Protocol Number: CA209651
IND Number: 125872
Ex-US Non-IND
EUDRACT Number 2016-000725-39
Date: 23-Mar-2016
Revised Date: 19-Dec-2019

Clinical Protocol CA209651

An Open Label, Randomized, Two Arm Phase III Study of Nivolumab in Combination with Ipilimumab versus Extreme Study Regimen (cetuximab + cisplatin/carboplatin + fluorouracil) as First Line Therapy in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)

(CheckMate 651: **CHECK**point pathway and nivolu**MA**b clinical **T**rial **E**valuation **651**)

Revised Protocol Number: 05

Incorporated: Administrative Letter 05 and Administrative Letter 07

Study Director **Medical Monitor**

[redacted]

24-hr Emergency Telephone Number

[redacted]

Bristol-Myers Squibb Research and Development
3401 Princeton Pike
Lawrenceville, NJ 08648
Avenue de Finlande 4
B-1420 Braine-l'Alleud, Belgium

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 05	19-Dec-2019	• Removed second interim analysis of OS • Added a Myocarditis adverse event management algorithm
Administrative Letter 07	11-Nov-2019	• Corrected typographical error in the statistical section to address the inconsistency in the number of death events required for interim analysis
Administrative Letter 05	23-Aug-2019	• Made changes to the Medical Monitor and Study Director and added abbreviation "EGFR, epidermal growth factor receptor" to Section 10, List of Abbreviations
Revised Protocol 04	20-Jun-2019	• The primary objectives were changed to compare: – OS for participants who are receiving nivolumab + ipilimumab versus EXTREME regimen in participants with PD-L1 CPS ≥ 20 (changed from tumor PD-L1 ≥ 1) and – OS for participants who are receiving nivolumab + ipilimumab versus EXTREME regimen in all study participants (irrespective of PD-L1 expression). • Description of the statistical analyses were changed based on the changes in objectives • Key secondary objective was changed to OS in subject with PD-L1 CPS ≥ 1. • Efficacy evaluation based on biomarker subgroups were added to exploratory objectives. • Added supporting data for change in objectives from recent years and updated literature references • Updated protocol to align with current standards for BMS clinical studies. • Minor formatting and typographical corrections.
Revised Protocol 03	01-May-2018	• The primary objectives were changed from PFS and OS in all randomized subjects to PFS and OS in subjects with PD-L1 expressing tumors. • PFS and OS in all study subjects moved to secondary endpoints. • The hierarchy for the analysis was updated – PFS in all study subjects would be tested hierarchically after PFS in subjects with PD-L1 expressing tumors. OS in all study subjects would be tested hierarchically after OS in subjects with PD-L1 expressing tumors. • The sample size was increased to allow for evaluation of the updated primary end-points. The sample size determination was updated accordingly. • Added brief description of the analysis of TMB data. • Change in medical monitor and study director for the study (Administrative Letter 04 (date of issue:20-Mar-2018)) • Added that nivolumab should be permanently discontinued in case of grade 3 drug-related myocarditis. • Minor formatting and typographical corrections.

Document	Date of Issue	Summary of Change
Revised Protocol 02	26-Oct-2017	• The sample size was increased. • A maximum duration of nivolumab and ipilimumab treatment of 24 months from the start of treatment was added. • Duration of response has been changed from an exploratory objective to a secondary objective based on the expected improvement in duration of response as seen in other nivolumab trials. Response to first therapy after disease progression was changed to an exploratory endpoint to limit the secondary objectives only to critical endpoints. • Exploratory biomarker objectives were added in order to evaluate the potential associations between efficacy outcomes (such as objective response rate, PFS, and OS) with select biomarkers, including tumor mutational burden, from tumor tissue and peripheral blood.
Administrative Letter 03	06-Oct-2016	Change in medical monitor for the study
Administrative Letter 02	14-Sep-2016	Change to section 5.8, Additional Research section modified
Revised Protocol 01	22-Jun-2016	Incorporates Amendment 02
Amendment 02	22-Jun-2016	Week 7 biopsy optional instead of required, Section 5.8 "Additional Research" added, PK and IMG Follow up visit samples no longer required to be collected, Radiographic Imaging wording updated for clarification. Updated Algorithms for Renal, Pulmonary and Skin to match with updated Nivolumab IB v15 (includes Nivo IB 15 erratum update). Other minor edits, clarifications, corrections
Original Protocol	23-Mar-2016	Not applicable

OVERALL RATIONALE FOR REVISED PROTOCOL 05:

Changes were made based on discussions with the [redacted].

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Made updates to Study Director and Medical Monitor names.	Personnel change
Synopsis, Statistical Considerations Section 8.1 Sample Size Determination Table 8.1-1 Statistical Assumption and Power Calculation Section 8.5 Interim Analyses	Removed second interim analysis and associated statistical assumptions. Corrected typographical error to ensure proper alignment in the approximate number of death events required for the interim analysis.	The analysis plan contained two formal interim analyses at 80% and 90% information fraction prior to the final analysis. Upon [redacted] recommendation, the analysis at 90% information was dropped. The new analysis plan has one formal interim analysis at 80% information fraction (approximately 593 events in all randomized participants) followed by final analysis.
Section 10 List of Abbreviations	Added abbreviation “epidermal growth factor receptor (EGFR)” to distinguish it from “estimated glomerular filtration rate (eGFR).”	Correction of error
Section 11 References	Removed “References for the use of condoms with spermicide” and the two listed references.	Correction of error, as the references are not applicable to the protocol.
Appendix 2 Management Algorithms	Added Myocarditis algorithm and revised date of the other algorithms to 2019.	Provided Myocarditis algorithm per recent Nivolumab Investigator Brochure.

SYNOPSIS

Clinical Protocol CA209651

Protocol Title: An Open Label, Randomized, Two Arm Phase III Study of Nivolumab in Combination with Ipilimumab versus Extreme Study Regimen (cetuximab + cisplatin/carboplatin + fluorouracil) as First Line Therapy in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)

(CheckMate 651: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 651)

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

Nivo/Ipi Combo Arm (Arm A):

- 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) until 24 months from first nivolumab treatment, disease progression or unacceptable toxicity.
  (1 Cycle =6 Weeks)

EXTREME regimen Arm (Arm B):

- Cetuximab 400 mg/m^2 IV once only, then 250 mg/m^2 weekly + cisplatin (100 mg/m^2) or carboplatin (Area Under the Curve of 5 mg per milliliter per minute) on day 1 and fluorouracil (1000 mg/m^2 per day for 4 days) every 3 weeks for maximum of 6 cycles followed by maintenance cetuximab at 250 mg/m^2 weekly until disease progression or unacceptable toxicity; the choice of cisplatin or carboplatin is at the discretion of the investigator.
  (1 Cycle = 3 weeks).

Study Phase: III

Research Hypothesis:

- Participants with Programmed death-ligand 1 combined positive score (PD-L1 CPS) ≥ 20 who receive nivolumab in combination with ipilimumab for first-line treatment of recurrent or metastatic SCCHN will have longer overall survival (OS) than comparable participants who receive the EXTREME regimen
- Participants who receive nivolumab in combination with ipilimumab for first-line treatment of recurrent or metastatic SCCHN will have longer OS than comparable participants who receive the EXTREME regimen

Objectives:

Primary Objectives:

- To compare the OS of participants with PD-L1 CPS ≥ 20 who are receiving nivolumab combined with ipilimumab to those receiving EXTREME regimen.
- To compare the OS of all study participants receiving nivolumab combined with ipilimumab to those receiving EXTREME regimen

Secondary Objectives:

- To compare the OS of participants with PD-L1 CPS ≥ 1 who are receiving nivolumab combined with ipilimumab to those receiving EXTREME regimen
- To evaluate progression-free survival (PFS) based on BICR in all study participants and those with PD-L1 CPS ≥ 20 who are receiving nivolumab combined with ipilimumab, and those receiving EXTREME regimen.

- To evaluate objective response rate (ORR) based on BICR in all study participants and those with PD-L1 CPS ≥ 20 who are receiving nivolumab combined with ipilimumab, and those receiving EXTREME regimen.
- To evaluate the duration of response (DOR) based on BICR in all study participants and those with PD-L1 CPS ≥ 20 who are receiving nivolumab combined with ipilimumab, and those receiving EXTREME regimen.

Exploratory Objectives:

- To evaluate OS of participants with tumor cell PDL-1 expression level < 1% and PD-L1 CPS < 20 who are receiving nivolumab combined with ipilimumab, and those receiving EXTREME regimen.
- To evaluate the OS of participants with tumor inflammation score measured as gene expression profile (GEP) ≥ 10 who are receiving nivolumab combined with ipilimumab, and those receiving EXTREME regimen.
- To evaluate the OS of participants with tumor mutation burden (TMB) ≥ 7 who are receiving nivolumab combined with ipilimumab, and those receiving EXTREME regimen.
- To evaluate clinical outcomes (OS, PFS, ORR, DOR) by select baseline and on-treatment biomarker expression levels in peripheral blood and tumor biopsy specimens.
- To assess safety and tolerability of nivolumab in combination with ipilimumab and of EXTREME regimen, in all study participants
- To characterize pharmacokinetics and immunogenicity of nivolumab in combination with ipilimumab as first line therapy in participants with recurrent or metastatic SCCHN
- To evaluate time to symptom deterioration (TTSD) in each arm as assessed using the Functional Assessment of Cancer Therapy - Head and Neck (FACT-H&N) 10-item Symptom Index (FHNSI-10), in participants with PD-L1 CPS ≥ 20 and also in all study participants
- To assess the participant's overall health status and health utility using the 3-level version of the EQ-5D (EQ-5D-3L) visual analog scale (VAS) and utility index, respectively, in participants with PD-L1 CPS ≥ 20 and also in all study participants
- To assess the participant's cancer-related symptoms and quality of life using components of the FACT-H&N questionnaire in participants with PD-L1 CPS ≥ 20 and also in all study participants.

Study Design:

This is a randomized, open-label, Phase 3 trial in participants ≥ 18 years old with untreated metastatic or recurrent SCCHN that is not amenable to curative therapy, evaluating nivolumab + ipilimumab versus the EXTREME regimen (Cetuximab + cisplatin/carboplatin + fluorouracil) as a first-line treatment.

HPV p-16 status and tumor cell PD-L1 status (expressing or non-expressing/non-evaluable) test results will be needed prior to randomization. Participants will undergo screening evaluations to determine eligibility prior to randomization.

The dose and treatment schedules for each arm are as follows:

- Arm A: Nivolumab + Ipilimumab Arm:
  - Nivolumab 3 mg/kg IV every 2 weeks + Ipilimumab 1 mg/kg IV every 6 weeks until progression, unacceptable toxicity, or a maximum of 24 months from first nivolumab treatment.
- Arm B: EXTREME regimen Arm:
  - Cetuximab 400 mg/m^2 IV for the initial dose only, then 250 mg/m^2 weekly + cisplatin (100 mg/m^2) or carboplatin (AUC of 5 mg per milliliter per minute) on Day 1 and fluorouracil (1000 mg/m^2 per day for 4 days) every 3 weeks for maximum of 6 cycles followed by maintenance cetuximab at 250 mg/m^2 weekly (or every 2 weeks, per local prescribing information) until disease progression or unacceptable toxicity; the choice of cisplatin or carboplatin is at the discretion of the investigator.

Approximately 930 participants will be randomized to the two treatment arms in a 1:1 ratio and stratified by the following factors:

- Tumor cell PD-L1 status (expressing [≥ 1%] vs non-expressing [< 1%] or non-evaluable). Up to 10% of randomized participants per cohort can be included into the study as "non-evaluable." After this point, participants 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 participant.
- HPV p-16 status (oropharyngeal HPV p-16 positive vs oropharyngeal HPV p-16 negative or non-oropharyngeal). Oropharyngeal CA sites defined in Appendix 5.
- Prior chemotherapy (adjuvant/neoadjuvant/multimodal treatment) status (Yes/No)

Tumor progression or response will be assessed by investigator using RECIST 1.1 criteria. Treatment with study medication will continue until RECIST 1.1 defined progression, unacceptable toxicity, a maximum of 24 months since the first dose of nivolumab, or withdrawal of consent.

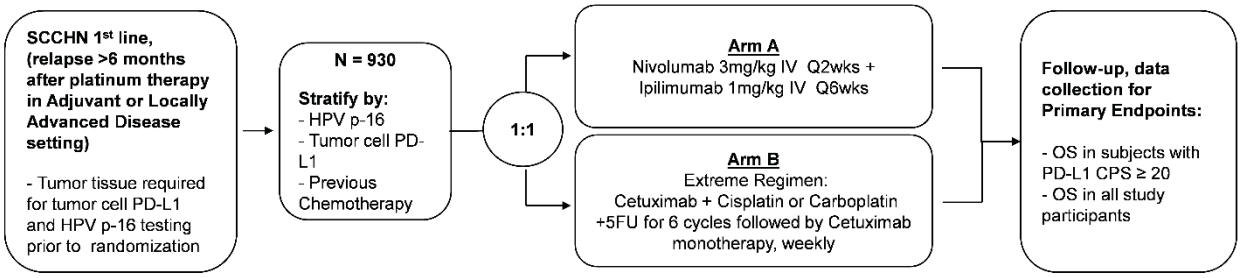
In addition to investigator assessment of response and progression, there will be a blinded independent central review (BICR) of tumor scans and study sites will need to submit tumor scans for central radiology review.

A DMC will be established and meet regularly during the study to ensure that participant safety is carefully monitored and to provide oversight regarding safety and efficacy considerations in protocol CA209651.

The maximum duration of the study from start of randomization to final analysis of OS is projected to be approximately 51 months, assuming 26 months accrual duration. Additional 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 1 below

Figure 1: Study Design Schematic



Study Population:

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

Key Inclusion Criteria (See Protocol Section 3.3.2 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.

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

c) No prior treatment with systemic anti-cancer therapy for recurrent or metastatic SCCHN, unless under all of the following conditions:

   i) Prior chemotherapy was given as adjuvant or neoadjuvant or as part of multimodal treatment for locally advanced disease

   ii) These treatments must have been completed > 6 months prior to enrollment

   iii) There is no evidence of disease progression for at least 6 months after completion of such treatment.

   iv) Participants having progression after 2 cycles of induction chemotherapy are excluded.

d) ECOG Performance Status of 0–1. (See Appendix 1).

e) Measurable disease by CT or MRI per RECIST 1.1 criteria

f) Documentation of HPV p-16 status is required for SCCHN tumor of the oropharynx.

g) Documentation of tumor cell PD-L1 status by IHC performed by the central lab prior to randomization.

Key Exclusion Criteria (See Protocol Section 3.3.1 for full list of criteria)

1. Target Disease Exceptions

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

b) Participants with untreated CNS metastases.

   Participants 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, participants 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) Participants with carcinomatous meningitis.

2. Medical History and Concurrent Diseases

a) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

b) Prior treatment with cetuximab or EGFR inhibitors in any treatment setting

c) Participants with previous malignancies (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, esophageal, colon, 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.

   i) A second primary squamous cell carcinoma of the head and neck is allowed if eligibility is based on a recurrent or a metastatic first primary squamous cell carcinoma of the head and neck.

d) Participants with an active, known or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

e) Participants 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 doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

3. Physical and Laboratory Test Findings

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

b) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

c) Inadequate hematologic, renal or hepatic function defined by any of the following screening laboratory values:

i) WBC < 2000/μL
ii) Neutrophils < 1500/μL
iii) Platelets < 100 x 10^3/μL
iv) Hemoglobin < 9.0 g/dL
v) Serum creatinine > 1.5 x ULN or creatinine clearance < 50 mL/min (using the Cockcroft Gault formula). Cisplatin should not be used if creatinine clearance is lower than 60 mL/min
vi) AST/ALT > 3.0 x ULN (> 5 x ULN if liver metastases)
vii) Total Bilirubin > 1.5 x ULN (except participants with Gilbert Syndrome who must have a total bilirubin level ≥ 3.0 x ULN)

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

Study Drug for CA209651		
Medication	**Potency**	**IP/Non-IP**
Nivolumab Injection	100 mg/vial (10 mg/mL)	IP
Ipilimumab Injection	200 mg/vial (5 mg/mL)	IP
Carboplatin Solution for IV Injection	450 mg/vial (10 mg/mL)	IP
Cisplatin Concentrate for solution for infusion	100 mg/vial (1 mg/mL)	IP
Cetuximab solution for infusion	500mg/vial (5 mg/mL)	IP
Fluorouracil Injection	1 g/vial (50 mg/mL)	IP

Study Assessments: Overall survival is defined as the time from randomization to the date of death. Participants will be assessed for response by CT or MRI beginning 6 weeks (± 1 week) after first dose and continuing every 6 weeks (± 7 days) until week 48 and then every 12 weeks (±1 week) until progression. Tumor assessments must continue per protocol until RECIST 1.1 progression has occurred. Participants will be followed for survival every 3 months via in person or telephone contact after the participant has discontinued study drug treatment. All randomized participants will be followed for survival.

Statistical Considerations:

Sample Size:

The primary objectives of this study are to compare OS between treatment groups, randomized participants with PD-L1 CPS ≥ 20 and in all randomized participants. OS will be compared at the 0.025 alpha level for each of the above two populations.

The OS comparison in all randomized participants will require up to 741 deaths. This number of events ensures that a two-sided, alpha=0.025 group sequential test using the O'Brien and Fleming spending function and with an interim analysis after approximately 80% of events will have overall 97% power for a HR of 1.2 for the first 7 months and 0.55 thereafter.

The final analysis of OS in all randomized participants is projected to occur 51 months after the first patient was randomized. An interim analysis in this population will be performed when approximately 593 deaths occur, or all randomized participants have been followed up for at least 12 months, whichever is later. It is projected for 39 months after the first patient was randomized.

At the same time as the OS analysis is done for all randomized participants, OS will also be compared between arms in the randomized participants with PD-L1 CPS ≥ 20 via a two-sided, alpha=0.025 group sequential test procedure incorporating the O'Brien and Fleming alpha spending function. The group sequential test would have an interim analysis and the final analysis of OS, at which approximately 298 and 372 deaths, respectively, are expected. With this many events, the test procedure would have an overall 99% power if the HR was 1.06 for the first 7 months and 0.45 thereafter. See Section 8.1, Sample Size Determination, for additional details.

Endpoints:

Primary Endpoints:

- OS in randomized participants with PD-L1 CPS ≥20
- OS in all randomized participants

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

Secondary Endpoints:

OS in randomized participants with PD-L1 CPS ≥ 1. OS is defined the same way as for the primary endpoints.

PFS is defined as the time from randomization to disease progression, using RECIST 1.1 criteria, or, if there is no documented progression, death. (The date of progression will be based on the BICR assessment of progression). Participants who neither progress nor die will be censored on the date of their last tumor assessment. Participants who receive subsequent anti-cancer therapy prior to documented progression, including tumor-directed radiotherapy and tumor-directed surgery, will have their PFS time censored on the date of their last tumor assessment prior to subsequent therapy.

The Objective Response Rate (ORR) is defined as the number of participants with a best overall response (BOR) of complete response (CR) or partial response (PR), divided by the number randomized in the population.

The BOR is defined as the best response, based on RECIST 1.1 criteria, recorded between randomization and either progression or subsequent anticancer therapy (including tumor-directed radiotherapy and tumor-directed surgery), whichever occurs first. (The BOR will be based on BICR assessments). For participants without evidence of RECIST 1.1 progression or subsequent anticancer therapy, all available tumor evaluations will contribute to the BOR assessment.

Duration of objective response (DOR) is the time between the first documented response (CR or PR) and progression, per RECIST 1.1, or, if no progression is reported, death. The DOR of a participant who neither progresses nor dies will be censored as in the primary definition of PFS. DOR is calculated on the subset of participants whose best response was either CR or PR, according to BICR assessments.

Analyses:

Demographics and Baseline Characteristics:

Demographics and baseline characteristics will be summarized by treatment arm as randomized using descriptive statistics. These analyses will be done on the PD-L1 CPS ≥ 20 population and on the all randomized population

Efficacy Analyses:

Efficacy analyses will be performed by treatment group as randomized.

OS will be compared between arms via a two-sided, overall alpha=0.025, group sequential log-rank test for each of the two primary endpoints population. The significance levels may be updated through graphical approach where the family-wise error rate will be protected in the strong sense.

The nominal significance levels for each look of the group sequential log-rank test will be determined by the alpha spending function with the O'Brien and Fleming boundary based on the actual number of events observed at the time of the analysis. These tests will be stratified by the stratification factors used in the randomization.

An estimate of the hazard ratio (HR) and a corresponding two sided 100*(1 - adjusted α)% confidence interval for the HR will be generated for each endpoint using a stratified Cox proportional hazards model with treatment arm as the sole covariate. The stratification factors will be the same as those used for testing. The level for the confidence interval for the OS hazard ratio will be based on the same nominal significance level for the group sequential log-rank test.

Survival distributions will be estimated, by arm, via the Kaplan-Meier (KM) product-limit method. Median survival times along with 95% confidence intervals for the medians, will also be presented. The confidence interval for the median will be constructed using a generalization of the Brookmeyer and Crowley method based on a log {-log} transformation of the survival function.

Safety Analyses:

The safety analysis will be restricted to treated participants. 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. Safety analyses will be performed on all treated participants.

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.

Biomarker Analyses:

Potential relationships between biomarker data and efficacy or safety endpoints may be investigated as part of an analysis plan aimed at identifying baseline biomarkers that may be used to prospectively identify participants likely to respond to nivolumab and ipilimumab and to identify participants who may be predisposed to having adverse reactions to treatment. These exploratory predictive biomarker analyses will be completed with biomarkers measured in blood and in tumor samples and will focus primarily on SNPs in select genes associated with immunity, on the expression of PD-1, PD-L1, and PD-L2 proteins in tumor specimens, and on tumor mutational burden (TMB) and gene expression profile (GEP).

Outcomes Research Analyses:

Exploratory analyses of EQ-5D and FACT-H&N (including FHNSI-10) data will be performed in randomized participants who have an assessment at baseline (Day 1, assessment prior to administration of drug on day of first dose) and at least 1 subsequent assessment while on treatment. Questionnaire completion rate, defined as the proportion of questionnaires actually received out of the expected number, will be calculated and summarized at each assessment point. Analyses of QOL will be performed on all randomized population.

Interim Analyses:

An independent data monitoring committee (DMC) will be responsible for monitoring safety and efficacy data at regular intervals. In addition, the DMC will review the data for the formal interim analysis.

A formal interim analysis for superiority of OS will be performed after approximately 593 OS events (out of 741 required) have occurred on all randomized participants, or all randomized participants have been followed up for at least 12 months, whichever is later. Both primary endpoints will be tested at interim using the group sequential test procedure with initial overall alpha=0.025 for each. The overall alpha will be updated following the graphical procedure which is detailed in the SAP. The stopping boundaries for the interim and final analyses will be determined by the O'Brien and Fleming alpha spending function, based on the actual number of events observed.

If interim comparison of OS in either all randomized participants or randomized participants with PD-L1 CPS ≥ 20 is significant, the DMC will inform the sponsor, as described in the DMC charter. If comparison of OS in the randomized participants with PD-L1 CPS ≥ 20 is significant, OS in randomized participants with PD-L1 CPS ≥ 1 will be

subsequently tested using group sequential testing procedure. The overall alpha for this secondary endpoint will be determined following the graphical procedure which is detailed in the SAP.

The DMC will have access to periodic un-blinded interim reports of efficacy and safety to allow a risk/benefit assessment. Details will be included in the DMC charter.

