory randomized subjects will be carried out using a two-sided Cochran Mantel Haenszel (CMH) test stratified by the stratification factors as recorded in the IVRS. The significance level will be adjusted for an interim analysis which will be performed when around 70% of platinum-refractory subjects have been followed for at least 6 months after randomization. Using Lan DeMets alpha spending function with O'Brien-Fleming boundaries, the significance level for this comparison will be determined by the fraction of subjects included in the interim analysis. If the analysis is performed when exactly 70% of platinum refractory subjects have reached 6 months follow up after randomization, the alpha level is 0.015 for the interim and 0.045 for the final. An associated odds ratio and corresponding CIs (98.5% CI for interim and 95.5% CI for final) will be calculated. ORR will be summarized by a binomial response rate and its corresponding two-sided exact CIs using Clopper-Pearson method for each treatment group. An estimate of the difference in ORRs and corresponding CIs will be calculated using CMH methodology and adjusted by the stratification factors as recorded in the IVRS. Summary statistics of TTR will be provided for each treatment group for subjects who achieve PR or CR. Duration of response (DOR) in each treatment group will be estimated using KM product-limit method for subjects who achieve PR or CR. Median values along with two-sided 95% CI will be calculated.

[redacted]

8.4.3 Safety Analyses

The safety analysis will be performed in all treated subjects. Descriptive statistics of safety will be presented using the NCI CTCAE version 4.0 by treatment arm. All AEs, drug-related AEs, SAEs and drug-related SAEs will be tabulated using the worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, coagulation, chemistry, liver function and renal function will be summarized using worse grade per NCI CCAE v 4.0 criteria.

[redacted]



[redacted]

9. STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study subjects. If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s), the deviation or change will be submitted as soon as possible to:

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

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority, must be sent to BMS. If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

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

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by BMS or designee internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

9.1.2.1 Source Documentation

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

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

9.2 Records

9.2.1 Records Retention

The investigator (or head of the study site in Japan) must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS or designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS or designee prior to destroying any records associated with the study.

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

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

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include investigational product and the following non-investigational product(s) Records or logs must comply with applicable regulations and guidelines and should include:

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

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

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. Subinvestigators in Japan may not be delegated the CRF approval task. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet Sponsor or designee training requirements and must only access the BMS electronic data capture tool using the unique user account provided by Sponsor or designee. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to BMS or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set

forth in the clinical trial agreement (CTA) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to BMS at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

10. LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
ACTH	adrenocorticotropic hormone
AIDS	Acquired Immune Deficiency Syndrome
ALP	Alkaline phosphatase
ALT	alanine aminotransferase
AR	Additional research
AST	aspartate aminotransferase
BID, bid	bis in die, twice daily
BICR	Blinded Independent Central Review
BMS	Bristol-Myers Squibb
BOR	Best Overall Response
BP	blood pressure
BUN	blood urea nitrogen
CA	cancer
Ca++	calcium
CBC	complete blood count
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CI	confidence interval
C1-	chloride
cm	centimeter
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
CR	Complete Response
CRC	Clinical Research Center
CRF	Case Report Form
CSR	Clinical Study Report
CTA	Clinical Trial Agreement
CTLA-4	cytotoxic T-lymphocyte-associated protein 4

Term	Definition
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
D/C	discontinue
DCR	Disease Control Rate
DILI	Drug Induced Liver Disease
Dl	deciliter
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	Duration of Response
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4th Edition)
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEG	electroencephalogram
eg	exempli gratia (for example)
EGFR	Estimated glomerular filtration rate
EQ-5D	EuroQol five-dimension scale
ESR	Expedited Safety Report
5-FU	Fluoracil
FACT-G	FACT-general
FACT-HN	Functional Assessment of Cancer Therapy-Head & Neck
FHNSI-10	FACT Head and Neck Symptom Index
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose-positron emission tomography
FFPE	formalin-fixed, paraffin-embedded
FISH	fluorescent in-situ hybridization
FU-1	Follow up visit 1
FU-2	Follow up visit 2
FSH	follicle stimulating hormone

Term	Definition
g	Gram
GCP	Good Clinical Practice
h	Hour
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCO3-	bicarbonate
HCG	Human chorionic gonadotrophin
HIV	Human Immunodeficiency Virus
HIPAA	Health Insurance Portability and Accountability Act
HLA	*human leukocyte antigen*
HNC	Head and Neck carcinoma
HPV	Human Papilloma Virus
hr	Hour
HR	Hazard Ratio
HRT	hormone replacement therapy
ICD	International Classification of Diseases
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ie	id est (that is)
IEC	Independent Ethics Committee
IMA	Immune-mediated adverse events
IMP	investigational medicinal products
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	International Unit
IV	intravenous
IVRS	Interactive Voice Response System

Term	Definition
K+	potassium
kg	kilogram
L	Liter
LDH	lactate dehydrogenase
LFT	Liver function test
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
Mg++	magnesium
min	minute
Ml	milliliter
MRI	Magnetic resonance imaging
MTD	maximum tolerated dose
µg	microgram
N	number of subjects or observations
Na+	sodium
N/A	not applicable
NaCl	Sodium Chloride
NCI	National Cancer Institute
ng	nanogram
NIMP	non-investigational medicinal products
NSCLC	Non-small cell lung cancer
OPC	Oropharynx
ORR	Objective Response Rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PD	Progressive Disease
PD-1	Programmed Death-1
PD-L1	Programmed death-ligand 1
PD-L2	Programmed death-ligand 2
PET	positron emission tomography
PFS	Progression free survival

Term	Definition
PK	pharmacokinetics
PO	per os (by mouth route of administration)
PR	Partial Response
PRO-CTCAE	Common Terminology Criteria for Adverse Events
PT	Preferred term
QD, qd	quaque die, once daily
RANK-L	Receptor activator of nuclear factor kappa-B ligand
RBC	red blood cell
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
SAE	serious adverse event
SCCHN	Squamous Cell Carcinoma Head and Neck
SD	standard deviation
SmPC	summary of product characteristics
SNP	Single nucleotide polymorphisms
SOP	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Time
T3	triiodothyronine
T4	thyroxine
TAO	Trial Access Online
TOI	Trial Outcome Index
TID, tid	ter in die, three times a day
TMB	Tumor mutational burden
TTSD	Time To Symptom deterioration
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
VAS	Visual Analog Scale
WBC	white blood cell
WOCBP	women of childbearing potential