TABLE OF CONTENTS

TITLE PAGE 1
DOCUMENT HISTORY 3
OVERALL RATIONALE FOR REVISED PROTOCOL 05: 5
SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 05 5
SYNOPSIS 6
TABLE OF CONTENTS 14
1 INTRODUCTION AND STUDY RATIONALE 18
1.1 Study Rationale 18
1.2 Rationale for revised protocol 04: 19
1.2.1 The Role of Human Papillomavirus (HPV) 21
1.2.2 Immunotherapy in SCCHN and role of PD-L1 21
1.2.3 Rationale for Combination of Nivolumab and Ipilimumab 24
1.2.4 Rationale for Shorter Infusion Times for Nivolumab and Ipilimumab 27
1.2.5 Rationale for Permitting Continued Treatment in Select Cases of Progressive Disease 28
1.2.6 Rationale for 24 Months Maximum Treatment Duration 29
1.3 Research Hypotheses 30
1.4 Objectives(s) 30
1.4.1 Primary Objectives 30
1.4.2 Secondary Objectives 30
1.4.3 Exploratory Objectives 30
1.5 Product Development Background 31
1.5.1 Mechanism of Action of Nivolumab 32
1.5.2 Mechanism of Action of Ipilimumab 32
1.5.3 Nivolumab Combined With Ipilimumab 32
1.6 Overall Risk/Benefit Assessment 33
2 STUDY GOVERNANCE CONSIDERATIONS 35
2.1 Regulatory and Ethical considerations 35
2.1.1 Good Clinical Practice 35
2.1.2 Institutional Review Board/Independent Ethics Committee 35
2.1.3 Informed Consent Process 36
3 INVESTIGATIONAL PLAN 37
3.1 Study Design and Duration 37
3.2 Post Study Access to Therapy 40
3.3 Study Population 40
3.3.1 Inclusion Criteria 41
3.3.2 Exclusion Criteria 43
3.3.3 Women of Childbearing Potential 45
3.4 Concomitant Treatments 46
3.4.1 Prohibited and/or Restricted Treatments 46
3.4.2 Other Restrictions and Precautions 46
3.4.3 Permitted Therapy 47
3.5 Discontinuation of Subjects following any Treatment with Study Drug 47
3.6 Post Study Drug Study Follow up 48

3.6.1 Withdrawal of Consent 49
3.6.2 Lost to Follow-Up 49
4 STUDY DRUG 49
4.1 Investigational Product 51
4.2 Non-investigational Product 51
4.3 Storage and Dispensing 51
4.4 Method of Assigning Participant Identification 52
4.5 Selection and Timing of Dose for Each Participant 52
4.5.1 Dosing 54
4.5.1.1 Nivolumab plus Ipilimumab (Arm A) 54
4.5.1.2 EXTREME Regimen (Arm B) 55
4.5.2 Dose Delays 57
4.5.2.1 Nivolumab and Ipilimumab (Arm A) 57
4.5.2.2 EXTREME Regimen 58
4.5.3 Dose Reductions 59
4.5.3.1 Nivolumab or Ipilimumab 59
4.5.3.2 EXTREME Regimen 59
4.5.4 Criteria to Resume Dosing 61
4.5.4.1 Criteria to Resume Nivolumab Dosing (Arm A) 61
4.5.4.2 Criteria to Resume Ipilimumab Dosing (Arm A) 62
4.5.4.3 Criteria to Resume Chemotherapy Dosing (Arm B) 63
4.5.5 Treatment Discontinuation Criteria 64
4.5.5.1 Nivolumab Dose Discontinuation (Arm A) 64
4.5.5.2 Ipilimumab Dose Discontinuation (Arm A) 65
4.5.5.3 EXTREME Regimen Dose Discontinuation (Arm B) 67
4.5.6 Treatment Beyond Disease Progression (Arm A only) 67
4.5.7 Management Algorithms for Immuno-Oncology Agents 68
4.5.8 Treatment of Infusion Reactions 69
4.5.8.1 Nivolumab or Ipilimumab Infusion Reactions 69
4.5.8.2 Treatment of Cetuximab Infusion Reactions 70
4.6 Blinding/Unblinding 71
4.7 Treatment Compliance 71
4.8 Destruction of Study Drug 71
4.9 Return of Study Drug 72
4.10 Retained Samples for Bioavailability / Bioequivalence 72
5 STUDY ASSESSMENTS AND PROCEDURES 73
5.1 Flow Chart/Time and Events Schedule 73
5.1.1 Retesting During Screening or Lead-in Period 81
5.2 Study Materials 81
5.3 Safety Assessments 81
5.3.1 ECOG Performance Status 82
5.3.2 Pregnancy Testing 82
5.3.3 Thyroid Function Testing 83
5.3.4 Electrocardiogram (ECG) 83
5.4 Efficacy Assessments 83
5.4.1 Primary Efficacy Assessment 85

5.4.2 Secondary Efficacy Assessment 85
5.5 Pharmacokinetic Assessments 85
5.6 Biomarker Assessments 87
5.6.1 Exploratory Serum Biomarkers 88
5.6.2 Circulating Tumor DNA in Plasma 88
5.6.3 Tumor Tissue Specimens 88
5.6.4 Peripheral Blood Gene Expression 89
5.6.5 T cell Repertoire Analysis (Whole Blood and Tumor Tissue Sample) 90
5.6.6 Characterization of Oral Microbiome 90
5.6.7 Whole Blood for Genomic Analyses 90
5.6.8 HPV Assessment 90
5.7 Outcomes Research Assessments 91
5.8 Additional Research 92
6 ADVERSE EVENTS 92
6.1 Serious Adverse Events 94
6.1.1 Serious Adverse Event Collection and Reporting 96
6.2 Nonserious Adverse Events 97
6.2.1 Nonserious Adverse Event Collection and Reporting 97
6.3 Laboratory Test Result Abnormalities 97
6.4 Pregnancy 98
6.5 Overdose 98
6.6 Potential Drug Induced Liver Injury (DILI) 99
6.7 Other Safety Considerations 99
6.7.1 Adverse Events of Interest 99
7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES 100
8 STATISTICAL CONSIDERATIONS 100
8.1 Sample Size Determination 100
8.2 Populations for Analyses 101
8.3 Endpoints 102
8.3.1 Primary Endpoints 102
8.3.2 Secondary Endpoints 102
8.3.3 Exploratory Endpoint(s) 103
8.4 Analyses 104
8.4.1 Demographics and Baseline Characteristics 104
8.4.2 Efficacy Analyses 104
8.4.2.1 Analysis Methods for Primary Endpoints 104
8.4.2.2 Analysis Methods for Secondary Endpoints 105
8.4.3 Safety Analyses 106
8.4.4 Pharmacokinetic Analyses 106
8.4.5 Biomarker Analyses 106
8.4.6 Outcomes Research Analyses 107
8.4.7 Other Analyses 108
8.5 Interim Analyses 108
9 STUDY MANAGEMENT 109
9.1 Compliance 109

9.1.1 Compliance with the Protocol and Protocol Revisions 109
9.1.2 Financial Disclosure 109
9.1.3 Monitoring 110
9.1.3.1 Source Documentation 110
9.1.4 Study Treatment Records 110
9.1.5 Investigational Site Training 111
9.2 Records 111
9.2.1 Records Retention 111
9.2.2 Study Drug Records 111
9.2.3 Case Report Forms 112
9.2.4 Clinical Study Report and Publications 112
9.2.4.1 Scientific Publications 113
10 LIST OF ABBREVIATIONS 114
11 REFERENCES 119
APPENDIX 1 ECOG PERFORMANCE STATUS 124
APPENDIX 2 MANAGEMENT ALGORITHMS 125
APPENDIX 3 RECIST 1.1 GUIDELINES 134
APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION 142
APPENDIX 5 HEAD AND NECK SQUAMOUS CELL CARCINOMAS CLASSIFIED AS FOLLOWS: 145
APPENDIX 6 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY 146

1 INTRODUCTION AND STUDY RATIONALE

CA209651 is a randomized, open-label, global Phase 3 trial of nivolumab (also known as BMS-936558) plus ipilimumab versus EXTREME regimen (cetuximab + cisplatin/carboplatin + fluorouracil) as first-line therapy in recurrent or metastatic head and neck squamous cell carcinoma (SCCHN). This study will determine if nivolumab plus ipilimumab improves overall survival (OS) over standard of care chemotherapy in all study participants and biomarker selected patient population. Additional objectives include further characterization of the efficacy, adverse event profile, pharmacokinetics, patient-reported outcomes, and potential predictive biomarkers of nivolumab plus ipilimumab in participants with SCCHN.

1.1 Study Rationale

Head and neck cancers are among the most common cancers worldwide, accounting for more than 550,000 cases and around 300,000 deaths each year,[1] and these trends are increasing. In the United States, ~45,780 new cases of oral cavity and pharynx cancer and ~8,650 people were expected to die of this disease in 2015.[2] About ~90% of all head and neck cancer cancers are squamous cell carcinomas. Most SCCHNs arise from the epithelial lining of the oral cavity, oropharynx, larynx and hypopharynx. The most important risk factors identified in SCCHNs, include tobacco and alcohol use, and, in a subgroup of SCCHNs (particularly oropharynx tumors), human papilloma as a strong independent prognostic factor, with HPV positive-infected tumors associated with more favorable clinical outcomes.[3]

The treatment approach and prognosis for patients with SCCHN is mostly determined by the tumor stage at presentation. About one-third of patients presents with early stage disease, whereas the majority present with advanced disease with lymph node metastasis. With standard of care treatment, the 5-year survival for localized oral cavity and pharynx cancer is 83%, but survival drops to 37.7% for metastatic disease.[2] Approximately half of the treated population returns with recurrent or refractory disease, and for these patients, the 1-year survival rate ranges from 5% to 33% with a median overall survival (OS) of 6 to 9 months. Recurrent disease that is not amenable to curative-intent radiation or surgery have the same treatment approach as metastatic disease, and participation in a clinical trial is a recommended treatment option for these patients.[4] A Phase 3 randomized trial in first-line recurrent or metastatic (1L R/M) SCCHN showed that cetuximab plus platinum-fluorouracil chemotherapy (EXTREME regimen) improved survival over platinum-fluorouracil alone as first-line treatment with a median OS of 10.1 months versus 7.4 months (Hazard Ratio [HR] = 0.80, 95% CI 0.64-0.99, p = 0.04). As a result, the EXTREME regimen has been adapted as a standard treatment approach in this population. While the addition of cetuximab to platinum-fluorouracil chemotherapy improved response rates and disease control rates, the duration of response did not differ significantly between treatment regimens. Since the introduction of the EXTREME regimen in 2008,[4] no marked improvement in survival has been achieved, with patients still frequently developing recurrences and distant metastasis. After progression, the limited treatment options available are associated with substantial morbidity and mortality. Thus, new treatment approaches need to be explored as the first-line treatment in this population.[5]

1.2 Rationale for revised protocol 04:

Emerging data from multiple studies in recent years demonstrated long term OS benefit with PD-1 inhibitor (nivolumab and pembrolizumab) therapy compared to standard of care chemotherapy in R/M SCCHN population. [6,7,8,9] These studies while suggesting OS benefit in all study subjects also showed a trend towards better efficacy in participants who express Programmed death-ligand 1 (PD-L1) in either their tumor or immune cells. However, PFS did not capture the benefit of PD-1 therapy versus standard of care therapy in both biomarker selected and unselected population.

Benefit of PD-1 inhibitors as a second-line therapy (2L) for R/M SCCHN population:

In the two year survival update of CheckMate-141,[6] Phase 3 trial evaluating nivolumab as a second line therapy (2L) in R/M SCCHN, single-agent nivolumab showed significant OS benefit over investigator's choice chemotherapy (IC) in all study participants (HR = 0.68, 95% CI 0.54 to 0.86; p = 0.01), with a relatively better efficacy noted in participants who expressed tumor cell PD-L1 ≥ 1% (HR = 0.55, 95% CI 0.39–0.78). In a sub-group analysis of this study, participants who had both tumor cell PD-L1 ≥ 1% and a high tumor-associated immune cell PD-L1 (TAIC) expression demonstrated a relatively better OS benefit (HR = 0.43, 95% CI 0.28, 0.67). However, significant PFS benefit for nivolumab was not demonstrated in the intent-to-treat population (HR=0.87, 95% CI 0.68–1.11) or in any of the biomarker selected sub-groups.

Similarly, in another Phase 3 trial in the same setting (KeyNote-040),[7] pembrolizumab showed OS benefit over IC in all study participants (HR = 0·80, 0·65–0·98), with a significant OS benefit in the sub-population who expressed PD-L1, on both tumor and immune cells, measured as PD-L1 combined positive score (PD-L1 CPS) ≥ 1 (HR = 0·74, 95% CI 0·58–0·93). In this study as well, PFS benefit was not demonstrated for pembrolizumab arm versus standard of care regimen (HR = 0·96, 95% CI 0·79–1·16). Thus both of these studies in 2L R/M SCCHN demonstrate long term OS benefit of PD-1 inhibitors in SCCHN participants, irrespective of biomarker expression. Additionally, these studies also establish that PD-1 inhibitors may provide a greater efficacy benefit in the sub-population of SCCHN participants who express PD-L1 in both tumor and immune cells.

Benefit of PD-1 inhibitors as a first-line therapy (1L) for R/M SCCHN population:

Other recent trials in SCCHN are evaluating PD-1 inhibitors as a first-line therapy (1L) for R/M SCCHN population. In a Phase 3 study of 1L R/M SCCHN (KeyNote-048), efficacy of pembrolizumab as a single agent or in combination with chemotherapy (cisplatin+5FU) was compared to EXTREME regimen in both PD-L1 CPS high expressers (cut-offs of ≥ 20 and ≥ 1) and in all study participants.[8,9] This study demonstrated significant improvement in OS compared to EXTREME regimen for pembrolizumab monotherapy (HR = 0.61, 95% CI 0.45-0.83, p = 0.0007) in participants whose tumors expressed PD-L1 CPS ≥ 20. This data further confirms that selection based on PD-L1 CPS, a measure of both tumor and immune cell PD-L1 expression, may offer efficacy benefit for single agent PD-1 inhibitor in this SCCHN population. However, this study also demonstrated the lack of PFS benefit for PD-1 inhibitors versus comparator.

Pembrolizumab demonstrated a numerically lower median PFS (3.4 months) versus EXTREME regimen (5.0 months) in PD-L1 CPS ≥ 20 sub-group (HR = 0.99, 95% CI 0.75-1.29).

Additionally, in the analysis of all study participants (irrespective of PD-L1 CPS) in KeyNote-048, only pembrolizumab + chemotherapy (P+C) arm demonstrated statistically significant improvement in the OS (HR = 0.77, 95% CI 0.63-0.93, p = 0.0034) compared to EXTREME regimen. This suggests that combination therapy with PD-1 inhibitors may be needed for optimal efficacy benefit in an unselected patient population. However, in KeyNote-048 P+C demonstrated only a modest median OS improvement in this population (13 months for P+C vs 10.7 months for EXTREME regimen). Additionally, the safety profile of P+C was not better than the EXTREME regimen with grade 3-4 treatment related adverse events reported in 71% of participants in P+C arm and 69% of participants in EXTREME regimen arm. This population does not currently have a treatment option that provides a good benefit-risk balance. Therefore, new combination treatment approaches need to be explored to not only improve the survival benefit in participants with high PD-L1 CPS but also provide safe and efficacious treatment options for participants irrespective of PD-L1 expression.

Benefit of combining ipilimumab to nivolumab:

Addition of ipilimumab (CTLA-4 inhibitor) to nivolumab has demonstrated efficacy benefit over single agent nivolumab in multiple disease indications including melanoma, non-small cell lung cancer and renal cell carcinoma. This efficacy benefit was not restricted to patients with tumor cell PD-L1 alone. [redacted] Thus the summary of available evidence across indications suggests that addition of ipilimumab to nivolumab may offer an opportunity to improve the OS in R/M SCCHN participants irrespective of PD-L1 expression status, with a relatively better efficacy benefit in participants with high PD-L1 CPS.

Summary of the rationale for the key end-point changes:

Based on the above evolving data in SCCHN in recent years suggesting PD-L1 CPS as a more appropriate PD-L1 measure for selecting participants who derive the best benefit for immunotherapy and potential for nivolumab + ipilimumab to benefit a broader SCCHN patient population than tumor cell PD-L1 expressers alone.

The primary end-points of the current study (CheckMate 651) will be revised to compare:

- OS of participants with PD-L1 CPS ≥ 20 who are receiving nivolumab combined with ipilimumab to those receiving EXTREME regimen (changed from tumor cell PD-L1 ≥ 1%).
- OS of all study participants (irrespective of PD-L1 expression) who are receiving nivolumab combined with ipilimumab to those receiving EXTREME regimen.

Additionally, OS for nivolumab + ipilimumab versus EXTREME regimen in participants with PD-L1 CPS ≥ 1 will be added as a key secondary end-point. The primary end-point of PFS for

nivolumab + ipilimumab versus EXTREME regimen will be removed as evolving data suggest that PFS is not an appropriate end-point for immunotherapy in SCCHN.

1.2.1 The Role of Human Papillomavirus (HPV)

HPV-associated head and neck cancer, largely presenting in the oropharynx has been increasing in incidence in the past few decades.[10,11] In the US, two-thirds of patients with oropharynx cancer have HPV-associated tumors. In 2010, approximately 4,200 squamous cancers of the oropharynx (OPC) caused by tobacco and alcohol and 8,400 new HPV-associated oropharynx cancer will present for treatment.[12] HPV status is an independent prognostic factor for OS and progression-free survival (PFS) among patients with squamous cell OPC.[13] In this study (CheckMate 651), 64% of OPC patients had HPV-positive tumors, as measured in-situ hybridization for the HPV subtype 16. The presence of HPV DNA correlated well with p-16 expression (kappa = 0.80; 95% CI, 0.73 to 0.87). Patients with HPV-positive tumors had significantly increased OS as well as PFS compared to patients with HPV-negative tumors. Furthermore, after adjusting for demographics, T stage, N stage, smoking, patients with HPV-positive OPC had a 58% reduction in the risk of death and a 51% reduction in risk of progression or death. Patients with HPV-negative tumors had a 25.1% reduction in OS at 3 years (57.1% vs 82.4%) when compared to patients with HPV-positive tumors.[11] Local-regional relapse at 3 years was 21% higher in patients with HPV-negative tumors: 35.1% (95% CI: 26.4 - 43.8) versus 13.6% (95% CI: 8.9 - 18.3) for HPV-positive tumors ($P < 0.001$). These poor outcomes for HPV-negative patients occur despite the gradual trend toward increasing intensification of treatment with altered fractionation schema,[14] concurrent chemoradiation,[15,16] multi-drug induction chemotherapy,[17] and targeted molecular therapies.[18] For patients with HPV-negative tumors altering the method of radiation delivery and the dosing and/or types of concurrent chemotherapy is not sufficient to improve oncologic outcomes.

Because HPV-associated head and neck cancers more frequently present in a younger population and seem particularly responsive to treatment with a better overall survival,[19] attention has focused on the subpopulation of > 10 pack-year smoking and N2-N3, whose prognosis is worse (60% - 70% 2 year PFS) as well as HPV-negative head and neck cancer patients, whose clinical outcome has not improved despite intensification of standard chemotherapeutic agents and combinations. Thus, novel therapeutic approaches, such as immune modulation and blockade of suppressive immune cells and signals, are needed in clinical evaluation.

1.2.2 Immunotherapy in SCCHN and role of PD-L1

Immunotherapeutic approaches recently have demonstrated clinical efficacy in several cancer types, including melanoma, hormone-refractory renal cell carcinoma, and non-small cell lung cancer.[20] Tumors may modulate and evade the host immune response through a number of mechanisms, including down regulation of tumor-specific antigen expression and presentation, secretion of anti-inflammatory cytokines, and upregulation of inhibitory ligands. In SCCHN, down-regulation of T-cell function is thought to be mediated by multiple mechanisms: i.) Reduced expression of co-stimulating molecules of the B7-CD28 family[21]; ii.) Increased expression of PD-L1 in tumor cells and tumor associated fibroblasts; and, iii.) Loss of HLA-class I and selective

down-regulation of HLA-A,B,C locus expression resulting in defective antigen presentation.[21,22,23] In a subset of HPV-infected SCCHN, data shows that antigen-processing machinery components are downregulated compared to the adjacent normal squamous epithelium with incomplete activation of tumor specific T cells or suboptimal target recognition enabling tumor progression.[24] T cell checkpoint regulators such as CTLA-4 and programmed death-1 (PD-1, CD279) are cell surface molecules that, when engaged by their cognate ligands, induce signaling cascades down-regulating T cell activation and proliferation.

PD-L1 expression has been associated with poor prognoses in certain tumor types such as renal, esophageal, gastric, ovarian, pancreatic, and lung cancer.[25,26,27,28,29,30] PD-1 engagement on T-cells by PD-L1-positive APC or PD-L1-positive tumor cells in the tumor microenvironment may limit effective immune responses. Conversely, PD-L1 expression may be a positive prognostic factor as it may indicate infiltration of tumor-specific T cells that secrete IFN-γ, which upregulates PD-L1 expression. Consistent with this hypothesis is the co-localization of lymphoid cell infiltrates and PD-L1 staining observed in human melanoma lesions.[31] PD-L1 expression in SCCHN has been reported; preliminary results from a Phase 1 trial in patients with [32] recurrent or metastatic disease observed that 77.9% of patients tested (N = 104) expressed PD-L1, defined as ≥ 1% of stained cells in the tumor microenvironment.

PD-L1 CPS is defined as the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100.[33] PD-L1 CPS is a composite score that incorporates both tumor and tumor-associated immune cell (TAIC) PD-L1 expression, whereas tumor proportion score (TPS) or tumor cell PD-L1 only reflects the percentage of tumor cells that are positive for PD-L1 expression. Emerging evidence suggests that PD-L1 CPS as the biomarker that could be a good predictor of response with check-point inhibitors.

The role of the PD-1 blockade in squamous non-small cell carcinoma of the lung has been established in CA209017 study,[34] where nivolumab monotherapy in the second-line treatment setting demonstrated clinically meaningful survival benefit regardless of PD-L1 expression compared to standard of care docetaxel. In a similar histology, for squamous cell carcinoma of the head and neck primary, the role of PD-1 blockade is evolving.

CheckMate 141 study (CA209141), is a randomized, open-label, Phase 3 trial that compared nivolumab, a fully human anti-programmed death 1 (PD-1) monoclonal antibody, to investigator's choice (IC) of systemic therapy in patients with recurrent or metastatic SCCHN who progressed from a platinum-containing therapy. At the primary analysis, the median OS was 7.5 months (95% confidence interval [CI], 5.5 to 9.1) with nivolumab versus 5.1 months (95% CI, 4.0 to 6.0) with IC. There is a 30% reduction in the risk of death for patients on the nivolumab arm (hazard ratio 0.70; 97.73% CI, 0.51 to 0.96; P = 0.0101) over IC. The overall response rate (ORR) was 13.3% with nivolumab versus 5.8% with IC. In addition, the overall safety profile of nivolumab was favorable compared to IC.[35] Clinical benefit seen in this chemotherapy pre-treated SCCHN suggests the potential clinical activity of nivolumab in earlier treatment setting.

In the long-term (2-year) follow-up of the CheckMate 141 study (CA209141), nivolumab showed a consistent long term benefit in OS compared to IC systemic therapy (HR = 0.68 [95% CI: 0.54, 0.86]) in the overall study-population. Furthermore, nivolumab demonstrated 45% reduction in risk of death versus IC in patients whose tumors expressed tumor cell PD-L1 ≥ 1% (HR = 0.55 [95% CI: 0.39, 0.78]). In a sub-group analysis of this study, participants who had both tumor cell PD-L1≥ 1% and a high tumor-associated immune cell PD-L1 (TAIC) expression demonstrated a relatively better OS benefit (HR: 0.43, 95% CI 0.28, 0.67) with median OS of 9 months. In participants who only showed high expression of TAICs a 33% reduction in risk of death was noted (HR = 0.67, 95% CI 0.38, 1.18), with a median OS of 11.73 months. This recent data, while confirming the clinical benefit of check-point inhibitors in the over-all SCCHN population (irrespective of baseline biomarker status), also demonstrates a relatively better efficacy in participants with high PD-L1 CPS. [36].

A recent Phase 3 study (KeyNote-048) evaluated immunotherapy either as a single agent (pembrolizumab) or in combination with chemotherapy (pembrolizumab+platinum+5FU) in 1L R/M SCCHN. The study demonstrated that the participants expressing high PD-L1 CPS ≥ 20 derive a significant survival benefit with immunotherapy compared to treatment with EXTREME regimen (HR = 0.61, 95% CI 0.45-0.83, p = 0.0007). This sub-group (PD-L1 CPS ≥ 20) covers approximately 40-45% of the 1L recurrent or metastatic SCCHN population. The study also evaluated pembrolizumab monotherapy in participants who expressed PD-L1 CPS ≥ 1 (approximately 85% of the study population) and pembrolizumab + chemotherapy in all study participants. The results showed a modest 2 months improvement in median OS for pembrolizumab monotherapy compared to EXTREME regimen in PD-L1 CPS ≥ 1 sub-group (HR= 0.78, 95% CI 0.64-0.96, p = 0.0086) and a 2.3 months improvement in median OS for pembrolizumab + chemotherapy compared to EXTREME regimen in all-comes population (HR = 0.77, 95% CI 0.63-0.93, p = 0.0034). The pembrolizumab + chemotherapy regimen did not offer significant benefit over EXTREME regimen for duration of tumor response (median 6.7 months for P+C versus 4.3 months with EXTREME regimen) or in terms of overall safety profile. This recent data, while supporting patient selection based on PD-L1 CPS level for treatment with immunotherapy, also suggests that neither pembrolizumab monotherapy or pembrolizumab + chemotherapy are optimal treatment options unselected 1L R/M SCCHN patient population or those with low PD-L1 CPS levels.

Similar encouraging data on PD-L1 CPS selection for PD-1 inhibitors have been recently reported in other indications as well. In KeyNote-059 Cohort 1, patients with advanced gastric cancer (GC) who had received ≥2 lines of prior chemotherapy were treated with pembrolizumab monotherapy (n = 257). Pembrolizumab showed promising clinical activity with antitumor response significantly associated with PD-L1 CPS (P = 0.002) but not TPS (P = 0.224) at PD-L1 CPS/TPS ≥ 1. The odds ratio between the PD-L1 positive and negative populations had increased from 1.4 for TPS ≥ 1 to 2.8 for PD-L1 CPS ≥ 1, indicating the better predictive value of PD-L1 CPS compared to TPS.

In CA209-032 GC cohorts, PD-L1 CPS has been associated with longer survival. The mOS for patients with PD-L1 CPS ≥ 5 was 7.7 months compared with 5.4 months for PD-L1 CPS < 5 when

all treatment regimens were combined. These data suggested PD-L1 CPS is a better predictor of treatment effects of immunotherapy in advanced or metastatic GC/GEJ.

Based on accumulating clinical data, PD-L1 CPS seems to better predict response than TPS and able to better select patients for treatment with checkpoint inhibitors.

Additionally, recent evolving data from multiple Phase 3 studies in SCCHN (Checkmate 141, KeyNote-040 and KeyNote-048) suggest that PFS did not capture the benefit of immunotherapy therapy versus standard of care therapy in both biomarker selected and unselected population. In 1L R/M SCCHN, pembrolizumab showed a median PFS of 3.4 months in participants with PD-L1 CPS ≥ 20 sub-group and 3.2 months in participants with PD-L1 CPS ≥ 1 sub-group versus 5.0 months with EXTREME regimen. This suggest that PFS is not an ideal end-point for immunotherapy.

Based on the review of available data, this study (CA209651) will be revised to compare the difference in OS between study arms in participants who express PD-L1 CPS ≥ 20 and in all study participants as the co-primary end-points.

1.2.3 Rationale for Combination of Nivolumab and Ipilimumab

Preclinical data indicate that the combination of PD-1 and CTLA-4 receptor blockade may improve antitumor activity. In vitro combinations of nivolumab plus ipilimumab increase IFN-γ production 2- to 7-fold over either agent alone in a mixed lymphocyte reaction. Increased antitumor activity of the combination was also observed in 3 of 5 syngeneic murine cancer models. In a murine melanoma vaccine model, blockade with either CTLA-4 or PD-1 antibodies increased the proportion of CTLA-4 and PD-1-expressing CD4/CD8 tumor infiltrating T effector cells, and dual blockade increased tumor infiltration of T effector cells and decreased intratumoral T regulatory cells, as compared to either agent alone.[19]

Checkmate 141 showed that nivolumab monotherapy increased the length of time patients lived when compared with standard, single agent chemotherapy with a relatively better efficacy noted in tumor cell PD-L1 expressers. In similar trials in lung cancer patients that had recurred after treatment with platinum-based chemotherapy, nivolumab monotherapy also prolonged survival versus single agent chemotherapy, both in tumors with squamous subtype, and non-squamous subtype. These trials led to approval of nivolumab for previously treated lung cancer in the US, Europe, and other countries.

In the clinical setting, the combination of nivolumab and ipilimumab was evaluated in CA209004 (MDX1106-04), a Phase 1b multiple ascending dose study in participants with treatment-naive and previously treated advanced melanoma. Results showed promising activity with higher, tolerable toxicity profile compared to ipilimumab alone. Based on this, CA209069, a randomized double-blind Phase 2 study of nivolumab in combination with ipilimumab versus ipilimumab monotherapy in participants with BRAF-wild type (WT) and mutant, with untreated unresectable or metastatic melanoma, was conducted. The regimens used were: nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks for 4 doses followed by nivolumab 3 mg/kg every 2 weeks versus ipilimumab 3 mg/kg every 3 weeks for 4 doses.[20] In patients with BRAF-WT tumors treated

with nivolumab and ipilimumab combination, there was improved ORR at 61% (44/72), with 22% (16/72) complete responses (CR), as compared to 11% (4/37) with 0 CRs in those treated with ipilimumab alone. The median PFS was not reached in the combination versus 4.4 months for ipilimumab alone (HR = 0.4). Improved clinical outcomes (PFS and ORR) with nivolumab and ipilimumab combination was confirmed by CA209067, a randomized Phase 3 study. In patients with previously untreated, unresectable or metastatic melanoma (n =945), the median PFS was 11.5 months (95% CI, 8.9 to 16.7) in the nivolumab plus ipilimumab group, 6.9 months (95% confidence interval [CI], 4.3 to 9.5) in the nivolumab group, and 2.9 months (95% CI, 2.8 to 3.4) in the ipilimumab group. Significantly longer PFS was observed in the nivolumab plus ipilimumab group than in the ipilimumab group (hazard ratio for death or disease progression, 0.42; 99.5% CI, 0.31 to 0.57; P<0.001) and in the nivolumab group than in the ipilimumab group (HR = 0.57; 99.5% CI, 0.43 to 0.76; P<0.001). The hazard ratio for the comparison between the nivolumab plus ipilimumab group and the nivolumab group was 0.74 (95% CI, 0.60 to 0.92).[37]

Clinical activity of nivolumab and ipilimumab combination was further evaluated in patients with stage IIB-IV NSCLC as first-line treatment in CA209012 study.[38] This was a large Phase 1, multi-arm safety study of nivolumab monotherapy and nivolumab in combination with various systemic anticancer therapies like ipilimumab, platinum-based chemotherapies and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor. Early combination cohorts evaluated 2 dosing schedules that were studied in the CA209004 melanoma study: nivolumab 1 mg/kg + ipilimumab 3 mg/kg (arms G and H, n = 24) and nivolumab 3 mg/kg + ipilimumab 1 mg/kg (arms I and J, n = 25). Both regimens were given every 3 weeks 4 doses, followed by maintenance nivolumab 3 mg/kg q 2 weeks. Unlike in melanoma, these regimens resulted in significant toxicity in the NSCLC population, with 39% of patients discontinuing treatment due to a treatment-related adverse events. Thus, additional combination cohorts were initiated (arms N, O, P, Q), using lower doses of both nivolumab and ipilimumab, or the approved dose of nivolumab with less frequent dosing of ipilimumab. These new regimens were better tolerated, and the safety profile was comparable to what has been observed in the nivolumab monotherapy cohort (arm F) in CA209012 study (Table 1.2.3-1).

Table 1.2.3-1: Treatment-related adverse events from selected cohorts in CA209012 (NSCLC)

Arm[a]	No. Participants / arm	Follow-up time (median, wks)	No. Participants still on treatment	No. Participants with drug-related AEs	No. Participants with grade 3-4 drug-related AEs	No. Participants d/c due to drug-related AEs (all grades)
N[b]	31	72	6 (19%)	24 (77%)	9 (29%)	4 (13%)
O[b]	40	27	14 (35%)	29 (73%)	14 (35%)	3 (8%)
P[b]	38	37	20 (53%)	28 (74%)	11 (29%)	2 (5%)
Q[b]	39	34	15 (39%)	27 (69%)	11 (28%)	4 (10%)

Table 1.2.3-1: Treatment-related adverse events from selected cohorts in CA209012 (NSCLC)

Arm[a]	No. Participants / arm	Follow-up time (median, wks)	No. Participants still on treatment	No. Participants with drug-related AEs	No. Participants with grade 3-4 drug-related AEs	No. Participants d/c due to drug-related AEs (all grades)
F[c]	52	62	5 (10%)	37 (71%)	10 (19%)	5 (10%)

[a] N:nivolumab 1 mg/kg plus ipilimumab 1 mg/kg every 3 weeks x 4, followed by nivolumab 3 mg/kg every 2 weeks; O: nivolumab 1 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks; P: nivolumab 3 mg/kg every 2 weeks plus ipilimumab every 12 weeks; Q: nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks; F: nivolumab 3 mg/kg every 2 weeks

[b] based on August 2015 database lock

[c] based on March 2015 database lock

Table 1.2.3-2: Efficacy of First-Line Treatment of Nivolumab/Ipilimumab Combination in CA209012 (NSCLC)

	Nivo 1 + Ipi 1 q3w→ Nivo 3 (Arm N; n = 31)	Nivo 1 q2w + Ipi 1 q6w (Arm O; n = 40)	Nivo 3 q2w + Ipi 1 q12w (Arm P; n = 38)	Nivo 3 q2w+ Ipi 1 q6w (Arm Q;n = 39)
Confirmed ORR, % (95% CI)	**13 (4, 30)**	**25 (13, 41)**	**39 (24, 57)**	**31 (17, 48)**
PFS rate at 24 wks (95% CI)	55 (36, 73)	58 (41, 73)	74 (57, 87)	51 (35, 68)
mPFS, mos (95% CI)	10.6 (2.1, 16.3)	4.9 (2.8,)	8.0 (4.2,)	8.3 (2.6,)
Median length of follow-up, months	16.6	6.2	8.4	7.7

Table 1.2.3-3: Efficacy by Tumor Cell PD-L1 Expression ((≥1%) in CA209012 (NSCLC)

	Nivo 1 + Ipi 1 q3w→ Nivo 3 (Arm N n = 12)	Nivo 1 q2w + Ipi 1 q6w (Arm O; n = 21)	Nivo 3 q2w + Ipi 1 q12w (Arm P; n = 21)	Nivo 3 q2w + Ipi 1 q6w (Arm Q; n = 23)
ORR, %	8	24	48	48
mPFS, wks (95% CI)	11.5 (7.1,)	21.1 (11.4,)	34.6 (15.9, 35.3)	NR (15.4,)
PFS rate at 24 wks, % (95% CI)	42 (15,67)	40 (18, 61)	74 (48,88)	65 (42, 81)

Clinical activity was observed in all combination cohorts (Table 1.2.3-2), but numerically higher response rates were observed in cohorts evaluating the approved dose of nivolumab 3 mg/kg in combination with ipilimumab, with confirmed response rates ≥ 30% (cohorts P and Q). When clinical activity was analyzed by tumor cell PD-L1 expression, there appears to be higher efficacy in participants with PD-L1 expressing tumors however interpretation is limited by the small number of patients. Those with tumor cell PD-L1 ≥ 1% expressing tumors treated with nivolumab and ipilimumab combination in cohorts P and Q had response rates of 48%. PFS appeared to be also higher in these subsets; of note, in cohort Q, PFS was not yet reached (Table 1.2.3-3). Although follow-up is still limited (7 to 8 months), the PFS and ORRs observed in these cohorts are highly encouraging. With comparable efficacy and safety data from cohorts P and Q, the nivolumab plus ipilimumab every 6 week dosing schedule (cohort Q) is the selected regimen moving forward.[39] Aside from utilizing the approved nivolumab dose in NSCLC, it would also provide the highest dose and frequency of ipilimumab feasible in a combination regimen.

The combination of ipilimumab with nivolumab showed increased activity versus nivolumab alone in multiple tumor types, including melanoma, multiple types of lung cancer, gastric cancer, and renal cancer as described below. This efficacy benefit is not restricted to tumor cell PD-L1 expressers alone. The combination is currently approved for the treatment of advanced or metastatic melanoma in the US and Europe.

Given the similarity in patient profiles of NSCLC and SCCHN, nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks [redacted] and will also be the treatment regimen for the experimental arm of the Phase 3 CA209651 study. [redacted] Thus the summary of available evidence across indications suggests that addition of ipilimumab to nivolumab may offer an opportunity to improve the efficacy OS in R/M SCCHN participants irrespective PD-L1 expression, with a relatively better efficacy benefit in participants with high PD-L1 CPS.

Overall, as discussed previously, based on the evolving data from SCCHN suggesting a relatively better efficacy for immunotherapy in PD-L1 CPS high expressers and potential for Nivolumab + Ipilimumab to benefit participants irrespective of PD-L1 CPS status, the CA209651 study will evaluate the co-primary end-points of OS of the combination of nivolumab with ipilimumab versus EXTREME regimen in participants with PD-L1 CPS ≥ 20 and in all study participants.

1.2.4 Rationale for Shorter Infusion Times for Nivolumab and Ipilimumab

Long infusion times place a burden on patients and treatment centres. Establishing that nivolumab and ipilimumab can be safely administered using shorter infusion times of 30 minutes duration in participants will diminish the burden provided no change in safety profile. Previous clinical studies of nivolumab monotherapy and ipilimumab monotherapy and the combination of nivolumab and ipilimumab have used a 60-minute infusion duration for nivolumab and 90-minute infusion

duration for ipilimumab (1 - 3 mg/kg dosing for both). However, both nivolumab and ipilimumab have been administered at up to 10 mg/kg with the same infusion duration.

Nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg safely over long treatment duration. In Study CA209010 (a Phase 2, randomized, double blinded, dose-ranging study of nivolumab in participants with advanced/metastatic clear cell RCC), a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg and 18.5% at 10 mg/kg). All the events were Grade 1 - 2 and were manageable. An infusion duration of 30 minutes for 3 mg/kg nivolumab (30% of the dose provided at 10 mg/kg) is not expected to present any safety concerns compared to the prior experience at 10 mg/kg nivolumab dose infused over a 60-minute duration.

Similarly, ipilimumab at 10 mg/kg has been safely administered over 90 minutes. In the CA184022 study, where ipilimumab was administered up to a dose of 10 mg/kg, on-study drug related hypersensitivity events (Grade 1 - 2) were reported in 1 (1.4%) participant in the 0.3 mg/kg and in 2 (2.8%) participants in the 10 mg/kg group. There were no drug-related hypersensitivity events reported in the 3 mg/kg group. Across the 3 treatment groups, no Grade 3 - 4 drug-related hypersensitivity events were reported, and there were no reports of infusion reactions. Ipilimumab 10 mg/kg monotherapy has also been safely administered as 90 minute infusion in large Phase 3 studies in prostate cancer (CA184043) and as adjuvant therapy for stage 3 melanoma (CA184029), with infusion reactions occurring in participants. Administering 1 mg/kg of ipilimumab represents one-tenth of the 10 mg/kg dose.

Overall, infusion reactions including high-grade hypersensitivity reactions have been uncommon across nivolumab or ipilimumab clinical studies or the combination of nivolumab and ipilimumab. Furthermore, a 30-minute break after the first infusion for the combination cohort will ensure the appropriate safety monitoring before the start of the second infusion. Overall, a change in safety profile is not anticipated with 30-minute infusion of nivolumab, ipilimumab or combination.

1.2.5 Rationale for Permitting Continued Treatment in Select Cases of Progressive Disease

Accumulating clinical evidence indicates some participants treated with immune system stimulating agents may develop progression of disease (by conventional response criteria) before demonstrating clinical objective responses and/or stable disease. This phenomenon was observed in approximately 10% of participants in the Phase 1 study of nivolumab and also with ipilimumab monotherapy[40] Two hypotheses have been put forth to explain this phenomenon. First, enhanced inflammation within tumors could lead to an increase in tumor size which would appear as enlarged index lesions and as newly visible small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease leading to overt signs of clinical improvement. Alternatively, in some individuals, the kinetics of tumor growth may initially outpace anti-tumor immune activity. With sufficient time, the anti-tumor activity will dominate and become clinically apparent. Therefore participants will be allowed to continue study therapy after initial investigator-assessed RECIST 1.1 defined progression if they are assessed to be

deriving clinical benefit and tolerating study drug. Such participants must discontinue study therapy upon evidence of further progression as defined in section 4.5.5.

1.2.6 Rationale for 24 Months Maximum Treatment Duration

The optimal duration of treatment by checkpoint blockade inhibitors in oncology is currently unknown. However, given their mechanism of action continuous treatment may not be required as opposed to targeted agents or most of cytotoxic therapies.

With almost a decade of experience using CTLA-4 and PD-1/PD-L1 inhibitors, accumulating evidence from different clinical trials in different tumor types indicates that most of the responses are generally occurring early, with a median time to response of 2 to 4 months including in patients with NSCLC, and most of the responses are likely to be durable as compared to conventional therapies.[41,42,43]

Limited duration of therapy was explored in few trials, for instance, ipilimumab the first checkpoint blockade inhibitor targeting CTLA-4 was initially approved in metastatic melanoma in participants who failed standard of care chemotherapy. This approval was based on overall survival improvement after a limited duration of ipilimumab therapy, including only 4 induction doses for a duration of treatment of 12 weeks, with a sustained plateau in survival starting at around year two.[44] Moreover, in Checkmate 003 a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in patients with advanced solid tumors implemented stopping nivolumab monotherapy at 96 weeks (~ 2 years). At 2 years, 16 NSCLC participants who were on still on therapy discontinued nivolumab per protocol, of these, 75% of patients (n = 12) were alive > 5 years and did not receive further therapy after stopping nivolumab and remained progression free.[45]

Moreover, long-term follow up data from study KeyNote-006 a phase 3 Melanoma study demonstrates that pembrolizumab provides durable efficacy after stopping the protocol-specified duration of treatment at 2 years. The median follow-up was of 33.9 months, among the 104 (19%) participants who completed pembrolizumab, median exposure was 24.0 months. After additional median follow-up of 9.0 months after completion of pembrolizumab, 102 (98%) pts were alive and responses were durable in pts who completed pembrolizumab.[46]

In addition, data from different series are showing that patients receiving immunotherapy-based treatment may discontinue treatment due to safety events. In a recent analysis in a melanoma study the majority of patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment.[47]

CheckMate 153 is the first randomized study to evaluate treatment duration with a PD-1/PD-L1 inhibitor. In this study, progression free survival appears to be durable with a plateau at 2 years from first dose including in pts who stopped nivolumab after 1 year, suggesting the risk of progression after 2 years of treatment is minimal, even in the absence of further treatment, which is consistent with existing data with PD-1/PD-L1 datasets. In addition, 34 out of 87 patients with clinical benefit who stopped therapy at 1 year were retreated upon progression as per protocol, in this group, nivolumab retreatment did not appear to re-induce responses and in the majority of the

cases, the tumor continues to progress suggesting that treatment change, using preferentially an agent or approach with a different MOA.[48]

Collectively, these data suggest that there is likely no benefit from treatment beyond two years in advanced tumors. However, even though immunotherapy is well tolerated, patients will be exposed to the risk of additional toxicity with longer-term treatment. Therefore, in CA209-651 treatment with nivolumab +/- ipilimumab will be given for up to 2 years from start of treatment.

1.3 Research Hypotheses

- Participants with PD-L1 CPS ≥ 20 who receive nivolumab in combination with ipilimumab for first-line treatment of recurrent or metastatic SCCHN will have longer OS than comparable participants who receive the EXTREME regimen
- Participants who receive nivolumab in combination with ipilimumab for first-line treatment of recurrent or metastatic SCCHN will have longer OS than comparable participants who receive the EXTREME regimen

1.4 Objectives(s)

1.4.1 Primary Objectives

- To compare the OS of participants with PD-L1 CPS ≥ 20 who are receiving nivolumab combined with ipilimumab to those receiving EXTREME regimen.
- To compare the OS of all study participants who are receiving nivolumab combined with ipilimumab to those receiving EXTREME regimen

1.4.2 Secondary Objectives

- To compare the OS of participants with PD-L1 CPS ≥ 1 who are receiving nivolumab combined with ipilimumab to those receiving EXTREME regimen
- To evaluate progression-free survival (PFS) based on BICR in all study participants and those with PD-L1 CPS ≥ 20 who are receiving nivolumab combined with ipilimumab, and those receiving EXTREME regimen.
- To evaluate objective response rate (ORR) based on BICR in all study participants and those with PD-L1 CPS ≥ 20 who are receiving nivolumab combined with ipilimumab, and those receiving EXTREME regimen.
- To evaluate the duration of response (DOR) based on BICR in all study participants and those with PD-L1 CPS ≥ 20 who are receiving nivolumab combined with ipilimumab, and those receiving EXTREME regimen.

1.4.3 Exploratory Objectives

- To evaluate OS of participants with tumor cell PD-L1 < 1% and PD-L1 CPS < 20 who are receiving nivolumab combined with ipilimumab, and those receiving EXTREME regimen.

- To evaluate the OS of participants with tumor inflammation score measured as gene expression profile (GEP) ≥ 10 who are receiving nivolumab combined with ipilimumab, and those receiving EXTREME regimen.
- To evaluate the OS of participants with tumor mutation burden (TMB) ≥ 7 who are receiving nivolumab combined with ipilimumab, and those receiving EXTREME regimen.
- To evaluate clinical outcomes (OS, PFS, ORR, DOR) by select baseline and on-treatment biomarker expression levels in peripheral blood and tumor biopsy specimens.
- To assess safety and tolerability of nivolumab in combination with ipilimumab and of EXTREME regimen, in all study participants
- To characterize pharmacokinetics and immunogenicity of nivolumab in combination with ipilimumab as first line therapy in participants with recurrent or metastatic SCCHN
- To evaluate time to symptom deterioration (TTSD) in each arm as assessed using the Functional Assessment of Cancer Therapy - Head and Neck (FACT-H&N) 10-item Symptom Index (FHNSI-10), in participants with PD-L1 CPS ≥ 20 and also in all study participants
- To assess the participant's overall health status and health utility using the 3-level version of the EQ-5D (EQ-5D-3L) visual analog scale (VAS) and utility index, respectively, in participants with PD-L1 CPS ≥ 20 and also in all study participants
- To assess the participant's cancer-related symptoms and quality of life using components of the FACT-H&N questionnaire, in participants with PD-L1 CPS ≥ 20 and also in all study participants.

1.5 Product Development Background

Nivolumab (Opdivo) is in clinical development for the treatment of patients with melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), head and neck carcinoma and other tumors (eg, gastric cancer, glioblastoma multiforme, Hodgkins lymphoma, small cell lung cancer). Opdivo as monotherapy has been approved in the US in multiple indications, including, unresectable or metastatic melanoma and disease progression following ipilimumab and a BRAF inhibitor, if BRAF V600 mutation positive; previously untreated patients with BRAF wild-type unresectable or metastatic melanoma; NSCLC with progression on or after platinum-based chemotherapy; and advanced renal cell carcinoma who have received prior anti-angiogenic therapy. The combination of nivolumab and ipilimumab has also been approved in the US for the treatment of previously untreated metastatic melanoma.

Patients with recurrent or metastatic SCCHN have poor prognosis and experience limited survival benefit with standard of care therapies. In patients with recurrent or metastatic SCCHN who progress with platinum chemotherapy, nivolumab demonstrated prolonged survival benefit over standard of care in the Checkmate 141 study and is poised to become the standard of care in this population. To further improve clinical outcomes in patients with recurrent or metastatic SCCHN in the first-line treatment setting, nivolumab in combination with ipilimumab is being explored in the CA209651 clinical study.

1.5.1 Mechanism of Action of Nivolumab

Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD 1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes[49]. Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

1.5.2 Mechanism of Action of Ipilimumab

CTLA-4, an activation-induced T-cell surface molecule, is a member of the CD28:B7 immunoglobulin superfamily that competes with CD28 for B7. CTLA-4 mediated signals are inhibitory and turn off T cell-dependent immune responses. Ipilimumab is a fully human monoclonal IgG1κ that binds to the CTLA-4 antigen expressed on a subset of T cells from human and nonhuman primates. The proposed mechanism of action for ipilimumab is interference of the interaction of CTLA-4 with B7 molecules on APCs, with subsequent blockade of the inhibitory modulation of T-cell activation promoted by the CTLA 4/B7 interaction[50,51].

1.5.3 Nivolumab Combined With Ipilimumab

The combination of nivolumab and ipilimumab has been studied in various tumor types such as melanoma and recently, as first line therapy in participants with previously untreated stage IV or recurrent NSCLC at different dose and schedules in study CA209012. As of 17 March 2015, 80 patients have been treated with this combination in the original cohorts (arms G, H, I, J, N). Additional combination dosing schedules were developed using lower doses of both nivolumab and ipilimumab (1 mg/kg), or using the approved dose of nivolumab (3 mg/kg) with more extended dosing of ipilimumab 1 mg/kg (q6w and q12w). An additional 117 patients have been treated in these newer cohorts, and compared to other cohorts, shows acceptable safety profile with lower treatment related AEs (all grade and Grade 3-4) as well as lower treatment related AEs leading to discontinuation (Table 1.5.3-1). Based on the efficacy and safety data, nivolumab plus ipilimumab every 6 week dosing schedule was determined to be optimal combination regimen in NSCLC. Additional clinical data and rationale for the combination regimen is discussed in Section 1.2.3.

Table 1.5.3-1: First-Line Nivolumab + Ipilimumab Safety Summary

	Treatment-Related AEs, %	Treatment-Related AEs leading to discontinuation, %
Nivo 1 Q2W + Ipi 1 Q6W (n = 40)		
Any Grade	73	8
Grade 3-4	35	8

Table 1.5.3-1: First-Line Nivolumab + Ipilimumab Safety Summary

	Treatment-Related AEs, %	Treatment-Related AEs leading to discontinuation, %
Nivo 3 Q2W + Ipi 1 Q12W (n = 38)		
Any Grade	74	5
Grade 3-4	29	3
Nivo 3 Q2W + Ipi 1 Q6W (n = 39)		
Any Grade	69	10
Grade 3-4	28	10

1.6 Overall Risk/Benefit Assessment

Patients with recurrent, unresectable or metastatic SCCHN represent an important unmet need. There is robust clinical data available to suggest the potential to improve clinical outcomes in SCCHN:

- CheckMate 141 study (CA209141), is a randomized, open label, Phase 3 trial that compared nivolumab, a fully human anti-programmed death 1 (PD 1) monoclonal antibody, to investigator's choice (IC) of systemic therapy in patients with recurrent or metastatic SCCHN who progressed from a platinum-containing therapy. At the primary analysis, the median OS was 7.5 months (95% confidence interval [CI], 5.5 to 9.1) with nivolumab versus 5.1 months (95% CI, 4.0 to 6.0) with IC. There is a 30% reduction in the risk of death for patients on the nivolumab arm (hazard ratio 0.70; 97.73% CI, 0.51 to 0.96; P = 0.0101) over IC. The overall response rate (ORR) was 13.3% with nivolumab versus 5.8% with IC. The long-term follow-up data from the study confirms the prolonged survival benefit in the overall study population, while suggesting a relatively better OS in subjects who express PD-L1 on both tumor and immune cells. In addition, the overall safety profile and patient reported outcomes of nivolumab was favorable compared to IC. Clinical benefit seen in this chemotherapy pre-treated SCCHN suggests the potential clinical activity of nivolumab in earlier treatment setting.
- A recent Phase 3 study (KeyNote-048) in 1L R/M SCCHN evaluated immunotherapy either as a single agent (pembrolizumab) or in combination with chemotherapy (pembrolizumab +platinum+5FU) in 1L R/M SCCHN. The study demonstrated that the participants expressing high PD-L1 CPS ≥ 20 derive a significant survival benefit with immunotherapy compared to treatment with EXTREME regimen (HR = 0.61, 95% CI 0.45-0.83, p = 0.0007). This study also demonstrated that immunotherapy had a favorable safety profile vs EXTREME. There was a lower incidence of any-grade, grade 3-4, and grade 5 treatment-related AEs, and lower incidence of treatment-related AEs leading to discontinuation.

[redacted]

[redacted]

- CheckMate 012 study (CA209112) is a multi-arm large phase 1 safety study of nivolumab as a single agent or in combination with various systemic anticancer therapies including ipilimumab in patients with stage IIIB-IV NSCLC as first-line treatment. Clinical activity was observed in all combination cohorts with numerically higher response rates observed in cohorts evaluating nivolumab 3 mg/kg plus ipilimumab 1 mg/kg, with confirmed response rates ≥ 30% and median PFS ~8 months.

Given the similarity in patient profiles of NSCLC and SCCHN, nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks (will be the treatment regimen for the experimental arm of this study.

The safety profile of nivolumab and ipilimumab is well characterized from a large safety database at different dose and schedules as monotherapy or in combination.[52,53] Consistent with the mechanism of action of nivolumab and ipilimumab, the most frequently reported drug-related adverse events observed in clinical trials are those associated with activation of the immune system. The most common types of immune-mediated adverse events include endocrinopathies, diarrhea/colitis, hepatitis, pneumonitis, nephritis and rash. In the combination regimen, the frequency and intensity of these events may vary and depend on the specific dose and schedule used. In the combination dosing schedule selected for this study (nivolumab 3 mg/kg Q2W plus ipilimumab 1 mg/kg Q6W), immune-mediated adverse events were mostly low grade and manageable with prompt use of corticosteroids.

Nivolumab was evaluated in 240 patients with recurrent or metastatic platinum refractory SCCHN in CA209141 study and demonstrated a favorable safety profile with nivolumab monotherapy as compared to standard of care chemotherapy. Nivolumab in combination with ipilimumab will be evaluated in the SCCHN population for the first time.

To assure an ongoing favorable risk/benefit assessment for participants enrolled onto CA209651, the following safety measures will be employed throughout the conduct of the study:

- Institution of a Data Monitoring Committee (DMC) to provide independent oversight of safety, study conduct and efficacy of nivolumab plus ipilimumab combination versus standard of care chemotherapy (EXTREME regimen).
- Rigorous safety monitoring by BMS to ensure participants' safety including regular and systematic review of safety data, close follow-up of reported safety events, intensive site and study investigator training/education on the implementation of the nivolumab and ipilimumab toxicity management algorithms as well as regular safety conference calls with study investigators.
- Open-label drug administration of study drugs to allow for prompt and accurate assessment of the unique toxicities associated with study treatments

In conclusion, the overall risk-benefit of nivolumab and ipilimumab as first-line treatment in recurrent or metastatic SCCHN is deemed acceptable.

2 STUDY GOVERNANCE CONSIDERATIONS

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

2.1 Regulatory and Ethical considerations

2.1.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the international ethical guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines Good Clinical Practice (GCP), in accordance with ethical principles underlying European Union Directive 2001/20/EC and the 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/participant's informed consent will receive approval/favorable opinion by Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable local regulations prior to initiation of the study.

All potential serious breaches must be reported to the Sponsor or designee immediately. A potential serious breach is defined as a Quality Issue (eg, protocol deviation, etc) that is likely to affect, to a significant degree one or more of the following: (1) the physical, the safety or mental integrity of one or more of the subjects /participants; (2) the scientific value of the study (eg, reliability and robustness of generated data). Items (1) or (2) can be associated with either GCP Regulation(s) or Trial protocol(s).

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).

2.1.2 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.

2.1.3 Informed Consent Process

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

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

1) 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.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3) 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.
4) 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.
5) 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.
6) 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 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 participants are the most important considerations and should prevail over interests of science and society.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

Protocol CA209651 is a randomized open-label, Phase 3 trial in subjects ≥ 18 years old with untreated metastatic or recurrent SCCHN that is not amenable to curative therapy, evaluating nivolumab + ipilimumab versus the EXTREME regimen (cetuximab + cisplatin/carboplatin + fluorouracil) as a first-line treatment.

HPV p-16 status and tumor cell PD-L1 status (expressing or non-expressing/non-evaluable) test results will be needed prior to randomization. Subjects will undergo screening evaluations to determine eligibility prior to randomization.

The dose and treatment schedules for each arm are as follows:

- Arm A: Nivolumab + Ipilimumab Arm:
  - Nivolumab 3 mg/kg IV every 2 weeks + Ipilimumab 1 mg/kg IV every 6 weeks until progression, unacceptable toxicity, or a maximum of 24 months from first study treatment.
- Arm B: EXTREME regimen Arm:
  - Cetuximab 400 mg/m^2 IV for the initial dose only, then 250 mg/m^2 weekly + cisplatin (100 mg/m^2) or carboplatin (AUC of 5 mg per milliliter per minute) on Day 1 and fluorouracil (1000 mg/m^2 per day for 4 days) every 3 weeks for maximum of 6 cycles followed by maintenance cetuximab at 250 mg/m^2 weekly (or every 2 weeks, per local prescribing information) until disease progression or unacceptable toxicity; the choice of cisplatin or carboplatin is at the discretion of the investigator.

Approximately 930 subjects will be randomized to the two treatment arms in a 1:1 ratio and stratified by the following factors:

- Tumor cell PD-L1 status (expressing [≥ 1%] vs non-expressing [< 1%] or non-evaluable). Up to 10% of randomized subjects per cohort can be included into the study as "non-evaluable." 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.
- HPV p-16 status (oropharyngeal HPV p-16 positive vs oropharyngeal HPV p-16 negative or non-oropharyngeal). Oropharyngeal CA sites defined in Appendix 5.
- Prior chemotherapy (adjuvant/neoadjuvant/multimodal treatment) status (Yes/No)

Tumor progression or response will be assessed by investigator using RECIST 1.1 criteria. Treatment with study medication will continue until RECIST 1.1 defined progression, unacceptable toxicity, a maximum of 24 months from the first study treatment, or withdrawal of consent. See Section 3.5 for full details of discontinuation of study drug treatment.

Dose reductions will be not be allowed for nivolumab or ipilimumab.

Treatment beyond initial investigator-assessed progression (either clinical or radiographical) is permitted for nivolumab and ipilimumab if the participant has an investigator-assessed clinical benefit and is tolerating study drug (see Section 4.5.6).

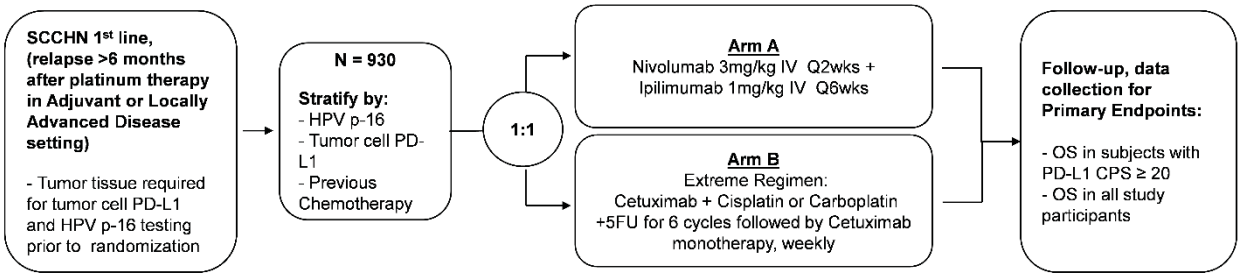
In addition to investigator assessment of response and progression, there will be a blinded independent central review (BICR) of tumor scans and study sites will need to submit tumor scans for central radiology review.

A DMC will be established and meet regularly during the study to ensure that participant safety is carefully monitored and to provide oversight regarding safety and efficacy considerations in protocol CA209651.

The maximum duration of the study from start of randomization to final analysis of OS is projected to be 51 months, assuming 26 months accrual duration. Additional 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 3.1-1.

Figure 3.1-1: Study Design Schematic



This study will consist of 3 phases: screening, treatment, and follow-up.

Screening Phase

- Begins by establishing the participant's initial eligibility and signing of the informed consent (ICF).
- Participant is enrolled using the Interactive Voice Response System (IVRS).
- Tumor tissue (archival or recent tumor biopsy) must be submitted by the site to a Central Lab for determination of tumor cell PD-L1 status. For this study we will use PD-L1 stained with the DAKO 28-8 antibody. Additional tumor tissue may be required by Central Lab if initial testing is unevaluable.
- HPV p-16 status must be available prior to randomization. If it is not available locally, then this will need to be tested by central lab, and the results need to be known prior to randomization. See Section 5.6.8.

  Participants will be stratified on tumor cell PD-L1 status (expressing vs non-expressing or non-evaluable. Up to 10% of randomized subjects can be included into the study as non-evaluable. 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).
- Participants must have the result of tumor cell PD-L1 IHC testing from the Central Lab available (and HPV p-16 result if not available locally) in order to randomize into the study.
- Participant is assessed for study eligibility.
- All screening assessments and procedures must be performed prior to randomization.

Treatment Phase

- The treatment begins with the contact to the IVRS to randomize the patient.
- Treatment to begin within 3 days of randomization.

Arm A: Nivolumab + Ipilimumab Combo (1 Cycle = 6 Weeks):

- 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).
- 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 Q2W and ipilimumab 1 mg/kg Q6W will be continued until the progression of disease, discontinuation due to toxicity, withdrawal of consent, or a maximum of 24 months from the first study treatment, or study closure (see Section 3.5 for full list of treatment discontinuation reasons). Participants may discontinue only ipilimumab and continue treatment with nivolumab if certain circumstances are met (See Section 4.5.6, Treatment Beyond Disease Progression (Arm A only).
- Treatment beyond initial investigator-assessed RECIST 1.1-defined progression is permitted for Arm A if the participant has investigator-assessed clinical benefit and is tolerating treatment.

Arm B: EXTREME regimen Arm (1 Cycle = 3 weeks):

- Cetuximab 400 mg/m^2 IV for the initial dose only, then 250 mg/m^2 weekly + cisplatin (100 mg/m^2) or carboplatin (AUC of 5 mg per milliliter per minute) on Day 1 and fluorouracil (1000 mg/m^2 per day for 4 days) every 3 weeks for maximum of 6 cycles followed by maintenance cetuximab at 250 mg/m^2 weekly (or every 2 weeks, per local prescribing information) until disease progression or unacceptable toxicity; the choice of cisplatin or carboplatin is at the discretion of the investigator.
- Study assessments are to be collected as outlined in Table 5.1-2
- Upon completion of dosing, participants will enter the Follow-up Phase.

Follow-up Phase

The post-treatment follow-up begins when the decision to discontinue a participant from all treatment is made.

- Participants 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.

Participants 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 a minimum of 100 days after the last dose of study medication.

After completion of the first 2 follow-up visits, participants will be followed every 3 months for survival. Survival Follow-up visits may be performed by phone contact or office visit. BMS may request that survival data be collected on all treated participants outside of the protocol-defined window. At that time of this request, each participant will be contacted to determine their survival status unless the participant had withdrawn consent for all contact.

3.2 Post Study Access to Therapy

At the conclusion of the study, participants who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study drug for the maximum treatment duration as described in Section 1.2.6. 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 participant can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

3.3 Study Population

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

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

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

b) Participants 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.

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

c) No prior treatment with systemic anti-cancer therapy for SCCHN, unless under all of the following conditions:

i) Prior chemotherapy was given as adjuvant or neoadjuvant chemotherapy, or part of multimodal (chemo, radiation) treatment for locally advanced disease

ii) These treatments must have been completed > 6 months prior to enrollment

iii) There is no evidence of disease progression for at least 6 months after completion of systemic treatment.

iv) Participants having progression after 2 cycles of induction chemotherapy are excluded.

d) ECOG Performance Status of 0–1. (See Appendix 1).

e) Measurable disease by CT or MRI per RECIST 1.1 criteria (see Appendix 3); radiographic tumor assessment performed within 28 days prior to first dose.

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. See Section 5.6.8 for additional guidance. 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 tumor cell PD-L1 status by IHC performed by the central lab prior to randomization.

Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections (archival or recent), with an associated pathology report, must be submitted for biomarker evaluation prior to randomization as described in Section 5.6.3. Biopsy should be excisional, incisional, or core needle. Fine needle aspiration is insufficient. Biopsies of bone lesions that do not have a soft tissue component are unacceptable for submission.

h) **As of Revised Protocol 02, this criterion has been altered and rewritten as criterion 2.l.** *Prior palliative radiotherapy must have been completed at least 8 weeks prior to randomization if radiotherapy was to the head and neck region and 4 weeks prior to randomization if radiotherapy was to other regions.*

i) All toxicities attributed to prior systemic anti-cancer therapy or surgery other than alopecia and fatigue must have resolved or returned to baseline at least 2 weeks before randomization.

j) Participants must have a life expectancy of at least 3 months. Any participants whose body weight decreased by > 10% between the screening visit and randomization must be excluded from the study.

k) **As of Revised Protocol 02, this criterion has been removed because it is already part of criterion c.** *Participants having progression after 2 cycles of induction chemotherapy are excluded.*

l) Prior radiotherapy must have been completed at least 2 weeks prior to randomization. All toxicities attributed to the radiotherapy must have resolved or returned to baseline prior to treatment.

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 from the time of enrollment for the duration of treatment plus 5 half-lives of nivolumab (half-life up to 25 days) plus 30 days (duration of ovulatory cycle) for a total of 5 months post treatment completion (Arm A).

   i. WOCBP must also agree to follow instructions for method(s) of contraception from the time of enrollment for the duration of treatment with chemotherapy plus 5-half-lives of chemotherapy plus 30 days (duration of ovulatory cycle) for a total of 30 days post-treatment completion or a duration specified by the local labels of the chemotherapy drugs received, whichever is longer (Arm B).

e) Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab plus 5 half-lives of nivolumab plus 90 days (duration of sperm turnover) for a total of 7 months post treatment completion (for participants treated in Arm A).

   i. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with chemotherapy plus 5 half-lives of chemotherapy plus 90 days (duration of sperm turnover) for a total of 90 days post-treatment completion or a duration specified by the local labels of the chemotherapy drugs received, whichever is longer (for participants treated in Arm B).

f) 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 participants 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 participants 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, participants must agree to use one highly effective method of contraception as listed in Appendix 4.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

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

b) Participants with untreated CNS metastases.

   Participants 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, participants 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) Participants with carcinomatous meningitis.

2. Medical History and Concurrent Diseases

a) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

b) Prior treatment with cetuximab or EGFR inhibitors in any treatment setting.

c) Other active malignancy.

d) Participants with previous malignancies (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, esophageal, colon, 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.

   i) A second primary squamous cell carcinoma of the head and neck is allowed if eligibility is based on a recurrent or a metastatic first primary squamous cell carcinoma of the head and neck.

e) Participants with an active, known or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

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

g) **As of Revised Protocol 02, this criterion is no longer applicable.** *Participants 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) Treatment with botanical preparations (eg herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to randomization/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 testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

c) Inadequate hematologic, renal or hepatic function defined by any of the following screening laboratory values:

   i) WBC < 2000/μL

   ii) Neutrophils < 1500/μL

   iii) Platelets < 100 x 10^3/μL

   iv) Hemoglobin < 9.0 g/dL

   v) **As of Revised Protocol 02, this criterion has been revised as 3.c.vii.** Creatinine > 1.5 x ULN or creatinine clearance < 60 mL/min (using the Cockcroft Gault formula).

   vi) AST/ALT > 3.0 x ULN (> 5 x ULN if liver metastases)

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

viii) Creatinine > 1.5 x ULN or creatinine clearance < 50 mL/min (using the Cockcroft Gault formula). Cisplatin should not be used if creatinine clearance is lower than 60 mL/min

4. Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to platinum-containing compounds or other study drug components

5. Other Exclusion Criteria

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

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

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

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

3.3.3 Women of Childbearing Potential

A woman 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 judgment in checking serum FSH levels. If the serum FSH level is > 40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal:

- 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.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

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

- Any live/attenuated vaccine (eg varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) during treatment and until 100 days post last dose.
- Immunosuppressive agents.
- Immunosuppressive doses of systemic corticosteroids (except as stated in section 3.4.2)
- 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 3.4.3), all other radiation therapy or surgery to any tumor lesion is not permitted during study treatment. Participants who require such non-palliative procedures must be discontinued from study treatment.

3.4.2 Other Restrictions and Precautions

Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization 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 participant attributes (eg, allergy history, diabetic history and renal status), the appropriate imaging modality and contrast regimen for each participant. Imaging contraindications and contrast risks should be considered in this assessment. Participants 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 participant because of an iodinated contrast allergy, then a contrast enhanced MRI of the neck, chest, abdomen and pelvis will be performed.

Specific to MRI, participants with severe renal insufficiency (ie, estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this participant population. In addition, safety screening for contraindications to MRI scanning should be performed according to the MR center's standards prior to each MRI procedure. The ultimate decision to perform MRI in an individual participant in this study rests with the site radiologist, the investigator and the standard set by the local Ethics Committee.

3.4.3 Permitted Therapy

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

Regular concomitant use of bisphosphonates and RANK-L inhibitors for prevention or reduction of skeletal-related events in participants 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 treatment.

Prior radiotherapy must have been completed at least 2 weeks prior to randomization. On study palliative radiotherapy is only allowed for treatment of painful bone lesions. Palliative surgical resection of tumor sites is not permitted. Participants 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 participants must either discontinue study drug treatment or they must meet criteria to continue treatment beyond progression (Section 4.5.6) 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/ipilimumab should be withheld for at least 1 week before, during, and 1 week after radiation. Participants should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs should resolve to Grade ≤ 1 or baseline prior to resuming study treatment.

3.5 Discontinuation of Subjects following any Treatment with Study Drug

Participants MUST discontinue investigational product (study treatment) for any of the following reasons:

- Participant'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 participant
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (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*
- Additional protocol-specified reasons for discontinuation (See Section 4.5.5)
- A maximum of 24 months from the first study treatment (Arm A only)

*In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the BMS Medical Monitor/designee must occur, if local regulations allow.

All participants 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 participant 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 participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records and entered on the appropriate case report form (CRF) page.

3.6 Post Study Drug Study Follow up

Participants 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 is 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 35 days from last dose. Follow-Up Visit 2 is to occur 90 days from Follow-Up Visit 1 (± 7 days). Survival Follow-Up Visits to occur approximately every 3 months 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 participants outside of the protocol defined window (Table 5.1-3). At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contact.

3.6.1 Withdrawal of Consent

Participants 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 participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information. Participants should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study 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 participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant as noted above. Lost to follow-up is defined by the inability to reach the participant after a minimum of three documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records. If it is determined that the participant has died, the site will use permissible local methods to obtain 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 participant's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining participant's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

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 CA209651

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Nivolumab Injection[a]	100 mg/vial (10 mg/mL)	IP	Open Label	10 mL vial containing a clear to opalescent, colorless to pale yellow liquid; may contain particulates; 5 vials/carton	Store 2 to 8°C. Store in original package. Do not freeze. Protect from light.
Ipilimumab Injection	200 mg/vial (5 mg/mL)	IP	Open Label	40 mL vial containing a clear, colorless liquid; may contain particulates; 4 vials/carton	Store 2 to 8°C. Store in original package. Do not freeze. Protect from light.
Carboplatin Solution for IV Injection[b]	450 mg/vial (10 mg/mL)	IP	Open Label	45 mL vial containing a sterile, colorless to slightly yellow aqueous solution; 4 vials/carton	Store at or below 25°C. Protect from light.
Cisplatin Concentrate for solution for infusion[b]	100 mg/vial (1 mg/mL)	IP	Open Label	100 mL vial containing a clear, colorless solution; 4 vials/carton	Do not store above 25°C. Do not refrigerate or freeze. Keep the vial in the outer carton.
Cetuximab solution for infusion[b]	500 mg/vial (5 mg/mL)	IP	Open Label	100 mL vial, colorless solution; 1 vial/carton.	Store in a refrigerator (2°C – 8°C).
Fluorouracil Injection[b]	1 g/vial (50 mg/mL)	IP	Open Label	1 g/20mL/ 1 vial/carton; Clear, colorless to slightly yellow solution.	Do not store above 25°C. Do not refrigerate or freeze. Keep the vial in the outer carton.

[a] May be labeled as either "BMS-936558-01" or "Nivolumab."

[b] These products may be obtained by the investigational sites as local commercial product in certain countries if allowed by local regulations. In these cases, products may be a different pack size/potency than listed in the table. These products should be prepared/stored/administered in accordance with the package insert or summary of product characteristics (SmPC).

4.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as 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 participants. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

- Carboplatin
- Cetuximab
- Cisplatin
- Fluorouracil
- Ipilimumab
- Nivolumab

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 and Dispensing

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% NaCl solution) will not be supplied by the sponsor and should be purchased locally if permitted by local regulations.

For nivolumab and ipilimumab, please refer to the current version of the Investigator Brochures and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information.

4.4 Method of Assigning Participant Identification

After the participant's initial eligibility is established and informed consent has been obtained, the participant must be enrolled into the study by IVRS to obtain the participant number. Every participant that signs the informed consent form must be assigned a participant 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 participant 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 participants that have met all eligibility criteria will be ready to be randomized through IVRS. Tumor cell PD-L1 expression data and HPV p-16 will be transferred directly from analyzing lab to IVRS (or the local HPV p-16 result, if available, can be entered by site directly into IVRS for the oropharyngeal cancer patients during the randomization call). The following information is required for participant randomization:

- Participant number
- Date of birth
- HPV p-16 status (oropharyngeal HPV p-16 positive vs oropharyngeal HPV p-16 negative or non-oropharyngeal) - Oropharyngeal CA sites defined in Appendix 5
- Tumor cell PD-L1 expression status: (≥ 1% vs < 1% or not evaluable)
- Prior chemotherapy (adjuvant/neoadjuvant/multimodal) status (Yes vs No)

Participants meeting all eligibility criteria will be stratified by tumor cell PD-L1 status (expressing [≥ 1%, non-expressing [< 1%] or non-evaluable), HPV p-16 status (oropharyngeal HPV p-16 positive versus oropharyngeal HPV p-16 negative or non-oropharyngeal) and prior chemotherapy status (Yes or No).

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

4.5 Selection and Timing of Dose for Each Participant

The dosing schedule is detailed below in Table 4.5-1.

All participants will be monitored continuously for AEs while on study treatment. Treatment modifications (eg, dose delay, reduction, retreatment, or 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.

Table 4.5-1: Dosing Schedule (Arm A 1 Cycle = 6 weeks, Arm B 1 Cycle = 3 weeks)

	Week 1 ± 3 Days[d]	Week 2 ± 3 Days[d]	Week 3 ± 3 Days[d]	Week 4 ± 3 Days[d]	Week 5 ± 3 Days[d]	Week 6 ± 3 Days[d]
Arm A:[a] Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W[b]	**Cycle 1, Day 1** Nivolumab + Ipilimumab		**Cycle 1, Day 15** Nivolumab		**Cycle 1 Day 29** Nivolumab	
Arm B: [a] **EXTREME Regimen** Cetuximab 400 mg/m^2 initial dose then 250 mg/m^2 weekly + Cis or Carbo + 5-FU Every 3 weeks for up to 6 Cycles followed by 250 mg/m^2 Cetuximab weekly[c] 1 hour infusions	**Cycle 1, Day 1** Cetuximab 2 hr infusion + Cis or Carbo 1 hr infusion + 5-FU (for 4 days, Day 1, 2, 3, 4)	**Cycle 1,Day 8** Cetuximab 1 hr infusion	**Cycle 1, Day 15** Cetuximab 1 hr infusion	**Cycle 2, Day 1** Cetuximab 1 hr infusion + Cis or Carbo 1 hr infusion + 5-FU (for 4 days, Day 1, 2, 3, 4)	**Cycle 2, Day 8** Cetuximab 1 hr infusion	**Cycle 2, Day 15** Cetuximab 1 hr infusion

[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
Arm B: Cetuximab is administered first followed by Cisplatin 100 mg/m^2 or Carboplatin (AUC 5) starting at least 1 hour after the completion of the Cetuximab infusion. 5-FU dose is 1000 mg/m^2 day 1 to day 4 (rounding of dosing for 5-FU is permitted per institutional standards).

[b] Continues until disease progression, discontinuation due to unacceptable toxicity, withdrawal of consent, 24 months maximum from the first study treatment, or study closure

[c] Cetuximab maintenance may be administered every 2 weeks, per local prescribing information.

[d] ± 3 Days window applies to Arm A only

4.5.1 Dosing

4.5.1.1 Nivolumab plus Ipilimumab (Arm A)

Participants randomized to Arm A will receive treatment with nivolumab 3 mg/kg every 2 weeks as a 30-minute infusion and ipilimumab 1 mg/kg every 6 weeks as a 30-minute infusion, starting on Day 1, until progression, unacceptable toxicity, withdrawal of consent, the study ends, or a maximum of 24 months from the first study treatment, whichever occurs first.

When nivolumab and ipilimumab are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The second infusion will always be ipilimumab and will start no sooner than 30 minutes after completion of the nivolumab infusion. Participants who require small volumes may infuse over < 30 minutes but no less than 20 minutes. The second infusion will always be the ipilimumab study treatment and will start after the infusion line has been flushed, filters changed and participant has been observed to ensure no infusion reaction has occurred.

Nivolumab and ipilimumab may be diluted in 0.9% Sodium Chloride Solution or 5% Dextrose solution.

Dosing calculations should be based on the body weight. If the participant's weight on the day of dosing differs by > 10% from the weight used to calculate the prior dose, the dose must be recalculated. All doses should be rounded to the nearest milligram. There will be no dose modifications allowed for both nivolumab and ipilimumab.

Participants may be dosed with nivolumab no less than 12 days from the previous dose. There are no premedications recommended for the first dose of study drug.

Participants should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 4.5.8

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

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. When the dose is based on patient weight (ie, mg/kg), nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL. When the dose is fixed (eg, 240 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 120 mL. Nivolumab infusion must be promptly followed by flush of diluent to clear the line. Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, or pharmacy reference sheet. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

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

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

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

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

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

4.5.1.2 EXTREME Regimen (Arm B)

Participants randomized to Arm B will receive treatment with an initial dose of cetuximab 400 mg/m^2 (over 2 hours infusion) then weekly 250 mg/m^2 (over 1 hour infusion) (or every 2 weeks, per local prescribing information), cisplatin (100 mg/m^2 IV on Day 1) or carboplatin (AUC 5 IV on Day 1) and 5-FU (1000 mg/m^2 continuous IV from Day 1 to Day 4) every 3 weeks per cycle for a maximum of 6 cycles.

Cetuximab maintenance begins after 6 cycles of the cetuximab, cisplatin or carboplatin, and 5-FU are complete and is considered cetuximab alone at 250 mg/m^2 weekly (1 hour infusion). Cetuximab maintenance can continue until progression, unacceptable toxicity, withdrawal of consent, or other reason (see Section 3.5 for complete list of reasons for discontinuing study medication).

The dosing calculations should be based on the body weight. If the participant's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. Doses can be rounded per institutional standards. Participants may be dosed no less than 7 days between doses.

The dose of Carboplatin during chemotherapy will be calculated using the following formula (Calvert equation):

- Carboplatin total dose in mg = AUC x (glomerular filtration rate [GFR] +25)

NOTE: When calculating carboplatin dose, GFR should not exceed 125 mL/min. Thus, the maximum carboplatin dose for AUC of 5 will be 750 mg.

Calculated creatinine clearance (CrCl) will be used to estimate the GFR. The modified Cockcroft-Gault formula below should be used to calculate the creatinine clearance.

- 140 – age (years) x actual weight (kg) / 72 x Serum creatinine (mg/dL) (for females, multiply the result by 0.85)

The actual weight will be used for the calculation of Creatinine Clearance.

If one of the study drugs is discontinued, the other study drugs may be continued for the remainder of the cycles.

Premedications

For cetuximab**:**

The recommended premedication is with an H1 antagonist (eg, 50mg Diphenhydramine) IV 30-60 minutes prior to the first dose; for subsequent doses, premedication should be administered based upon clinical judgement and presence/severity of prior infusion reactions in accordance with local institutional standard practice.

For carboplatin or cisplatin:

The recommended premedication are dexamethasone (dosing according to local standard; an equivalent dose of another corticosteroids may be substituted) and a 5-HT3 receptor antagonist (type per investigator discretion and local standards of care) prior to each dose. Additional use of emetics premedication may be employed at the discretion of the investigator. Refer to the local product label for more detail.

For cisplatin:

Hydration guidelines may be modified at the discretion of the treating physician provided adequate pre- and post-cisplatin hydration is achieved, and renal function remains adequate. One suggested regimen consists of administering cisplatin in 500 cc to 1000 cc of IV fluids following adequate hydration and the establishment of adequate urinary output. It is suggested the pre-cisplatin hydration consist of NS at 500 cc/hr x 1 liter and post-cisplatin hydration consist of 1/2 NS + 10 meq KCl/liter + 1 gram magnesium sulfate/liter + 25 grams mannitol/liter at 500 cc/hr for at least one hour, followed by additional hydration at the discretion of the investigator.

It is suggested that patients receive antiemetic therapy, acute and delayed, including dexamethasone, 5-HT3 serotonin receptor antagonists. However, the specifics of the regimen are at the discretion of the treating physician, provided adequate control is achieved. One potential regimen consists of 20 mg of oral or IV dexamethasone and a high dose of oral or IV 5-HT3 antagonist (such as 2 mg oral or 10 mg/kg IV granisetron, or 32 mg oral or IV ondansetron) on the day of cisplatin administration. Followed by additional anti-emetics consisting of oral dexamethasone and scheduled 5-HT3 serotonin receptor antagonists on days 2-5. For example, 8 mg orally, twice daily for days 2 and 3, and then 4 mg orally, twice daily for days 4 and 5, especially if aprepitant is not given.

All supportive measures consistent with optimal patient care should be used throughout the study. Recombinant erythropoietin or similar compound may be administered for symptomatic and/or progressive > Grade 2 anemia. Agents such as G-CSF may also be used at the investigators' discretion.

The use of cisplatin or carboplatin is at the discretion on the investigator. Switch from cisplatin to carboplatin is allowed. If patients develop specific intolerable cisplatin-associated toxicities (see dose modifications, carboplatin substitution), such as neuropathy, renal impairment, ototoxicity, or nausea/vomiting, carboplatin at an AUC of 5 will be substituted for cisplatin.

Doses of cetuximab, cisplatin or carboplatin and 5-FU (EXTREME regimen) may be interrupted, delayed, reduced or discontinued depending on how well the participant tolerates the treatment. For more details, see Sections 4.5.2 (dose delays), 4.5.3 (dose reductions), 4.5.4 (resuming treatment), and 4.5.5 (discontinuation).

Participants should be carefully monitored for infusion reactions. If an acute infusion reaction is noted, participants should be managed according to Section 4.5.8.

4.5.2 Dose Delays

Recommendations for dose modifications for EXTREME regimen should be considered with local institutional standards.

4.5.2.1 Nivolumab and Ipilimumab (Arm A)

Dose delay criteria apply for all drug-related AEs. Treatment delay is up to 6 weeks for nivolumab and up to 12 weeks for ipilimumab from the last dose are allowable (any dose delays greater than these will require approval from the medical monitor). It is permissible in cases of a dose held due to AE to skip the dose in the cycle in order to bring the patient back on track with the next Cycle visit.

Tumor assessments for all participants should continue as per protocol even if dosing is delayed.

Nivolumab and ipilimumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related AE, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related AE
- 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 adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.
- Participants receiving ipilimumab in combination with nivolumab that have drug-related toxicities that meet the criteria for dose delay, should have both drugs (ipilimumab and nivolumab) delayed until retreatment criteria are met. (Exceptions apply to the retreatment criteria after dose delay of ipilimumab 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 alone.)

- 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.

Rescheduling:

- Nivolumab may be delayed until the next planned ipilimumab dose if the next ipilimumab dose is scheduled within the next 12 days. This will permit periodic ipilimumab dosing to be synchronized with nivolumab dosing.
- Ipilimumab 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 and nivolumab, the dosing days of nivolumab and ipilimumab 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 dose is delayed beyond 6 weeks from the prior ipilimumab dose, then subsequent ipilimumab doses should be rescheduled to maintain the 6 week interval between consecutive ipilimumab doses.
- A dose delay of ipilimumab which results in no ipilimumab dosing for > 12 weeks requires ipilimumab discontinuation, with exceptions as noted in Section 4.5.5.2.

For both nivolumab and ipilimumab: A dose given more than 3 days after the intended dose date will be considered a dose delay. Longer delays may be allowed following discussion with the Study Director/Medical Monitor.

4.5.2.2 EXTREME Regimen

It is permissible in cases of a dose held due to AE to skip the dose in the cycle in order to bring the patient back on track with the next Cycle visit. Cetuximab, cisplatin, carboplatin, and 5-FU should be delayed for the following:

- Presence of febrile neutropenia or neutropenia < 1500 cells/mm^3 for greater than one week despite the use of Growth factors
- Any Grade ≥ 2 non-skin, drug-related adverse event, except for alopecia, fatigue or laboratory abnormalities
- Any Grade 3 skin drug-related AE
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia does not require a dose delay
  - Delay if total bilirubin > 1 x ULN or if AST and/or ALT > 1.5 x ULN occurs concomitant with alkaline phosphatase > 2.5 x ULN
- Any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, warrants skipping the dose of study medication.

Subsequent dose reductions may be required as per Section 4.5.3.2. Participants may receive growth factors (including G-CSF and erythropoietin) at the discretion of the investigator.

A dose given more than 3 days after the intended dose date will be considered a dose delay. A maximum delay of 6 weeks between doses is allowed. Longer delays may be allowed following discussion with the Medical Monitor.

4.5.3 Dose Reductions

4.5.3.1 Nivolumab or Ipilimumab

There will be no dose reductions for nivolumab or ipilimumab.

4.5.3.2 EXTREME Regimen

This section includes information on dose modifications for cetuximab, cisplatin or carboplatin and 5-FU treatment related toxicities.

A maximum of 2 dose reductions per study drug are permitted; if additional reductions are required, that particular study drug must be discontinued. Once a dose has been decreased, it should remain reduced for all subsequent dosing unless dose is further reduced. No dose escalations will be allowed. If one of the study drugs is delayed due to drug related toxicities during a treatment cycle, the other study drugs in the regimen may be administered at the discretion of the investigator; when dosing is resumed, dose reduction should only be applied to the study drug that was withheld.

Participants who discontinue one of the study drugs may, at the investigators discretion continue administration of the other study drugs in the regimen.

For Cetuximab: Dose modifications are permitted, as follows:

Infusion Reactions:

- Reduce the infusion rate by 50% for NCI CTC Grade 1 or 2 and non-serious NCI CTC Grade 3 infusion reactions.
- Immediately and permanently discontinue cetuximab for serious infusion reactions, requiring medical intervention and/or hospitalization.
- See Section 4.5.8.2 for treatment of Cetuximab Infusion Reactions.

Dermatologic Toxicity: Table 4.5.3.2-1 contains the recommended dose modifications for severe (CTCAE v4 Grade 3 or 4) acneiform rash.

Table 4.5.3.2-1: Cetuximab Dose Modification Guidelines for Rash

Severe Acneiform Rash	Cetuximab	Outcome	Cetuximab Dose Modification
1st Occurrence	Delay infusion 1 to 2 weeks	Improvement No Improvement	Continue at 250 mg/m^2 Discontinue Cetuximab
2nd Occurrence	Delay infusion 1 to 2 weeks	Improvement No Improvement	Continue at 200 mg/m^2 Discontinue Cetuximab
3rd Occurrence	Delay infusion	Improvement	Continue at 150 mg/m^2

Table 4.5.3.2-1: Cetuximab Dose Modification Guidelines for Rash			
Severe Acneiform Rash	**Cetuximab**	**Outcome**	**Cetuximab Dose Modification**
	1 to 2 weeks	No Improvement	Discontinue Cetuximab
4th Occurrence	Discontinue Cetuximab permanently		

For Cisplatin, Carboplatin and 5-FU:

Recommendations for dose modifications for cisplatin, carboplatin and 5-FU should be considered with local institutional standards. The dose levels for 5-FU, cisplatin and carboplatin are listed in Table 4.5.3.2-2:

Table 4.5.3.2-2: Dose Levels for 5-FU, Cisplatin, and Carboplatin

	5-FU Dose	Cisplatin Dose	Carboplatin Dose
Starting Dose	1000 mg/m^2	100 mg/m^2	AUC 5.0
Dose Level -1	750 mg/m^2	75 mg/m^2	AUC 4.0
Dose Level -2	560 mg/m^2	56 mg/m^2	AUC 3.0

4.5.3.2.1 Recommended Dose Modifications for Hematologic Toxicity

Dose adjustments are based on nadir blood counts since the preceding chemotherapy administration. Dose level adjustments are relative to that of the preceding administration, and are described in Table 4.5.3.2-3

Table 4.5.3.2-3: 5-FU, Cisplatin, and Carboplatin Dose Modifications for Hematologic Toxicity[a]

Drug Related Toxicity	5-FU	Cisplatin	Carboplatin
Neutrophils (ANC) < 500/mm^3 lasting ≥ 5 days	Decrease by -1 dose level	Decrease by -1 dose level	Decrease by -1 dose level
Febrile neutropenia (body temperature ≥ 38.5°C and ANC < 1,000/mm^3)	Decrease by -1 dose level	Decrease by -1 dose level	Decrease by -1 dose level
Platelets < 25,000/mm^3	Decrease by -1 dose level	Decrease by -1 dose level	Decrease by -1 dose level
Platelets < 50,000/mm^3 with significant bleeding or requiring blood transfusion	Decrease by -1 dose level	Decrease by -1 dose level	Decrease by -1 dose level
Grade 4 hemoglobin (< 6.5 g/100 mL)	Decrease by -1 dose level	Decrease by -1 dose level	Decrease by -1 dose level

[a] If considered in the best interest of the participant, and consistent with local practice, investigators may decide to use supportive measures/treatment, and/or secondary prophylaxis instead of dose reductions for the next cycle.

Also, if toxicity can clearly be attributed to one of the drugs, the investigator may choose to only dose reduce one of the cytotoxics

4.5.3.2.2 Recommended Dose Modifications for Non-hematologic Toxicity

Dose adjustments for non-hematologic toxicity during treatment are described in Table 4.5.3.2-4. All dose modifications should be made based on the worst grade toxicity per CTCAE v4.0.

Table 4.5.3.2-4: 5-FU, Cisplatin, and Carboplatin Dose Modifications for Non-hematologic Toxicity[a]

Drug Related Toxicity	5-FU	Cisplatin	Carboplatin
Nausea/vomiting ≥ Grade 3 despite optimal medical treatment	Decrease by -1 dose level	Decrease by -1 dose level	Decrease by -1 dose level
Stomatitis ≥ Grade 3	Decrease by -1 dose level	Decrease by -1 dose level	Decrease by -1 dose level
Diarrhea ≥ Grade 3 despite optimal medical treatment	Decrease by -1 dose level	Decrease by -1 dose level	Decrease by -1 dose level
Neuropathy (sensory or motor), Grade 2 lasting > 7 days OR Grade 3 lasting < 7 days	No modification	Decrease to -2 dose level	No modification
Neuropathy Grade 4 (sensory or motor)	No modification	Discontinue	No modification
Nephrotoxicity (Creatinine Clearance 50-59mL/min or Grade 3 Creatinine)	No modification	Decrease to -2 dose level or according to local practice	No modification
Total bilirubin > 1.5 x ULN	50% of previous dose	No modification	No modification
Total bilirubin > 2.5 x ULN	25% of previous dose	No modification	No modification
Total bilirubin > 4.0 x ULN	Discontinue	No modification	No modification
Other Grade ≥ 3 toxicities (except fatigue and transient arthralgia and myalgia)	Decrease by -1 dose level	Decrease by -1 dose level	Decrease by -1 dose level

[a] If considered in the best interest of the participant, and consistent with local practice, investigators may decide to use supportive measures/treatment, and/or secondary prophylaxis instead of dose reductions for the next cycle. Also, if toxicity can clearly be attributed to one of the drugs, the investigator may choose to only dose reduce one of the cytotoxics.

4.5.4 Criteria to Resume Dosing

4.5.4.1 Criteria to Resume Nivolumab Dosing (Arm A)

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

- Participants may resume treatment in the presence of Grade 2 fatigue.

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

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

4.5.4.2 Criteria to Resume Ipilimumab Dosing (Arm A)

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

- Participants may resume treatment in the presence of Grade 2 fatigue.
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Participants 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.
- Participants 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.
- Participants 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 which results in no ipilimumab dosing for > 12 weeks requires ipilimumab discontinuation, with exceptions as noted in Section 4.5.5.2.
- Ipilimumab may not be resumed sooner than 6 weeks (± 3 days) after the prior ipilimumab dose.
- In general, participants who meet criteria to resume ipilimumab will also have met criteria to resume nivolumab, so it should be feasible to synchronize dosing of both drugs when resuming

ipilimumab. In order to facilitate this, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted ± 3 day window, as long as consecutive nivolumab doses are given at least 12 days apart.

- One exception to note is when ipilimumab 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 and not related to nivolumab, nivolumab may be resumed when the amylase or lipase abnormality resolves to Grade < 3 but ipilimumab may only be resumed when the amylase or lipase abnormality resolves to Grade 1 or baseline. Investigator attribution of this toxicity to the ipilimumab dosing must be clearly noted in the participant's medical chart. The BMS Medical Monitor should be consulted prior to resuming nivolumab in such participants.

4.5.4.3 Criteria to Resume Chemotherapy Dosing (Arm B)

Participants may resume treatment with study drug when the drug-related AE(s) resolved or returned to baseline value, with the following exceptions below.

- Participants may resume treatment in the presence of ANC ≥ 1500 / mm^3 and Platelets ≥ 100 x 10^3 /μL
- Participants may resume treatment in the presence of Grade 2 fatigue.
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Participants 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.
- Participants with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 4.5.5.3) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed.
- For Cetuximab:
  - Pulmonary Toxicity: Permanently discontinue for confirmed interstitial lung disease.
  - Skin Reaction: If a participant experiences a Grade 3 skin reaction, cetuximab therapy is to be withheld for up to 2 consecutive infusions; the dose level should not be changed. The investigator can also consider concomitant treatment with topical and/or oral antibiotics; topical corticosteroids are not recommended. If the toxicity resolves to Grade 2 or less within 2 weeks, treatment may resume. For repeat occurrences of a Grade 3 skin reaction, see Table 4.5.3.2-1 above.

If the criteria to resume treatment are met, the participant should restart treatment at the next scheduled time-point per protocol. If treatment is delayed > 6 weeks, the participant must be permanently discontinued from study therapy, except as specified in Section 4.5.5.3.

4.5.5 Treatment Discontinuation Criteria

For all participants, 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 participants who discontinue study treatment or who have clinically progressed without radiographic progression, should continue as per protocol until radiographic progression per RECIST 1.1 is determined.

4.5.5.1 Nivolumab Dose Discontinuation (Arm A)

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

- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related 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, uveitis, pneumonitis, bronchospasm, myocarditis, 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 participant 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. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for ipilimumab but not for nivolumab, treatment with nivolumab may continue if ipilimumab is discontinued.

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

4.5.5.2 Ipilimumab Dose Discontinuation (Arm A)

Ipilimumab 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 > 8x 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.
  - 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 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 participant 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 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 participant 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 participant with continued ipilimumab dosing

The assessment for discontinuation of ipilimumab 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 but not for nivolumab, treatment with nivolumab may continue if ipilimumab is discontinued.

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

4.5.5.3 EXTREME Regimen Dose Discontinuation (Arm B)

Treatment should be permanently discontinued for the following:

- Any drug-related Grade 4 toxicity including laboratory abnormalities the subject will be discontinued from the relevant study drug, with the following exceptions:
  - Isolated Grade 4 electrolyte abnormalities not associated with clinical sequelae and are adequately managed and corrected within 72 hours of onset.
  - Grade 4 neutropenia or lymphopenia ≤ 7 days
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions:
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation, except for the following scenarios:
    - Grade 3 drug-related thrombocytopenia associated with bleeding
    - Any of the following drug-related liver function test (LFT) abnormalities:
      - AST or ALT > 8 x ULN
      - Total bilirubin > 5 x ULN
      - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
    - Calculated creatinine decreases to < 60 mL/min based on Cockcroft Gault formula on participants receiving cisplatin. Switch to carboplatin is allowed at the discretion of investigator for the remaining cycles. See re-treatment criteria section 4.5.4.3
- Any dosing delay lasting > 6 weeks, with the following exceptions:
  - If local standards allow dosing delays > 6 weeks for drug-related AEs, contact the BMS Medical Monitor prior to re-initiating treatment.
  - Dosing delays > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor. Prior to reinitiating treatment in a participant with a dosing delay lasting > 6 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 participant with continued treatment.

Participants who discontinue one of the study drugs in Arm B may, at the investigators discretion, continue administration of the other study drugs. For example, if 5-FU is discontinued, cetuximab and platinum agent may be continued at the intended dose and schedule.

4.5.6 Treatment Beyond Disease Progression (Arm A only)

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of PD.

Participants will be permitted to continue on nivolumab combined with ipilimumab for treatment beyond initial RECIST 1.1 defined PD up to a total of 24 months total treatment duration from the start of study treatment as long as they meet the following criteria:

- Investigator-assessed clinical benefit and no rapid disease progression
- Participant is tolerating study treatment
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- **Participant** provides written informed consent prior to receiving additional nivolumab and ipilimumab 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. A follow-up scan should be performed within six (6) weeks ± 1 week of original PD to determine whether there has been a decrease in the tumor size, or continued progression of disease. Subsequent scans should be performed every six (6) weeks ± 1 week until further progression is determined. In the event of unscheduled scans, efforts should be made to get subsequent scan back on the every six (6) weeks ± 1 week until further progression is determined.

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

For the participants 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 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 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**.

4.5.8 Treatment of Infusion Reactions

4.5.8.1 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 NCI 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 participant until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab or ipilimumab 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 ≤ 24 hours)

- Stop the nivolumab or ipilimumab infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further nivolumab or ipilimumab will be administered at

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

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

4.5.8.2 Treatment of Cetuximab Infusion Reactions

Treatment recommendations are provided below and may be modified based on local institutional standards, package inserts, and guidelines as appropriate.

Monitor participants for 1 hour following cetuximab infusions in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (eg, epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen). Monitor longer to confirm resolution of the event in participants requiring treatment for infusion reactions. Immediately and permanently discontinue cetuximab in participants with serious infusion reactions.

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

Remain at bedside and monitor participant until recovery from symptoms. Decrease the cetuximab infusion rate by 50% and monitor closely for any worsening. The total infusion time for cetuximab should not exceed 4 hours.

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 ≤ 24 hours):

Stop cetuximab infusion, administer bronchodilators, oxygen, etc. as medically indicated, and resume infusion at 50% of previous rate once allergic/hypersensitivity reaction has resolved or decreased to Grade 1 in severity, and monitor closely for any worsening.

For **Grade 3 or Grade 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; presser or ventilatory support indicated)

Immediately discontinue infusion of cetuximab and disconnect participant from tubing. Begin an IV infusion of normal saline, and treat the participant as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participants have to be withdrawn immediately from the treatment and must not receive any further cetuximab treatment. Participant should be monitored until the investigator is comfortable that the symptoms will not recur. Cetuximab will be permanently discontinued.

Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery from symptoms. In the 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).

Once the cetuximab infusion rate has been decreased due to an allergic/hypersensitivity reaction, it will remain decreased for all subsequent infusions. If the participant has a second allergic/hypersensitivity reaction with the slower infusion rate, the infusion should be stopped and cetuximab treatment should be discontinued. If there is any question as to whether an observed reaction is an allergic/hypersensitivity reaction of Grade 1 - 4, the sponsor should be contacted immediately to discuss and grade the reaction.

4.6 Blinding/Unblinding

Not applicable.

4.7 Treatment Compliance

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

4.8 Destruction of Study Drug

For this study, study drugs (those supplied by BMS 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 (CA209651)

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	Original IC before start of screening procedures for protocol participation; Study allows for re-enrollment of a participant that has discontinued the study as a pre-treatment failure. If re-enrolled, the participant must be re-consented and assigned a new participant 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	Tumor sample prior to therapy is mandatory for PD-L1 testing (sample to be shipped to Central Lab) and for HPV p-16 testing for participants with oropharyngeal CA (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 2 full block or a minimum of 25 slides, obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen). Contact the Study Director if sufficient tissue is not available.
Screening/Baseline Tumor Assessment	X	Must be performed within 28 days prior to first dose. CT with IV contrast of Neck, Chest, Abdomen, Pelvis (CAP) and all other known sites of disease should be imaged during the screening period. Gadolinium contrast enhanced MRI of the neck and CAP may be obtained if CT iodinated contrast is contraindicated. MRI of brain without and with Gadolinium is required for ALL participants in screening to rule out brain metastases. Note: MRI of the brain is preferred but CT scan is acceptable. CT of the head (with and without contrast) to be performed if MRI is contraindicated or unavailable. TAs following RECIST 1.1 criteria.

Table 5.1-1: Screening Procedural Outline (CA209651)

Procedure	Screening Visit	Notes
Prior Medications	X	Dates and doses of platinum-based therapy plus prior medications subjects received to treat cancer.
ECOG Performance Status	X	During screening; within 28 days prior to the first dose.
Safety Assessments		
Vital Signs	X	Including BP, HR, and temperature. Obtain vital signs at the screening visit and within 72 hours prior to first dose.
Physical Measurements/Physical Examination	X	Height and Weight. BSA. Within 28 days prior to first dose
12 lead ECG		12 Lead ECG Required at Screening, See Section 5.3.4
Assessment of Signs and Symptoms	X	Within 14 days prior to first dose
Concomitant Medication Collection	X	Within 14 days prior to first dose
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 randomization and again within 72 hours 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. Participants 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.

Table 5.1-1: Screening Procedural Outline (CA209651)

Procedure	Screening Visit	Notes
Biomarker Assessments		
Tumor Biopsy sample:	X	See Table 5.6-1 and above.
Study Drug		
Enrollment In IVRS	X	

Table 5.1-2: On Treatment Procedural Outline (All Treatments) CA209651 (All Cohorts)

Procedure	During Treatment Visit [a,b]	Notes
Safety Assessments		
Targeted Physical Examination	X	
Vital Signs	X	Including BP, HR, and temperature prior to dosing for all treatment Arms.
Physical Measurements (including performance status)	X	Weight and ECOG status within 72 hours prior to each dose. The dosing calculations should be based on the body weight. If the participant'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	
Laboratory Tests	X	Arm A: On-study local laboratory assessments should be done within 72 hours prior to each dose. For Arm B: Within 72 hours prior to dosing of Day 1 of each Cycle, and every 3 weeks or more frequently as clinically indicated for weekly cetuximab dosing visits). 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 (ONLY if TSH is abnormal). (Thyroid Function Testing to be evaluated every 6 weeks).
Pregnancy Test (WOCBP only)	X	Serum or urine within 24 hours prior to first dose and then every 4 weeks (± 1 week) regardless of dosing schedule.
Concomitant Medications	X	
Efficacy Assessments		
Tumor Assessment	X	• Tumor assessments should occur every 6 weeks (starting from first dose ± 1 week) for the first 48 weeks, then every 12 weeks (± 1 week) until disease progression or treatment is discontinued, whichever occurs later. If treatment beyond progression is approved, then scanning should continue every 6 weeks ± 1 week until further progression is determined. • CT or MRI of the neck, chest, abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline.

Table 5.1-2: On Treatment Procedural Outline (All Treatments) CA209651 (All Cohorts)

Procedure	During Treatment Visit [a,b]	Notes
		• MRI of the brain (without AND with Gadolinium contrast) is required for participants with a history of brain metastasis. Note: MRI of the brain is preferred but CT scan is a participant acceptable. Surveillance scans should be performed approximately every 12 weeks, or sooner if clinically indicated. (CT of the head without AND with contrast may be performed if MRI is contraindicated).
Outcomes Research Assessment		
FACT-H&N	X	Assessed following randomization but before treatment every 6 weeks (± 1 week) regardless of dosing. Can be collected over the phone at regularly scheduled time if needed.
EQ-5D-3L	X	Assessed following randomization but before treatment every 6 weeks (± 1 week) regardless of dosing. Can be collected over the phone at regularly scheduled time if needed.
Health care resource utilization questions	X	To be completed by the site in CRF
Pharmacokinetic Assessments		
PK samples (Arm A Only)	X	See Table 5.5-1.
Immunogenicity blood samples	X	See Table 5.5-1.
Biomarker Assessments		See Table 5.6-1.
Serum sample: Soluble Biomarkers	X	See Table 5.6-1.
Whole Blood sample: SNP (pre dose D1 only) & Gene expression	X	See Table 5.6-1
Plasma samples	X	See Table 5.6-1
Tumor Biopsy Sample:	X	Tumor biopsy specimens will be obtained from consenting participants within all treatment arms at Week 7 and once disease progression has been documented (See Table 5.6-1). Biopsy should be excisional, incisional or core needle (fine needle aspiration is insufficient) and submitted to central lab see also Table 5.6-1

Table 5.1-2: On Treatment Procedural Outline (All Treatments) CA209651 (All Cohorts)

Procedure	During Treatment Visit [a,b]	Notes
Saliva Sample: Oral microbiome	X	See Table 5.6-1
Clinical Drug Supplies		
IVRS Drug Vial Assignment	X	
Dispense Study Drug	X	Within 3 days from randomization, the participant must receive the first dose of study medication.

[a] For Ipilimumab/Nivolumab Arm: Visits occur every 2 weeks

[b] For EXTREME regimen Arm: Visits occur every 3 weeks

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, phosphate, glucose, amylase, lipase. TSH (+ reflex Free T4 and Free T3 collected ONLY if TSH is abnormal). To be done at FU1, to be repeated at FU2, if study related toxicity persists.
Pregnancy Test (WOCBP only)	X		Serum or urine.
Efficacy Assessments			
Tumor Assessment	X	X	Only for participants 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 the neck, chest, abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline. - MRI of the brain (without AND with Gadolinium contrast) is required for participants with a history of brain metastasis. Note: MRI of the brain is preferred but CT scan is acceptable. Surveillance scans should be performed approximately every 12 weeks, or sooner if clinically indicated. (CT of the head without AND with contrast may be performed if MRI is contraindicated).
Outcomes Research Assessment			
FACT-H&N	X		Can be collected over the phone.
FHNSI-10		X	Can be collected over the phone.

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

Procedure	Follow Up, Visits 1 and 2[a]	Survival Follow-Up Visits [b]	Notes
EQ-5D-3L	X	X	Can be collected over the phone.
Health care resource utilization questions	X		To be completed by the site in CRF
Participant 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 visits 1 (FU1) and 2 (FU2) are in clinic visits. Follow-up visit 1 (FU1) = 30 days from the last dose ± 7 days or coincides with the date of discontinuation (± 7 days) if date of discontinuation is greater than 35 days after last dose, Follow-up visit 2 (FU2) = 90 days (± 7 days) from Follow-up Visit 1

[b] Survival Follow Up Visits may be conducted in clinic or via telephone contact: 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 within any single Screening or Lead-in period will be permitted (in addition to any parameters that require a confirmatory value).

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 participant'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 participants. 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 Interactive Voice Response System (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 randomization and are to include: CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, albumin, Ca, Mg, Na, K, Cl, phosphate, LDH, glucose, amylase, lipase, Thyroid function tests includes TSH, free T4, and free 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

For Arm A: local laboratory assessments should be done within 72 hours prior to each dose.

For Arm B: to be performed within 72 hours prior to dosing of Day 1 of each Cycle, every cycle (3 weeks) or more frequently as clinically indicated for weekly cetuximab dosing visits, including 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). Free T4 and Free T3 assessment will be done only if TSH is abnormal

Participants 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 participants reach the survival follow-up phase either in person or documented telephone calls to assess the participant'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 required 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 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 24 hour window. This is participant to medical monitor 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 participants who have met the eligibility criteria are required to have a 12-lead ECG performed during 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 Time and Events tables in Section 5.1 and according to RECIST 1.1 Appendix 3.

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

Screening (baseline) tumor assessments are to be performed prior to first dose. In addition to the brain/head, neck, chest, abdomen, pelvis, all known sites of disease should be assessed at baseline. Subsequent assessments should include brain (only if brain metastases are detected at screening, or if clinically indicated during the course of the trial), 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 of the brain without and with Gadolinium contrast, including base of skull involvement, is preferred but CT scan is acceptable for all participants, in order to rule out active metastases. A CT of the head (with and without contrast) to be performed if MRI is contraindicated or unavailable.

Radiographic tumor response will be assessed at Week 6 (± 1 week) from first dose date, then every 6 weeks (± 1 week) for the first 12 months (until week 48) and every 12 weeks (± 1 week) thereafter, until disease progression is documented or treatment is discontinued (whichever occurs later). Previously treated CNS metastases are not considered measurable lesions for purposes of RECIST determined response. MRI of the brain (without AND with Gadolinium contrast) is required for participants with a history of brain metastasis. Surveillance scans should be performed approximately every 12 weeks, or sooner if clinically indicated (CT of the head without AND with contrast may be performed if MRI is contraindicated).

CT with PO and IV contrast or contrast-enhanced MRI are the preferred imaging modalities for assessing radiographic tumor response. If a participant 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 participant have a contraindication for CT IV contrast, contrast-enhanced MRI of the head, neck, chest, abdomen and pelvis may be obtained. Every attempt should be made to image each participant using the same image modality, acquisition protocol, and same scanner for all imaging time points.

Use of CT component of a PET/CT scanner: Combined modality scanning such as with 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 participants 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 off-treatment disease progression, the site must complete the tumor assessment pages in TAO documenting disease progression and submit a fresh biopsy sample of metastatic site to Central Lab for biomarker analysis as specified in Section 5.6.3.

In addition, participants receiving nivolumab and ipilimumab treatment beyond progression must continue tumor assessments until such treatment has been discontinued.

Refer to the study Imaging Manual for further guidance on obtaining and submitting study related scans.

5.4.1 Primary Efficacy Assessment

The primary endpoints are OS in participants with PD-L1 CPS ≥ 20 and all randomized participants. See Section 8.3.1 for the definitions of OS. Every effort will be made to collect survival data on all participants including participants 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 participant is not reported, all dates in this study representing a date of participant contact will be used in determination of the participant's last known date alive.

5.4.2 Secondary Efficacy Assessment

Secondary efficacy endpoints include OS in selected subgroups and ORR in participants with PD-L1 CPS ≥ 20 and in all randomized participants. See Section 8.3.2 for the definition of ORR. All randomized participants will be monitored by radiographic assessment every 6 weeks (± 1 week) for the first 12 months (until Week 48) and every 12 weeks (± 1 week) until progression or treatment is discontinued, whichever occurs later, [beginning from the first on-study assessment on Week 6 (± 1 week)], to determine changes in tumor size. RECIST 1.1 criteria will be used for the assessment.

The assessments of progression from the blinded independent central review (BICR) will be used for the principal analyses of PFS.

The assessments of best overall response from the blinded independent central review (BICR) will be used for the principal analyses of ORR. For details regarding response criteria using RECIST 1.1 refer to **Appendix 3.**

5.5 Pharmacokinetic Assessments

Samples for PK and immunogenicity assessments will be collected for all participants receiving nivolumab and ipilimumab as described in Table 5.5-1. All time points are relative to the start of study drug administration. All on-treatment time points are intended to align with days on which study drug is administered, if dosing occurs on a different day, the PK and immunogenicity sampling should be adjusted accordingly. Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual.

Pharmacokinetic and Immunogenicity Collection and Processing

A detailed schedule of PK and immunogenicity evaluations is provided in Table 5.5-1. PK samples will be analyzed for nivolumab/ipilimumab by a validated ligand binding assay. Immunogenicity samples will be analyzed for anti-nivolumab antibodies / anti-ipilimumab antibodies by a validated immunogenicity assay; samples may also be analyzed for neutralizing antibodies by a validated method. Serum samples may be analyzed by an exploratory method that measures anti-drug antibodies for technology exploration purposes; exploratory results will not be reported. Serum samples designated for PK or biomarker assessments may also be used for immunogenicity analysis if required (eg, insufficient volume for complete immunogenicity assessment or to follow up on suspected immunogenicity related AE).

Table 5.5-1: Pharmacokinetic (PK) and Immunogenicity Sample Collections for Nivolumab and Ipilimumab (Arm A)

Study Day[a] (1 Cycle = 6 weeks)	Event (Relative To Dosing) Hour	Time (Relative To Dosing) Hour: Min	Pharmacokinetic Blood Sample for Nivolumab	Immunogenicity Blood Sample for Nivolumab	Pharmacokinetic Blood Sample for Ipilimumab	Immunogenicity Blood Sample for Ipilimumab
C1D1 (Nivolumab dose 1 & Ipilimumab dose 1)	Predose[b]	00:00	X	X	X	X
C1D1	0.5 (EOI[c]	See footnote c	X		X	
C1D15 (Nivolumab dose 2)	Predose[b]	00:00	X	X	X	X
C2D15 (Nivolumab dose 5)	Predose[b]	00:00	X	X	X	X
C4D15 (Nivolumab dose 11)	Predose[b]	00:00	X	X	X	X
D15 of every 4th cycle after C4D15 until end of study treatment or maximum up to two years of treatment	Predose[b]	00:00	X	X	X	X

[a] If ipilimumab is discontinued and nivolumab continues, ipilimumab PK and ADA should be collected only for the next 2 time points (corresponding to nivolumab sample collection) according to the PK table.

[b] Predose samples should be taken prior to the start of the first drug (preferably within 30 minutes). If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected.

[c] EOI: End of Infusion. This sample should be collected at the end of infusion of the second drug administered. If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly. EOI samples may not be collected from the same IV access as drug was administered.

5.6 Biomarker Assessments

A variety of factors that could potentially predict clinical response to nivolumab in combination with ipilimumab will be investigated in peripheral blood and in tumor specimens taken from all participants prior to- and on-treatment and as outlined in Table 5.6-1. Data from these investigations will be evaluated for associations with response, survival (OS, PFS) and/or safety (adverse event) data. In addition, analyses of markers between the treatment arms will provide the necessary data to identify and validate biomarkers with predictive vs. prognostic value. All samples collected may also be used for future exploratory analyses (unless restricted by local requirements) to assess biomarkers associated with SCCHN or immunotherapy treatment. Complete instructions on the collection, processing, handling and shipment of all samples described herein will be provided in a separate procedure manual.

Table 5.6-1: Biomarker Sample Collection Schedule (Arms A and B):

Study Day	Serum[a]	Plasma[a]	Whole Blood		Tumor[b,c]	Saliva
	Soluble Biomarkers	ctDNA	Gene expression	SNP	Biopsy	Oral microbiome
Screening					X	
D1	X	X	X	X (pre-dose)		X (pre-dose)
W3,D1[d]	X	X	X			
W7,D1[d]	X	X	X		X[e]	X
W15,D1[d]	X	X	X			
Progression[e]	X[f]	X[f]	X[f]		X[f]	

[a] Plasma, serum and whole blood should be collected on all patients on study, including active and newly enrolled patients.

[b] All tumor samples may be obtained ± 7 days of the indicated time.

[c] Tumor sample prior to therapy is mandatory. 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 obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen

[d] The Biomarker week collections correspond to the following Cycle visits: W3D1 corresponds to C1D15 for treatment Arms A and B (in cases of no dose delays) W7D1 corresponds to C2D1 for Arm A and C3D1 for Arm B (in cases of no dose delays). W15D1 corresponds to C3D15 for Arm A and C5D15 for Arm B (in cases of no dose delays). Blood samples can follow Cycle visits in cases of dose delays, however the Week 7 biopsy should be collected at week 7 irrespective of dosing delays.

[e] Week 7 (± 7days) Biopsy is optional. If progression occurs within 6 months from first dose and a week 7 biopsy was done, then biopsy samples upon progression (± 7 days) are optional. If progression occurs at greater than 6 months from first dose then progression biopsy is required. On study biopsies should be done if deemed medically safe per investigators judgement.

[f] For samples at progression, the timing of this collection should be after the participant has come off study medication and before they have started new therapy (subsequent anti-cancer therapy). For participants that have consented to be treated beyond progression, it is better to wait to perform the biopsy after further progression of the disease, after they have come off study therapy and before they have started new therapy (subsequent anti-cancer therapy).

5.6.1 Exploratory Serum Biomarkers

Blood samples for exploratory serum biomarker analyses will be drawn at the time points indicated in Table 5.6-1. Samples may be assessed by ELISA, seromics and/or other relevant multiplex-based protein assay methods for immune or SCCHN-related factors that may predict benefit or correlate with efficacy to study treatment. These factors may include levels of soluble PD-L1, anti-tumor antibodies, cytokines, chemokines, inflammatory factors and/or microRNAs (such as, but not limited to, soluble CD25, soluble PD-1, soluble LAG-3, and CXCL-9).

5.6.2 Circulating Tumor DNA in Plasma

Circulating tumor DNA (ctDNA) may be extracted to assess tumor mutation burden or other mutations in the blood. Additional use of these data may include correlative analyses aimed at identifying genotypic associations with clinically-relevant biomarkers identified by other methodologies described in this section.

5.6.3 Tumor Tissue Specimens

Screening Biopsies:

The screening tumor biopsy tissue needs to be shipped and to the central laboratory prior to randomization for tumor cell PD-L1 and HPV p-16 testing (if needed). Two FFPE blocks or 25 slides should be submitted. Contact the Study Director if sufficient tissue is not available. In the event the tumor sample is deemed unevaluable due to insufficient tumor content, the medical monitor may request the site to send another specimen, if available. The presence of either an archival or a fresh biopsy specimen is an inclusion criterion and hence a prerequisite for full eligibility of a participant.

An archived biopsy prior to therapy is acceptable if the fresh biopsy cannot be obtained and if the archived tissue meets the defined criteria as stated below.

- Obtained in the metastatic setting or from an unresectable site of disease obtained within 6 months of enrollment
- An archived biopsy (block or slides) must contain tumor tissue.
- The patient has not received systemic therapy subsequent to archived biopsy and prior to screening.
- If an archived block is not available, 25 slides containing tumor are available for exploratory use.

Biopsy at 7 weeks:

An on-treatment tumor biopsy to be collected at Week 7 (± 7 days) is optional but strongly encouraged. This time point coincides with the completion of the first full cycle of nivolumab + ipilimumab treatment combination and also with the first on-treatment tumor assessment. Pharmacodynamic changes within candidate biomarkers (see Section 5.6.1) within the tumor and tumor microenvironment may inform on mechanism(s) associated with rapid progression (ie, intrinsic resistance) as well as inform on mechanism(s) associated with disease control. Those

biomarkers will be evaluated for their potential utility as early response/non-response prediction biomarkers.

Biopsy at time of Progression:

Changes in biomarkers (including but not limited to genomic alterations, gene expression, and protein expression) in the tumor biopsy collected at progression will be evaluated for their utility in informing the mechanism(s) underlying acquired resistance to nivolumab + ipilimumab combination treatment. For the biopsy at progression, the biopsy should be after the participant has come off study medication and before they have started new therapy (subsequent anti-cancer therapy).

Tumor sample collection details

A minimum of 2 formalin-fixed paraffin embedded (FFPE) tumor tissue block (preferred) OR a minimum of 25 unstained sections are required for assessment of tumor cell PD-L1 status and other biomarker evaluations. Specimens should contain a minimum of 100 evaluable tumor cells.

Tissue Biomarkers:

Tumor samples may be assessed for global gene expression, global protein expression, and/or for tumor mutation burden using a variety of methodologies inclusive of, but not limited to RNA seq (or similar), mass-spectrometry, whole exome sequencing and fluorescent in-situ hybridization (FISH).

Immunohistochemistry (IHC) may be used to assess the number and composition of immune infiltrates in order to define the immune cell subsets present within formalin-fixed, paraffin-embedded (FFPE) tumor tissue before and after exposure to therapy. These IHC analyses will include, but not necessarily be limited to, the following markers: CD4, CD8, FOXp3, PD-1, PD-L1, and PD-L2. HLA and antigen loss variants may be investigated in tumor tissues, focused on HLA class I, antigen processing machinery (APM) components, and expression of common SCCHN tumor antigens including but not limited to HPV oncogenes, EGFR, p53, etc. In cases where fresh tumor is available prior to therapy and/or on treatment, separation and isolation of TIL from tumor and stromal cells may be performed. Isolated TIL may be utilized to assess the gene expression, phenotype, and function of immune cells.

The investigator, in consultation with the radiology staff, must determine the degree of risk associated with the procedure and find it acceptable. Biopsies may be done with local anesthesia or conscious sedation. Institutional guidelines for the safe performance of biopsies should be followed. Excisional biopsies may be performed to obtain tumor biopsy samples. Invasive procedures that require general anesthesia should not be performed to obtain a biopsy specimen. However, if a surgical procedure is performed for a clinical indication, excess tumor tissue may be used for research purposes with the consent of the participant.

5.6.4 Peripheral Blood Gene Expression

Gene expression analyses from whole blood may provide important information on the broad effects of nivolumab on immune modulation. Thus, genomic expression patterns of whole blood

collected at baseline and during on-study treatment as specified in Table 5.6-1 may be assessed by global gene expression profiling using a platform such as, but not limited to RNA seq.

5.6.5 T cell Repertoire Analysis (Whole Blood and Tumor Tissue Sample)

A standing theory in immuno-oncology therapy suggests that a diverse and activated immune environment is better adept at eradicating tumor compared to a skewed repertoire of naïve and tolerized T cells. In order to explore whether a diverse T cell repertoire is predictive of response to therapy, next generation, high-throughput, DNA sequencing will be performed on DNA isolated from peripheral blood and from tumor tissue to quantitate the T-cell receptor repertoire prior to, and on-treatment.

5.6.6 Characterization of Oral Microbiome

The oral microflora of an individual can harbor up to 750 distinct bacterial species. Certain species may induce chronic inflammation or lead to the presence of alcohol or tobacco-related carcinogens. The association of clinical outcomes to nivolumab in combination with ipilimumab with the composition of oral microflora is uncharacterized. In order to better understand whether components of the oral microbiome are associated with drug treatments or disease progression, saliva will be taken prior to therapy and prior to the Week 7 dose for preparation of DNA. Pyrosequencing, or a similar technique, will be performed to characterize oral microflora prior to and post treatment.

5.6.7 Whole Blood for Genomic Analyses

Whole blood samples for exploratory pharmacogenetic assessment will be collected from all participants (unless restricted by local regulations) and put in frozen storage. Genomic DNA will be extracted and subsequently assessed for single nucleotide polymorphisms (SNPs) and other genetic variations in candidate genes that may predispose participants to clinical benefit or adverse events (unless restricted by local requirements.) Such genes may include, but are not limited to, the PD-1 axis as well as to other genes related to immune function. Additional use of these data may include correlative analyses aimed at identifying genotypic associations with clinically-relevant biomarkers identified by other methodologies described in this section. Additionally, genomic DNA from whole blood will be collected and may be used as a comparator for participants with tumors examined by whole exome for tumor mutation burden analyses.

5.6.8 HPV Assessment

Tumor p-16 status is an established clinical surrogate of tumor HPV status, which is a stratification factor in this study (positive/negative status required only for oropharyngeal CA). Evaluation of tumor p-16 status may be performed locally, but the assay is to be performed by use of a mouse monoclonal antibody to p-16 (CINtec E6H4, MTM Laboratories, Heidelberg, Germany) visualized with the Ventana XT.[54] Determination of p-16 status by PCR or ISH is also acceptable.

If documentation of p-16 expression status as per inclusion criterion 2f (local HPV p-16 result) is not available, then a sample needs to be sent to the central laboratory for analysis to ensure full eligibility. Tissue requirements for the central laboratory are either tissue on microscopic slides,

tissue block or a fresh tissue biopsy in formalin. More detail will be provided in the laboratory manual.

5.7 Outcomes Research Assessments

The evaluation of health-related quality of life is an increasingly important aspect of clinical efficacy in oncology trials. Such data provide an understanding of the impact of treatment from the patient's perspective and offer insights into patient experience that may not be captured through physician reporting. Additionally, generic health-related quality of life measures provide data needed for calculating utility values to inform health economic models.

Participants will be asked to complete the EQ-5D-3L and FACT-H&N before any clinical activities are performed during on-study clinic visits and at follow up visits 1 and 2. In addition, the EQ-5D and FHNSI-10 will be completed at designated time points during the survival follow-up phase. The questionnaires will be provided in the participant's preferred language if available and may be administered by telephone during the survival follow-up phase. A standardized script will be used to facilitate telephone administration of the EQ-5D. A similar script does not exist for the FHNSI-10, though participants will be provided with a hard copy of the questionnaire to take home and use as a visual aid during telephone interviews. Participants not able to vocalize responses over the phone will be afforded the opportunity to complete the questionnaires by pen and paper (initialing and dating each page) and return them by mail to the study site. Table 5.1-2 and Table 5.1-3 provide information regarding the timing of participant-reported outcomes assessments.

The EQ-5D is a standardized instrument used to measure self-reports of health status and functioning. The instrument's descriptive system consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels, reflecting "no health problems," "moderate health problems," and "extreme health problems." A dimension for which there are no problems is said to be at level 1, while a dimension for which there are extreme problems is said to be at level 3. Thus, the vectors 11111 and 33333 represent the best health state and the worst health state, respectively, described by the EQ-5D. Altogether, the instrument describes $3^5 = 243$ health states. Empirically derived weights can be applied to an individual's responses to the EQ-5D descriptive system to generate an index measuring the value to society of his or her current health. Such preference-weighting systems have been developed for the UK, US, Spain, Germany, and numerous other populations. In addition, the EQ-5D includes a VAS that allows respondents to rate their own current health on a 101-point scale ranging from "best imaginable" to "worst imaginable" health. The EQ-5D is available for use in over 150 languages.

The FACT-H&N questionnaire will be used to assess the effects of disease symptoms on functioning and well-being. As a generic cancer-related core, the FACT-H&N includes the 27-item FACT-General (FACT-G) to assess physical well-being (PWB; seven items), social/family well-being (SWB; seven items), emotional well-being (EWB; six items), and functional well-being (FWB; seven items). The FACT-H&N includes a 12-item disease-specific Head and Neck Cancer (HNC) subscale that assesses concerns related to vocalization, communication, breathing, eating, swallowing, appearance, and bother due to adverse events. Ten items included in the PWB, EWB,

FWB, and HNC subscales contribute to the scoring of the FHNSI-10, which can be used to provide a targeted assessment of the effects of head and neck cancer symptoms. Each FACT-H&N item is rated on a five-point scale ranging from 0 (not at all) to 4 (very much). Scores for the PWB, FWB, SWB, and EWB subscales can be combined to produce a FACT-G total score, which provides an overall indicant of generic quality of life, while the FACT-G and HNC subscale scores can be combined to produce a total score for the FACT-H&N, which provides a composite measure of general and targeted quality of life. A variant of the total score that is often more sensitive to physical and functional outcomes, the Trial Outcome Index (TOI), can be derived by summing scores for the PWB, FWB, and HNC subscales. All scores are scaled so that higher values indicate better functioning as well as lower symptom burden. The FACT-H&N is available for use in over 40 languages.

In addition to the aforementioned participant-reported outcomes, health care resource utilization data will be collected for all randomized participants using an internal case report form developed for use in previous trials. The form, which is completed by study staff, records information about hospital admissions, including number of days spent in various wards and discharge diagnosis, as well as non-protocol specified visits related to study therapy, including date of visit, reason for visit, and type of visit. The health care resource utilization data will be used to support subsequent economic evaluations.

5.8 Additional Research

Additional research collections and retention are mandatory for all participants, except where prohibited by local laws or regulations, ethics committees, or where a waiver is provided by BMS or their designee. This protocol will include residual sample storage for additional research (AR). This collection for additional research is intended to expand the translational R&D capability at Bristol-Myers Squibb, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health authority requests for analysis, and advancement of pharmacodiagnostic development to better target drugs to the right patients. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression, and response to treatment, etc. All requests for access to samples or data for additional research will be vetted through a diverse committee of the study sponsor's senior leaders in Research and Development to ensure the research supports appropriate and well-defined scientific research activities. Additionally, residual blood and tissue collection will also be retained by the BMS Biorepository in Hopewell, NJ or at a BMS approved third party storage management facility for additional research purposes. Additional research samples will be retained for 15 years or the maximum allowed by applicable law. No additional sampling is required for residual collections. Further details of sample collection and processing will be provided to the site in the laboratory procedure manual.

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 participant administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be

any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.

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

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 participant. Care should be taken not to introduce bias when collecting AE 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.

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.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term

Events NOT Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

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 participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [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)

EVALUATING AES AND SAES

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

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 participant's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures.

All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy). For participants 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 BMS (or designee) within 24 hours of awareness of the event.

SAEs must be recorded on the SAE Report Form;

Pregnancies on a Pregnancy Surveillance Form (electronic or paper forms).

The required 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. When paper forms are used, the original paper forms are to remain on site. 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.

Follow-up of AEs and SAEs

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

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

All SAEs must be followed to resolution or stabilization.

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 participants. All nonserious adverse events (not only those deemed treatment-related) are to be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

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 participant to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the participant to receive specific corrective therapy

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

6.4 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy.

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant participant may continue study drug after a thorough discussion of benefits and risk with the participant, if allowed by local regulations.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

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 BMS. 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. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term.

All instances of accidental overdose and/or dosing errors should be reported on the Dosage Administration Record CRF. (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 participants 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.

Table 6.7.1-1 below provides a summary of the IMAEs category and their respective PTs. This list is participant 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 participants enrolled in this study. The DMC will be charged with assessing such actions in light of an acceptable risk/benefit profile for nivolumab. The DMC will act in an advisory capacity to BMS and will monitor participant safety data for the study.

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.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The primary objectives of this study are to compare OS between treatment groups, in all randomized participants and randomized participants with PD-L1 CPS $\geq$ 20. OS will be compared at the 0.025 alpha level for each of the above two populations.

The OS comparison in all randomized participants will require up to 741 deaths. This number of events ensures that a two-sided, alpha = 0.025 group sequential test using the O'Brien and Fleming spending function and with an interim analysis after approximately 80% of events will have overall 97% power for a HR of 1.2 for the first 7 months and 0.55 thereafter.

Delayed separation of KM curves is included in the alternative hypotheses for OS because it was observed in CA209141, a randomized phase 3 study of nivolumab versus investigator's choice therapy in platinum-refractory, recurrent/metastatic SCCHN,[35] and in KEYNOTE-048, a randomized phase 3 study of pembrolizumab or pembrolizumab with chemotherapy versus cetuximab with chemotherapy in untreated recurrent/metastatic SCCHN.[55]

The final analysis of OS in all randomized participants is projected to occur 51 months after the first patient was randomized. An interim analysis in this population will be performed when approximately 593 deaths occur, or all randomized participants have been followed up for at least 12 months, whichever is later. It is projected for 39 months after the first patient was randomized.

Power for OS comparisons in randomized participants with PD-L1 CPS ≥ 20

At the same time as the OS analysis is done for all randomized participants, OS will also be compared between arms in the randomized participants with PD-L1 CPS ≥ 20 via a two-sided, alpha = 0.025 group sequential test procedure incorporating the O'Brien and Fleming alpha spending function. The group sequential test would have an interim analysis and the final analysis of OS, at which approximately 298 and 372 deaths, respectively, are expected. With this many events, the test procedure would have an overall 99% power if the HR was 1.06 for the first 7 months and 0.45 thereafter. Table 8.1-1 summarizes the statistical assumption and power calculation.

Table 8.1-1: Statistical Assumption and Power Calculation

Primary endpoints	OS for ITT (N = 930)	OS for PD-L1 CPS ≥ 20 (N = 465)
Median OS months (N+I/EXTREME regimen)	13/10.8	14.9/10.8
Average hazard ratio	0.74	0.61
Alpha level (IA/FA)	0.01/0.022	0.01/0.022
Event Number (IA/FA)	593/741	298/372
Critical hazard ratio (IA/FA)	0.81/0.845	0.74/0.788
Power (IA/FA)	66%/97%	87%/99%
Estimated time of LPLV (IA/FA)	39/51 months	39/51 months

All sample size and power calculations were done using EAST 6.4.1.

8.2 Populations for Analyses

- All Enrolled Participants: All participants who signed an informed consent form and were registered into the IVRS.

- All Randomized Participants: All enrolled participants who were randomized to either treatment arm.
- All Randomized PD-L1 CPS ≥ 20 Participants: All randomized participants with PD-L1 CPS ≥ 20
- All Randomized PD-L1 CPS ≥ 1 Participants: All randomized participants with PD-L1 CPS ≥ 1.
- All Treated Participants: All participants who received at least one dose of nivolumab, ipilimumab, cetuximab, cisplatin, carboplatin or 5-FU.
- Treated Participants with PD-L1 CPS ≥ 20: All participants who received at least one dose of nivolumab, ipilimumab, cetuximab, cisplatin, carboplatin or 5-FU and have PD-L1 CPS ≥ 20 at baseline.
- All PK Participants: All participants with available serum time-concentration data
- Immunogenicity Evaluable Participants:
  - Nivolumab ADA Evaluable Participants: all treated participants with baseline and at least 1 post-baseline pre-infusion nivolumab immunogenicity assessment.
  - Ipilimumab ADA Evaluable Participants: all treated participants with baseline and at least 1 post-baseline pre-infusion ipilimumab immunogenicity assessment.
- All PD-L1 Tested participants: All participants, randomized or not, who had a tumor biopsy specimen available for tumor cell expression testing. This includes both randomized and screen failure participants.

Key analyses of study conduct, demographics, and efficacy will be done on the all randomized population and repeated on the randomized PD-L1 CPS ≥ 20 population. Participants in these analyses will be grouped as assigned at randomization.

Key analyses of exposure and safety will be done on the all treated population and repeated on the treated PD-L1 CPS ≥ 20 population. Participants in these analyses will be grouped by treatment received rather than treatment assigned at randomization. (Treatment arm received will be equal to treatment arm as randomized, unless the participant received the non-assigned regimen for all doses.)

8.3 Endpoints

8.3.1 Primary Endpoints

- OS in randomized participants with PD-L1 CPS ≥ 20
- OS in all randomized participants

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

8.3.2 Secondary Endpoints

Overall survival (OS) in randomized participants with PD-L1 CPS ≥ 1. OS is defined the same way as for the primary endpoints.

PFS is defined as the time from randomization to disease progression, using RECIST 1.1 criteria, or, if there is no documented progression, death. (The date of progression will be based on the BICR assessment of progression). Participants who neither progress nor die will be censored on the date of their last tumor assessment. Participants who receive subsequent anti-cancer therapy prior to documented progression, including tumor-directed radiotherapy and tumor-directed surgery, will have their PFS time censored on the date of their last tumor assessment prior to subsequent therapy.

The Objective Response Rate (ORR) is defined as the number of participants with a best overall response (BOR) of complete response (CR) or partial response (PR), divided by the number randomized in the population.

The BOR is defined as the best response, based on RECIST 1.1 criteria, recorded between randomization and either progression or subsequent anticancer therapy (including tumor-directed radiotherapy and tumor-directed surgery), whichever occurs first. (The BOR will be based on BICR assessments). For participants without evidence of RECIST 1.1 progression or subsequent anticancer therapy, all available tumor evaluations will contribute to the BOR assessment.

Duration of objective response (DOR) is the time between the first documented response (CR or PR) and progression, per RECIST 1.1, or, if no progression is reported, death. The DOR of a participant who neither progresses nor dies will be censored as in the primary definition of PFS. DOR is calculated on the subset of participants whose best response was either CR or PR, according to BICR assessments.

8.3.3 Exploratory Endpoint(s)

Overall survival (OS) in randomized participants with tumor cell PD-L1 < 1%, or PD-L1 CPS of < 20, or tumor inflammation score measured as GEP ≥ 10, or tumor mutation burden (TMB) ≥ 7 is defined the same way as for the primary endpoints.

PFS, ORR, and DOR in randomized participants with tumor cell PD-L1 < 1%, or CPS of <20, or tumor inflammation score measured as GEP ≥ 10, or tumor mutation burden (TMB) ≥ 7 is defined the same way as for the secondary endpoints.

ORR and DOR in subpopulation based on selected biomarkers are defined the same way as in the secondary endpoints. Time to Objective Response (TTR) is defined as the time from randomization to the first documented response (CR or PR).

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 National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Tumor cell 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. Participant's PD-L1 expression status using ≥ 1% expression level will be determined prior to randomization:

- Tumor cell PD-L1 expressing (≥ 1% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells)
- Tumor cell PD-L1 non-expressing (< 1% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells)
- Tumor cell PD-L1 non-evaluable

Time to symptom deterioration (TTSD) is defined as the time from randomization to a clinically meaningful decline from baseline in the FHNSI-10 score. A clinically meaningful decline will be defined as a reduction of FHNSI-10 score ≥ 3 points. [56] Subjects who die without a reported deterioration will be considered to have deteriorated on the date of their death. Those who neither deteriorate nor die will be censored at the time of their last FHNSI-10 assessment.

Serum concentration will be used to characterize the PK of nivolumab and ipilimumab using a population PK approach.

Other exploratory endpoints are discussed in detail in the statistical analysis plan

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment arm as randomized using descriptive statistics. These analyses will be done PD-L1 CPS ≥ 20 population and on the all randomized population.

8.4.2 Efficacy Analyses

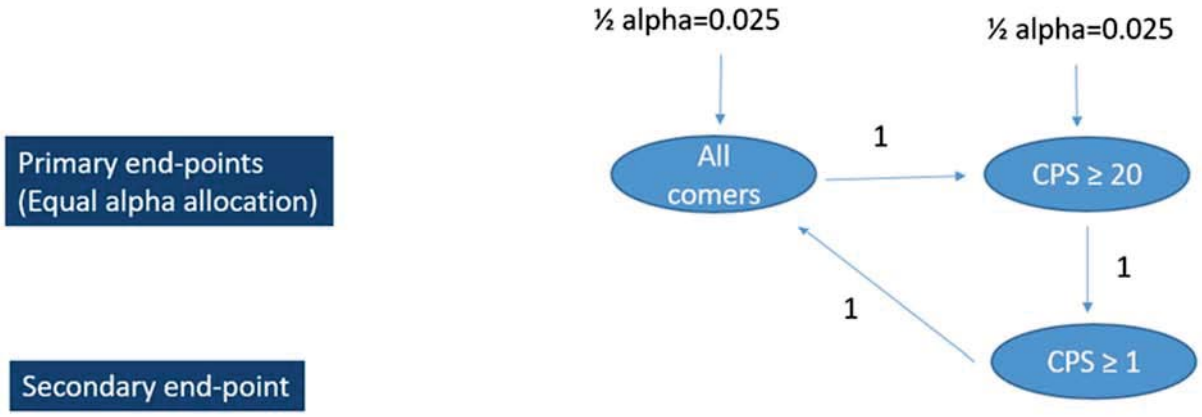
Efficacy analyses will be performed using all randomized participants by treatment group as randomized.

8.4.2.1 Analysis Methods for Primary Endpoints

OS will be compared between arms via a two-sided, overall alpha = 0.025, group sequential log-rank test for each of the two primary endpoints population. The significance levels may be updated through graphical approach where the family-wise error rate will be protected in the strong sense.

Rules for updating significance levels following the Bonferroni-based graphic approach by Maurer and Bretz (2013) will be detailed in the SAP. Figure 8.4.2.1-1: is the graphic display of the testing hierarchy for the endpoints to be tested in this study. The numbers next to the arrows indicate the fraction of alpha that could be passed from the source endpoint to the target endpoint if the source endpoint is statistically significant.

Figure 8.4.2.1-1: testing hierarchy for the endpoints



The nominal significance levels for each look of the group sequential log-rank test will be determined by the alpha spending function with the O'Brien and Fleming boundary based on the actual number of events observed at the time of the analysis. These tests will be stratified by the stratification factors used in the randomization.

An estimate of the hazard ratio (HR) and a corresponding two sided 100*(1 - adjusted α)% confidence interval for the HR will be generated for each endpoint using a stratified Cox proportional hazards model with treatment arm as the sole covariate. The stratification factors will be the same as those used for testing. The level for the confidence interval for the OS hazard ratio will be based on the same nominal significance level for the group sequential log-rank test,.

Survival distributions will be estimated, by arm, via the Kaplan-Meier (KM) product-limit method. Median survival times along with 95% confidence intervals for the medians, will also be presented. The confidence interval for the median will be constructed using a generalization of the Brookmeyer and Crowley method based on a log {-log} transformation of the survival function.[57]

Greater detail on the analyses of primary endpoints, including sensitivity analyses of OS, will be provided in the statistical analysis plan.

8.4.2.2 Analysis Methods for Secondary Endpoints

The analyses of OS in the randomized participants with PD-L1 CPS ≥ 1 population will be similar to those in the randomized participants with PD-L1 CPS ≥ 20, except that testing will be contingent upon a significant result for the primary OS comparison in PD-L1 CPS ≥ 20 population, On the other hand, if the test for this secondary endpoint is significant and the initial test for OS in all randomized participants is not significant, the latter can be retested with full alpha = 0.05.

The analysis of PFS in the participants with PD-L1 CPS ≥ 20 and in all randomized participants will be performed using a stratified Cox proportional hazards model with treatment arm as the sole covariate. An estimate of the hazard ratio (HR) and a corresponding two sided 95% CI for the HR will be generated. Survival distributions will be estimated, by arm, via the Kaplan-Meier (KM)

product-limit method. Median survival times along with 95% CI for the medians, will also be presented. The confidence interval for the median will be constructed using a generalization of the Brookmeyer and Crowley method based on a log {-log} transformation of the survival function. No statistical test will be performed.

ORR and its associated 95% CI will be presented per arm, in all randomized participants and participants with PD-L1 CPS ≥ 20. The confidence interval for ORR will be computed using the Clopper and Pearson method. The odds ratio (OR) and 95% confidence interval for the ratio will be generated using the Cochran-Mantel-Haenszel (CMH) method.

The distribution of DOR will be estimated via the KM method for participants whose best response is PR or CR, by arm. Medians and 6, 9, and 12 month rates will also be estimated. These analyses will be conducted on the all randomized population and PD-L1 CPS ≥ 20 subpopulation.

No statistical test will be performed for ORR, DOR for all randomized participants and participants with PD-L1 CPS ≥ 20.

8.4.3 Safety Analyses

Safety analyses are restricted to treated participants. 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. 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. These analyses will be performed on both the population of treated participants with PD-L1 expressing tumors and on all treated participants.

8.4.4 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. This model may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of nivolumab and to determine measures of individual exposure (such as steady-state peak, trough, and time-averaged concentration). In addition, model determined exposures may be used for exposure-response analyses. Results of population PK and exposure response-analyses will be reported separately.

8.4.5 Biomarker Analyses

Analyses of PD-L1 expression will include:

- KM Plots of efficacy by arm for each PD-L1 CPS status subset (analyses with PD-L1 CPS cutoff of ≥ 20, ≥ 1, < 20, and other exploratory cut-points). This analysis will include HRs of the experimental to control arm within subset and corresponding 95% CI.
- KM Plots of PFS and OS by arm for each tumor cell PD-L1 status subset (< 1%, ≥ 1%, unknown). (Similar analyses with 5%, 10%, 50%, other exploratory PD-L1 cutoffs will be conducted). This analysis will include HRs of the experimental to control arm within subset and corresponding 95% CI.

- Box plots of PD-L1 expression at baseline versus response status, by treatment group
- Odds ratios for tumor response of the experimental to the control arm by PD-L1 status subset and corresponding 95% CI
- Model-based assessment of the interaction between treatment and PD-L1 status for PFS, OS, and ORR.

The analyses of tumor mutational burden (TMB) and tumor inflammation gene expression profile (GEP) will also include KM plots by TMB and GEP subgroups, box plots of TMB by response, and model based assessments of interaction between treatment and TMB/GEP for PFS, OS, and ORR.

Associations between other potential biomarkers and efficacy and safety may be investigated as well. These analyses will be completed with biomarkers measured in blood and in tumor samples and will focus primarily on SNPs in select genes associated with immunity or on the expression of PD-1 and PD-L2 proteins in tumor specimens. Similar analyses may be completed with data regarding serum-soluble factors, serum miRNA content, T-cell populations, and putative additional analyses to be completed using FFPET. Associations between biomarkers and efficacy measures will be analyzed on all randomized participants with available biomarker data. Efficacy measures will include response, PFS, and OS. Demographic and case-history factors will be examined to determine whether stratification or adjustments should be made within the subsequent statistical analyses, and if necessary, the appropriate stratification or adjustment will be made. Biomarkers will be summarized graphically as they relate to efficacy and safety endpoints, as applicable. Summary statistics may be tabulated. SNP allele frequencies may be summarized. The relationships between binary measures (eg. response) and candidate biomarkers will be investigated using logistic regression. Associations may be summarized in terms of point and interval estimates of hazard ratios, odds ratios, or other statistics, as appropriate for the analyses completed. Models to predict clinical activity based on combinations of biomarkers may also be investigated. Additional post hoc statistical analyses not specified in the protocol, such as alternative modeling approaches may be completed. All analyses described above are based on the availability of the data.

8.4.6 Outcomes Research Analyses

Exploratory analyses of EQ-5D and FACT-H&N (including FHNSI-10) data will be performed in randomized participants who have an assessment at baseline (Day 1, assessment prior to administration of drug on day of first dose) and at least 1 subsequent assessment while on treatment. Questionnaire completion rate, defined as the proportion of questionnaires actually received out of the expected number, will be calculated and summarized at each assessment point.

EQ-5D data will be described by treatment group as randomized in the following ways:

- EQ-5D index scores and post-baseline changes in scores will be summarized at each assessment time point using descriptive statistics (ie, N, mean with SD and 95% CI, median, first and third quartiles, minimum, maximum). In the base case, scores will be calculated using the UK preference-weighting algorithm.

- EQ-5D VAS scores and post-baseline changes in scores will be summarized at each assessment time point using descriptive statistics (ie, N, mean with SD and 95% CI, median, first and third quartiles, minimum, maximum).
- The proportion (N) of participants reporting no, moderate, or extreme problems will be presented for each of the 5 EQ-5D dimensions at each assessment time point. Participants with missing data will be excluded from the analysis.
- A by-participant listing of the level of problems in each dimension, corresponding EQ-5D health state (ie, 5-digit vector), EQ-5D index score, and EQ-5D VAS score will be provided.

FACT-H&N data collected during on-study clinic visits and at follow up visits 1 and 2 will be described by treatment group as randomized in the following ways:

- Scores and post-baseline changes in scores for the following components of the FACT-H&N will be summarized at each assessment time point using descriptive statistics (ie, N, mean with SD and 95% CI, median, first and third quartiles, minimum, maximum): FACT-G, PWB, SWB, EWB, FWB, HNC, FHNSI-10, FACT-H&N TOI, FACT-H&N total, and individual FACT-H&N items.

FHNSI-10 data will be described by treatment group as randomized in the following ways:

- Scores and post-baseline changes in scores will be summarized at each assessment time point (i.e., first, second, third, etc. survival follow-up visit recognizing that the timing of visits will vary among participants) using descriptive statistics (ie, N, mean with SD and 95% CI, median, first and third quartiles, minimum, maximum).
- The proportion (N) of participants with symptomatic deterioration, defined as a clinically meaningful decline in score (worsening from baseline ≥ 3 points) or death, will be summarized at each assessment time point (ie, first, second, third, etc. survival follow-up visit recognizing that the timing of visits will vary among participants).
- Time to symptom deterioration (TTSD) will be estimated using the KM product-limit method, by arm as randomized. Two-sided 95% confidence intervals for median TTSD will be computed.

Analyses of patient-reported outcomes will be performed on both the randomized PD-L1 CPS ≥ 20 population and the all randomized population.

8.4.7 Other Analyses

Methodology for exploratory analyses including immunogenicity is described in the statistical analysis plan.

8.5 Interim Analyses

A formal interim analysis for superiority of OS will be performed after approximately 593 OS events (out of 741 required) have occurred on all randomized participants, or all randomized participants have been followed up for at least 12 months, whichever is later. Both primary endpoints will be tested at interim using the group sequential test procedure with initial overall

alpha = 0.025 for each. The overall alpha will be updated following the graphical procedure (Figure 8.4.2.1-1:). The stopping boundaries for the interim and final analyses will be determined by the O'Brien and Fleming alpha spending function, based on the actual number of events observed.

If interim comparison of OS in either all randomized participants or randomized participants with PD-L1 CPS ≥ 20 is significant, the DMC will inform the sponsor, as described in the DMC charter. If comparison of OS in the randomized participants with PD-L1 CPS ≥ 20 is significant, OS in randomized participants with PD-L1 CPS ≥ 1 will be subsequently tested using group sequential testing procedure. The overall alpha for this secondary endpoint will be determined following the graphical procedure which is detailed in the SAP.

The DMC will have access to periodic un-blinded interim reports of efficacy and safety to allow a risk/benefit assessment. Details will be included in the DMC charter.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects/participants.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from participants 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 participants prior to enrollment.

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

9.1.2 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and

accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

9.1.3 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. Certain CRF pages and/or electronic files may serve as the source documents.

In addition, the study may be evaluated by BMS 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.

9.1.3.1 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.

9.1.4 Study Treatment Records

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

9.1.5 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator 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, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator 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, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

Supplied by BMS (or its vendors)

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:

- 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 participant, including unique participant identifiers
- amount transferred to another area/site for dispensing or storage
- non study disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS

retain samples for bioavailability/bioequivalence, if applicable dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

Source 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 treatment integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy.

BMS 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 BMS 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 Sponsor or designee.

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

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

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub investigator and who is delegated this task on the Delegation of Authority Form. Sub investigators 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 BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.2.4 Clinical Study Report and Publications

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

For each CSR related to this protocol, the following criteria will be used to select the signatory investigator:

- Study Steering Committee

- Participant recruitment (eg, among the top quartile of enrollers)
- Regional representation (eg, among top quartile of enrollers from a specified region or country)

9.2.4.1 Scientific Publications

The data collected during this study are confidential and proprietary to BMS. 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.

Scientific Publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any principal investigator, sub-investigator or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications at BMS is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). Authorship selection is based upon significant contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

1. Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable participants with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights and conclusion); AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those who make the most significant contributions, as defined above, will be considered by BMS for authorship of the primary publication. Sub-investigators will generally not be considered for authorship in the primary publication. Geographic representation will also be considered.

Authors will be listed by order of significant contributions (highest to lowest), with the exception of the last author. Authors in first and last position have provided the most significant contributions to the work.

10 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
ACTH	adrenocorticotropic hormone
AIDS	Acquired Immune Deficiency Syndrome
ALP	Alkaline phosphatase
ALT	alanine aminotransferase
ANC	Absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BID, bid	bis in die, twice daily
BICR	Blinded Independent Central Review
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
Ca++	calcium
CBC	complete blood count
CD279	Cluster of differentiation 279
CFR	Code of Federal Regulations
CI	confidence interval
C1-	chloride
cm	centimeter
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
CPS	combined positive score
CR	Complete Response
CRC	Clinical Research Center
CRF	Case Report Form, paper or electronic
CTA	Clinical Trial Agreement
CTLA-4	cytotoxic T-lymphocyte-associated protein 4

Term	Definition
CV	coefficient of variation
CT	Computed tomography
CTC	Common Terminology Criteria
D/C	discontinue
DILI	Drug Induced Liver Disease
Dl	deciliter
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4th Edition)
EA	extent of absorption
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEG	electroencephalogram
eg,	exempli gratia (for example)
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
ECOG	Eastern Cooperative Oncology Group
ESR	Expedited Safety Report
5-FU	Fluoracil
FACT-H&N	Functional Assessment of Cancer Therapy-Head & Neck
FDA	Food and Drug Administration
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
g	gram
GC	gas chromatography
GCP	Good Clinical Practice
h	hour

Term	Definition
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCO3-	bicarbonate
HCG	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
IMP	investigational medicinal products
IND	Investigational New Drug
IRB	Institutional Review Board
IU	International Unit
IV	intravenous
IVRS	Interactive Voice Response System
K	slope of the terminal phase of the log concentration-time curve
K+	potassium
kg	kilogram
KM	Kaplan-Meier
L	liter
LDH	lactate dehydrogenase

Term	Definition
mg	milligram
Mg++	magnesium
MIC	minimum inhibitory concentration
min	minute
Ml	milliliter
MRI	Magnetic resonance imaging
MRT	mean residence time
MS	mass spectrometry
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
PD	Progressive Disease
PD-1	Programmed Death-1
PD-L1	Programmed death-ligand 1
PD-L2	Programmed death-ligand 2
PFS	Progression free survival
PK	pharmacokinetics
PO	per os (by mouth route of administration)
QD, qd	quaque die, once daily
RANK-L	Receptor activator of nuclear factor kappa-B ligand
RBC	red blood cell

Term	Definition
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SCCHN	Squamous Cell Carcinoma Head and Neck
SD	standard deviation
SmPC	summary of product characteristics
SOP	Standard Operating Procedures
t	temperature
T	time
T3	triiodothyronine
T4	thyroxine
TAO	Trial Access Online, the BMS implementation of an EDC capability
TID, tid	ter in die, three times a day
TTSD	Time To Symptom deterioration
TSH	Thyroid-stimulating hormone
VAS	Visual Analog Scale
WBC	white blood cell
WOCBP	women of childbearing potential

11 REFERENCES

1 Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011 ; 6(2):69-90

2 NCI SEER Statistics Review http://seer.cancer.gov/statfacts/html/oralcav.htmlaccessed March 5,2016

3 Leemans CR, Braakhuis B, Brakenhoff R. Molecular biology of head and neck cancer. Nature Reviews Cancer Vol 11 Jan 2011

4 NCCN Guidlines Version 2.2014 Head and Neck Cancers

5 Vermoken et al Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116-27

6 Ferris et al. Nivolumab vs investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck: 2-year long-term survival update of CheckMate 141 with analyses by tumor PD-L1 expression. Oral Oncology 81 (2018) 45–51

7 Cohen et al. The Lancet. VOLUME 393, ISSUE 10167, P156-167, JANUARY 12, 2019)

8 B Burtness, K J Harrington, R Greil, et al. Phase III study of first-line pembrolizumab (P) for recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). Annals of Oncology, Volume 29, Issue suppl_8, October 2018, mdy424.045

9 Phase III study of first-line pembrolizumab (P) for recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). Annals of Oncology, Volume 29, Issue suppl_8, October 2018, mdy424.045

10 Chaturvedi AK, Engels EA, Anderson WF, et al. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. J Clin Oncol 2008;26:612-9

11 Argiris A, Heron DE, Smith RP, et al. Induction Docetaxel, Cisplatin, and Cetuximab Followed by Concurrent Radiotherapy, Cisplatin, and Cetuximab and Maintenance Cetuximab in Patients With Locally Advanced Head and Neck Cancer. J Clin Oncol 2010;28:5294-300.

12 Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol. 2011 Nov 10;29(32):4294-301.

13 Ang KK, Harris J, Wheeler R, et al. Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer. NEJM 2010;363:24-35.

14 Brizel DM, Albers ME, Fisher SR, et al. Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. N Engl J Med 1998;338:1798-804

[15] Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemo radiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol 2003;21:92-8.

[16] Gilbert J, Li Y, Pinto HA, et al. Phase II trial of taxol in salivary gland malignancies (E1394): a trial of the Eastern Cooperative Oncology Group. Head Neck 2006;28:197-204

[17] Posner MR, Hershock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 2007;357:1705-15.

[18] Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006;354:567-78

[19] Fakhry C, Westra WH, Li S, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst 2008;100:261-9.

[20] Mellman I, Coukos G & Dranoff G. Cancer immunotherapy comes of age. Nature 2011 Dec 22;29 4 8 0:480-89

[21] Alberts AE, Strauss L, Liao T, et al. T cell-tumor interaction directs the development of immunotherapies in head and neck cancer. Clinical and Developmental Immunology 2010 doi: 10.1155/2010/236378 epub.

[22] Leibowitz MS, Pedro A, Fiho A, Ferrone S, Ferris RL. Deficiency of activated STAT 1 head and neck cancer cells mediates TAP1-dependent escape from cytotoxic T lymphocytes. Cancer Immunol Immunotherapy 2011;60:525-535

[23] Cho YA, Hong SD. Relation between expression of PDL-1 and tumor infiltrating lymphocytes in oral squamous cell carcinoma. Oral Oncology 2011;12:1148

[24] Albers A, Abe K, Hunt J, et al. Antitumor activity of human papillomavirus type 16 E7-specific T cells against virally infected squamous cell carcinoma of the head and neck. Cancer Res 2005;65(23):11146-55.

[25] Dong H, Chen L. B7-H1 pathway and its role in the evasion of tumor immunity. J Mol Med 2003;81(5):281-7

[26] Thompson RH, Kuntz SM, Leibovich BC, et al. Tumor B7-H1 is associated with poor prognosis in renal cell carcinoma patients with long-term follow-up. Cancer Res 2006;66(7):3381-5

[27] Ohigashi Y, Sho M, Yamada Y, et al. Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand-2 expression in human esophageal cancer. Clin Cancer Res 2005;11(8):2947-53.

[28] Wu C, Zhu Y, Jiang J, et al. Immunohistochemical localization of programmed death-1 ligand-1 (PD-L1) in gastric carcinoma and its clinical significance. Acta Histochem 2006;108(1):19-24.

[29] Nomi T, Sho S, Akahori T, et al. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. Clin Cancer Res 2007;13(7):2151-7

[30] Zitvogel L, Tesniere A, Kroemer G. Cancer despite immunosurveillance: immunoselection and immunosubversion. Nat Rev Immunol 2006;6:715-27.

[31] Taube, J. Anders RA, Young GD, et al. Colocalization of inflammatory response with B7-H1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape. Sci Transl Med 2012;4(127):127ra37

[32] Seiwert TY. A phase Ib study of MK-3475 in patients with human papillomavirus (HPV)-associated and non-HPV-associated head and neck (H/N) cancer. J Clin Oncol. 32:5s, 2014 suppl; abstr 6011

[33] https://www.agilent.com/cs/library/usermanuals/public/29219_pd-l1-ihc-22C3-pharmdx-gastric-interpretation-manual_us.pdf

[34] Brahmer J, Reckamp K, Baas P et al. Nivolumab versus docetaxel in squamous-cell non-small-cell lung cancer. N Engl J Med 2015;373:123-35.

[35] Robert L. Ferris, George Blumenschein Jr, Jerome Fayettec, Joel Guigay et al.Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med 2016; 375:1856-1867

[36] Robert L. Ferris, George Blumenschein Jr, Jerome Fayettec, Joel Guigayd,et al. Nivolumab vs investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck: 2-year long-term survival update of CheckMate 141 with analyses by tumor PD-L1 expression. Oral Oncology. Volume 81, June 2018, Pages 45–51.

[37] Larkin J, Chiarion-Sileni V, Gonzalez R et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med 2015;373:23-34.

[38] Study of Nivolumab (BMS-936558) in Combination With Gemcitabine/Cisplatin, Pemetrexed/Cisplatin, Carboplatin/Paclitaxel, Bevacizumab Maintenance, Erlotinib, Ipilimumab or as Monotherapy in Subjects With Stage IIIB/IV Non-small Cell Lung Cancer (NSCLC) (CheckMate 012) ClinicalTrials.gov Identifier: NCT01454102

[39] An Open-Label, Trial of Nivolumab, or Nivolumab Plus Ipilimumab, or Nivolumab Plus Platinum-doublet Chemotherapy Versus Platinum Doublet Chemotherapy in Subjects With Stage IV Non-Small Cell Lung Cancer (NSCLC) (CheckMate 227) ClinicalTrials.gov Identifier: NCT02477826

[40] Andrea Ardizzoni; Rafael Rosell, et al. Cisplatin- Versus Carboplatin-Based Chemotherapy in First-Line Treatment of Advanced Non – Small-Cell Lung Cancer: An Individual Patient Data Meta-analysis JNCI J Natl Cancer Inst (2007) 99 (11): 847-857

[41] Brahmer J, et al, Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small –Cell Lung Cancer. N Engl J Med 2015;373:123-35.

[42] Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer. N Engl J Med 2015; 373:1627-1639.

[43] Belani CP, Ramalingam S, Perry MC, et al. Randomized, phase III study of weekly paclitaxel in combination with carboplatin versus standard every-3-weeks administration of carboplatin and paclitaxel for patients with previously untreated advanced non-small-cell lung cancer. J Clin Oncol 2008; 26: 468-73.

[44] F. Hodi et al, Improved Survival with Ipilimumab in Patients with Metastatic Melanoma, N Engl J Med 2010; 363:711-723August 19, 2010.

[45] Brahmer J, Horn L, Jackman D, et al. Five-year follow-up from the CA209-003 study of nivolumab in previously treated advanced non-small cell lung cancer: clinical characteristics of long-term survivors. Oral presentation presented at: American Association for Cancer Research (AACR) Annual Meeting; April 1-5, 2017; Washington, DC, USA.

[46] Caroline Robert et al. Long-term outcomes in patients with ipilimumab-naive advanced melanoma in the phase 3 KeyNote-006 study who completed pembrolizumab treatment; Journal of Clinical Oncology 2017 35:15_suppl, 9504-9504.

[47] Schadendorf D. Efficacy and quality of life outcomes in patients with advanced melanoma who discontinued treatment with nivolumab (NIVO) plus ipilimumab (IPI) due to toxicity in a phase III trial (CheckMate 067). 2016 Annual Meeting of the European Association of Dermato-Oncology.

[48] Spigel DR, et al. Randomized results of continuous vs 1-year fixed-duration in patients with advanced non-small cell lung cancer. Oral presentation at the European Society of Medical Oncology Annual Meeting. 2017 Sep 8-12; Madrid, Spain.

[49] Sharpe AH, Wherry EJ, Ahmed R, et al. The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. Nat Immunol 2007;8(3):239-45)

[50] Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 20/5/2014)

[51] Postow MA, Harding J, Wolchok JD. Targeting immune checkpoints: Releasing the restraints on anti-tumor immunity for patients with melanoma. Cancer J 2012; 18:153-159

[52] Nivolumab (BMS-936558) Investigator Brochure

[53] Ipilimumab (BMS-734016) Investigator Brochure

[54] Ventana CINtec p-16 Histology Prescribing Information. Ventana Medical System. Tucson, AZ. 2015.

[55] Burtness B, Harrington KJ, Greil R, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. Lancet. 2019;394:1915-1928.

[56] Yount S et al. A randomized validation study comparing embedded versus extracted FACT Head and Neck Symptom Index scores. Qual Life Res (2007) 16:1615–1626.

[57] Klein, JP, Moeschberger, ML, Survival Analysis, Techniques for Censored and Truncated Data, New York, Springer-Verlag, 1997.

APPENDIX 1 ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS [a]	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

[a] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, and Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-655.

APPENDIX 2 MANAGEMENT ALGORITHMS

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

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

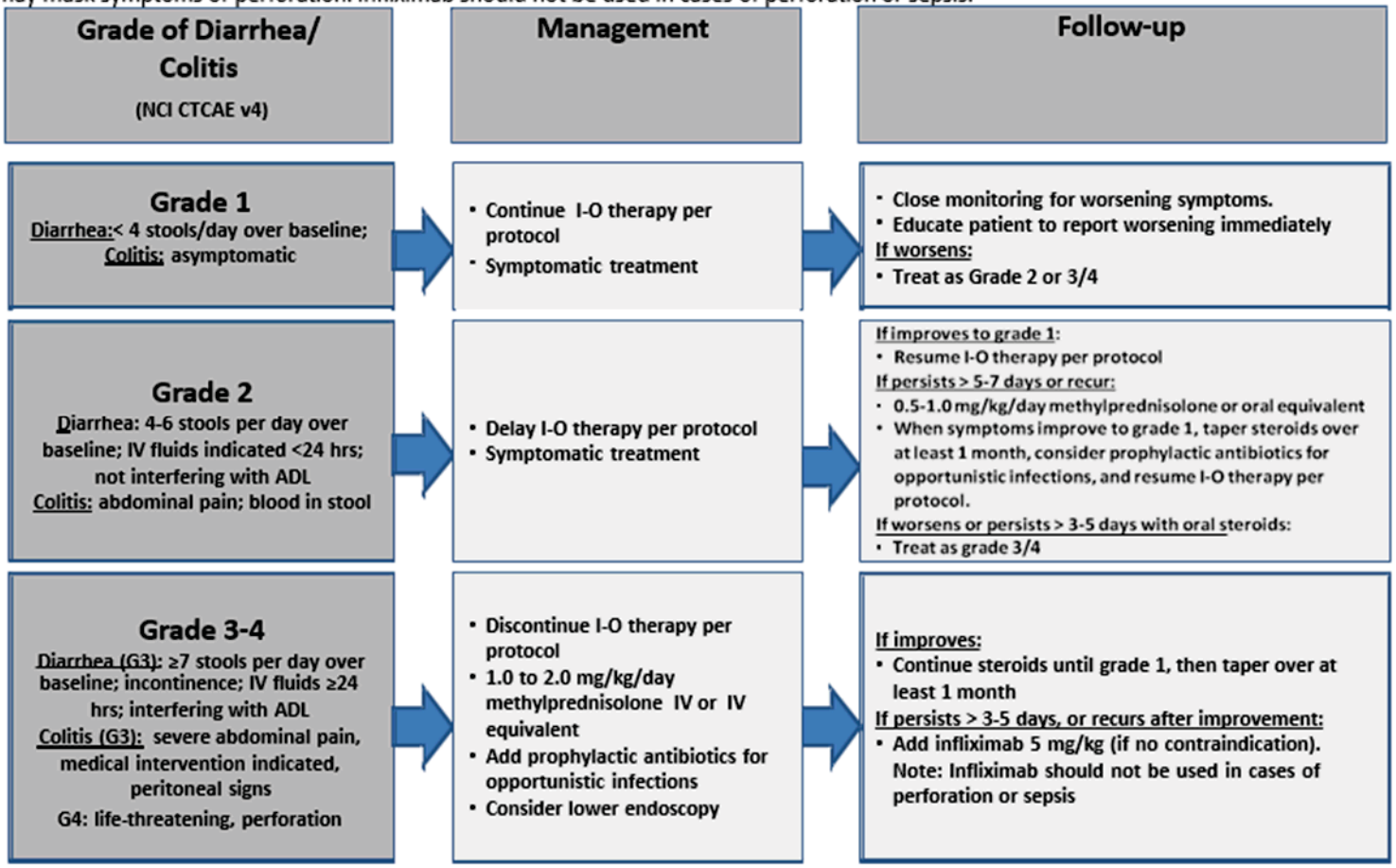
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

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

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

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

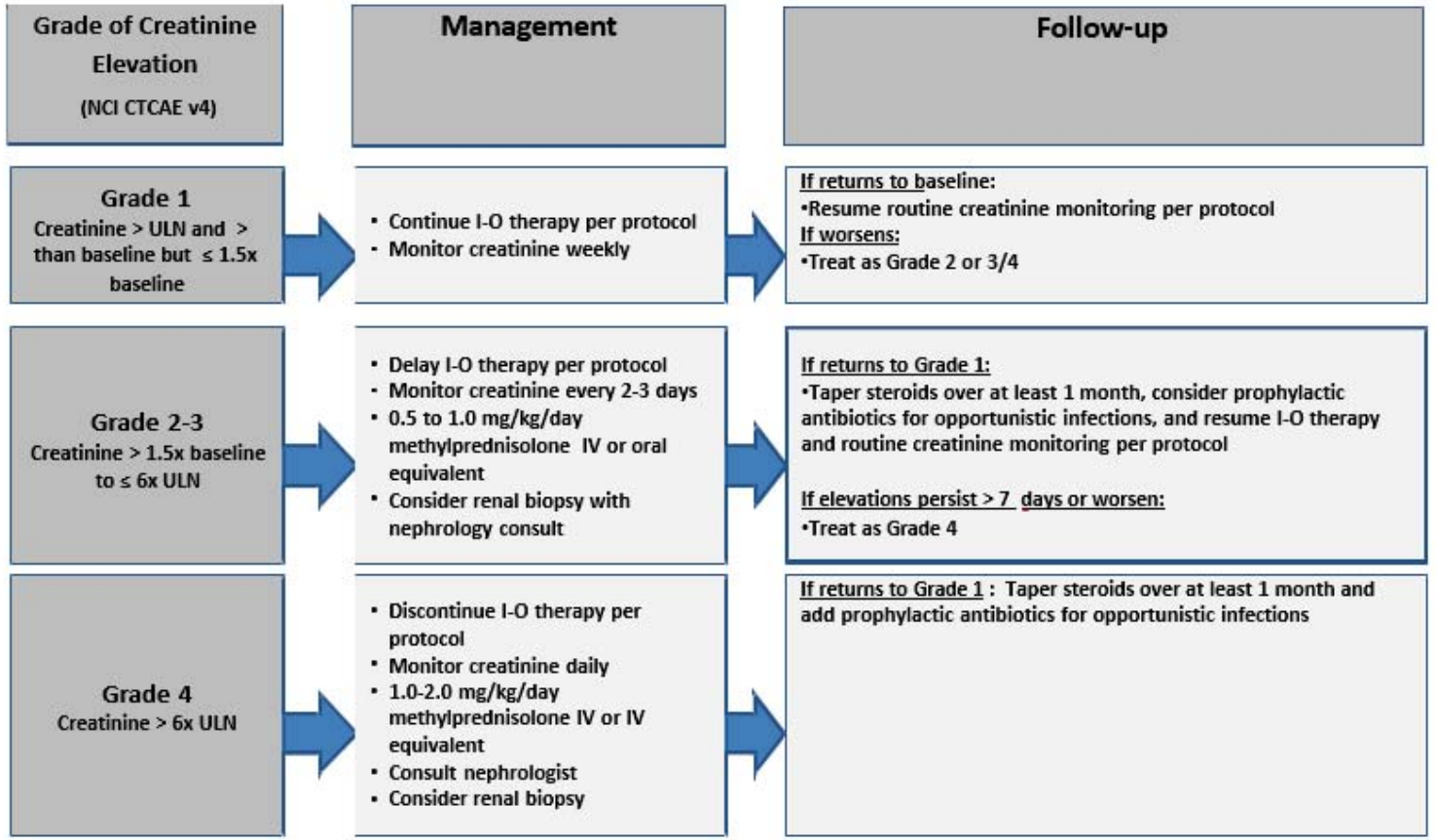


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

27-Jun-2019

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

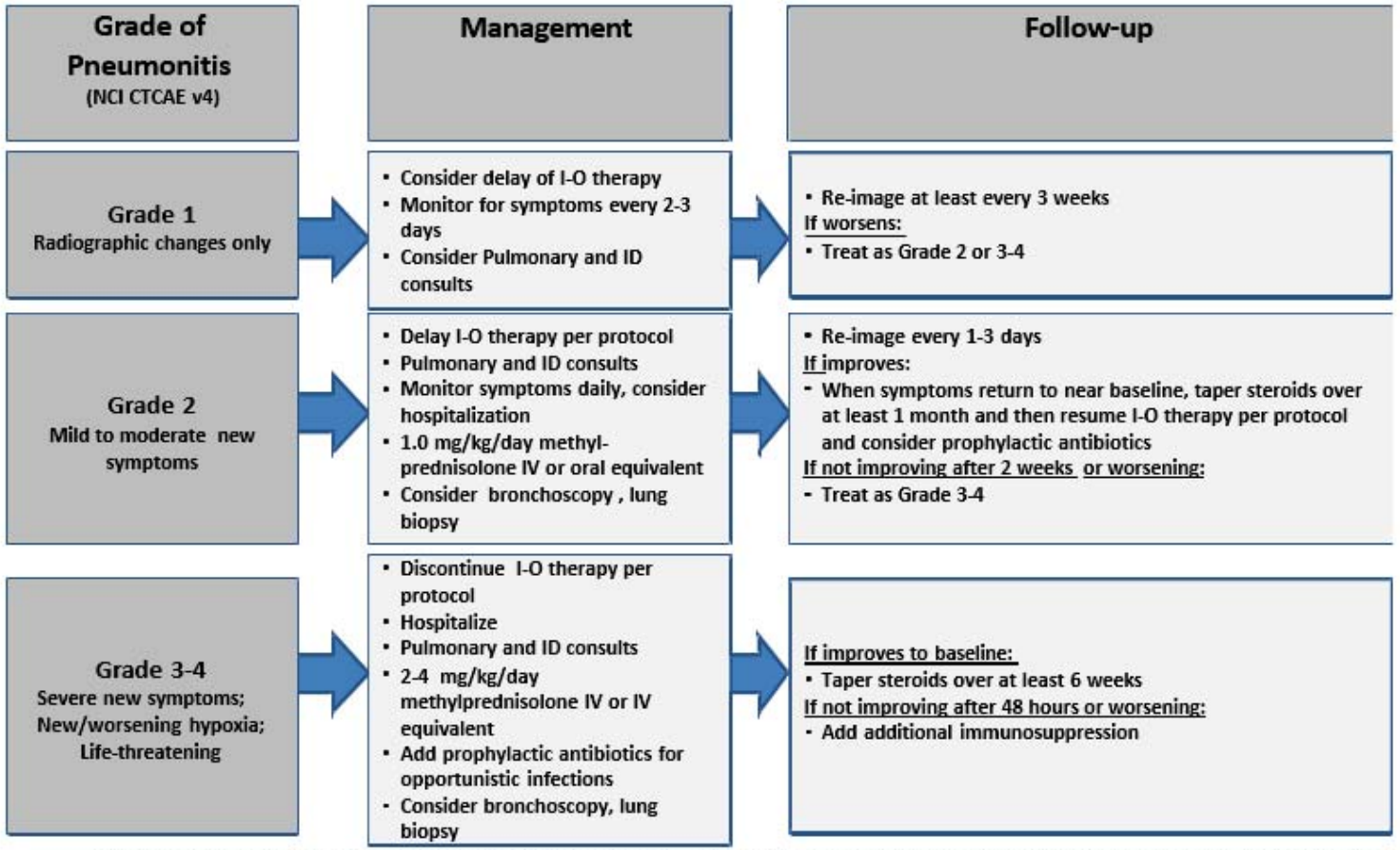


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

27-Jun-2019

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids

27-Jun-2019

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or T. bili > ULN to 1.5 x ULN	• Continue I-O therapy per protocol	• Continue LFT monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen : • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent* • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1 g BID • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

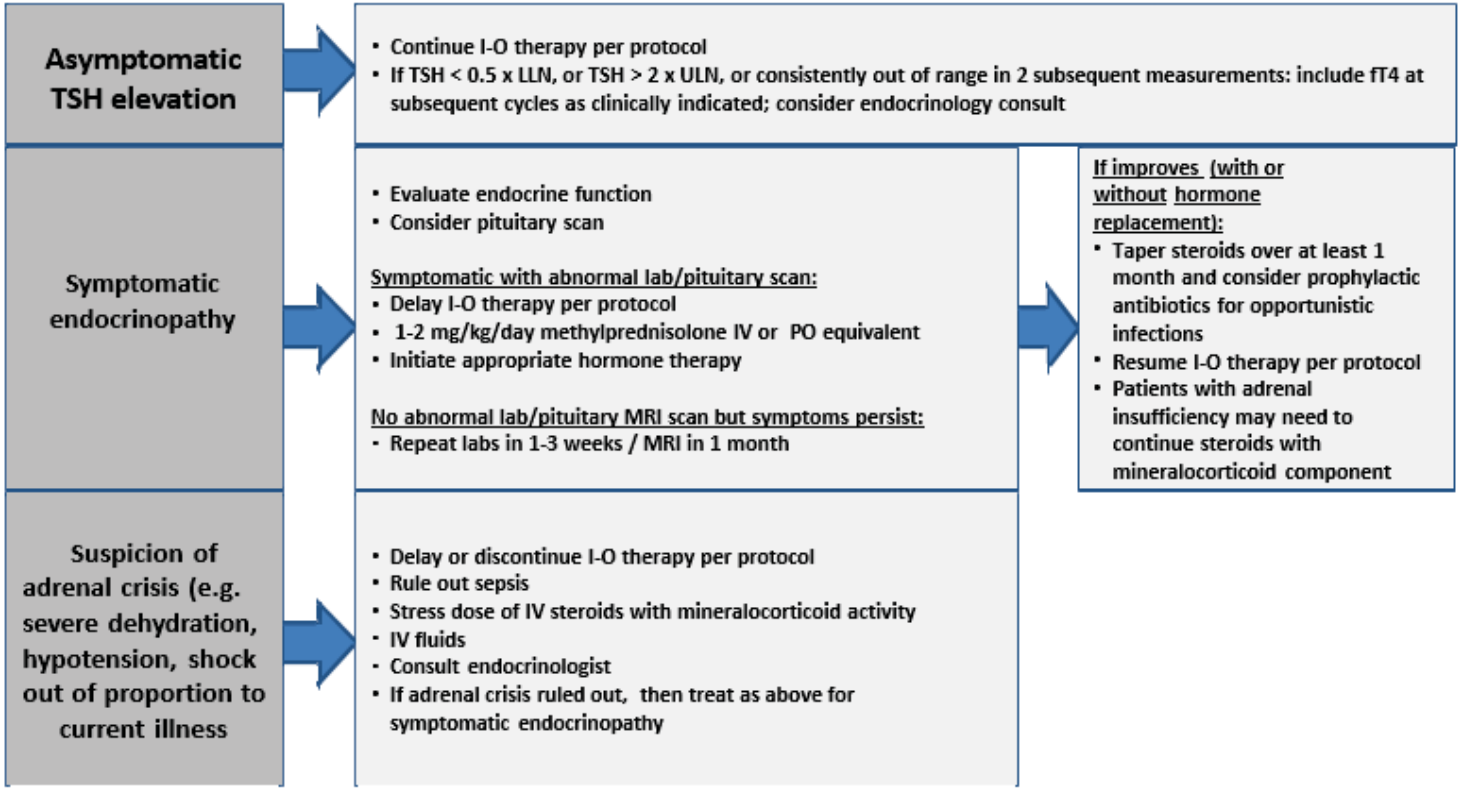
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

27-Jun-2019

Endocrinopathy Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.

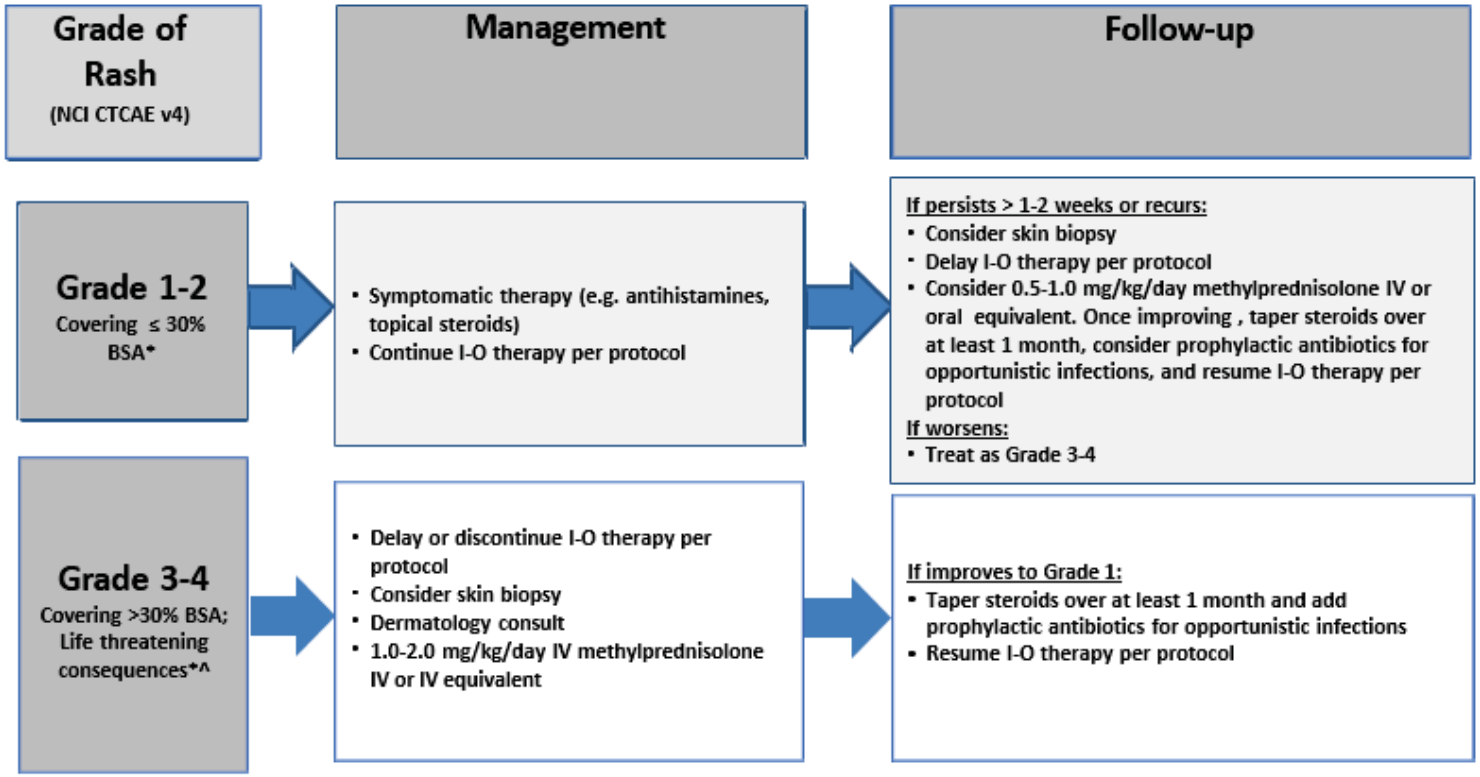


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

27-Jun-2019

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

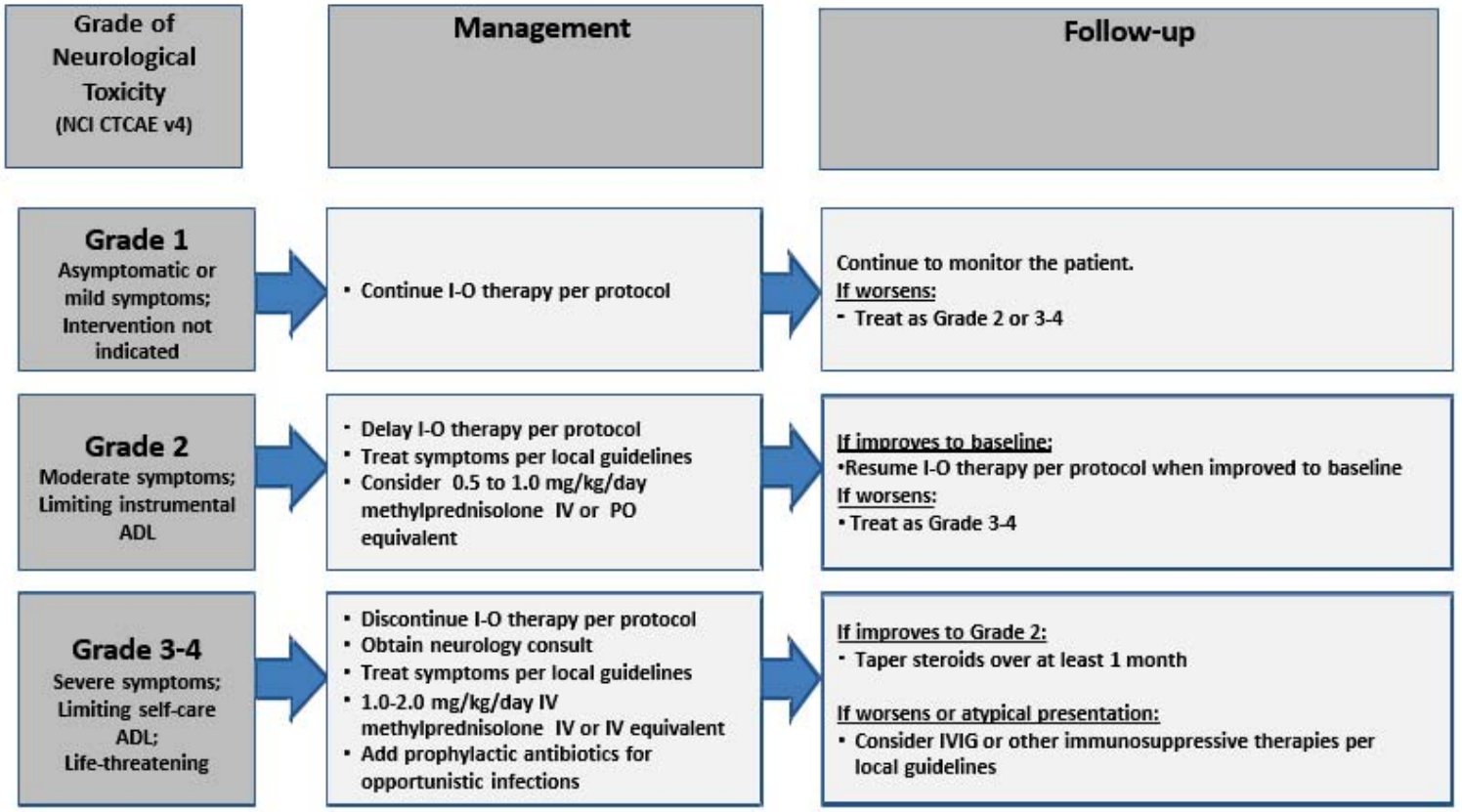
*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

27-Jun-2019

Neurological Adverse Event Management Algorithm

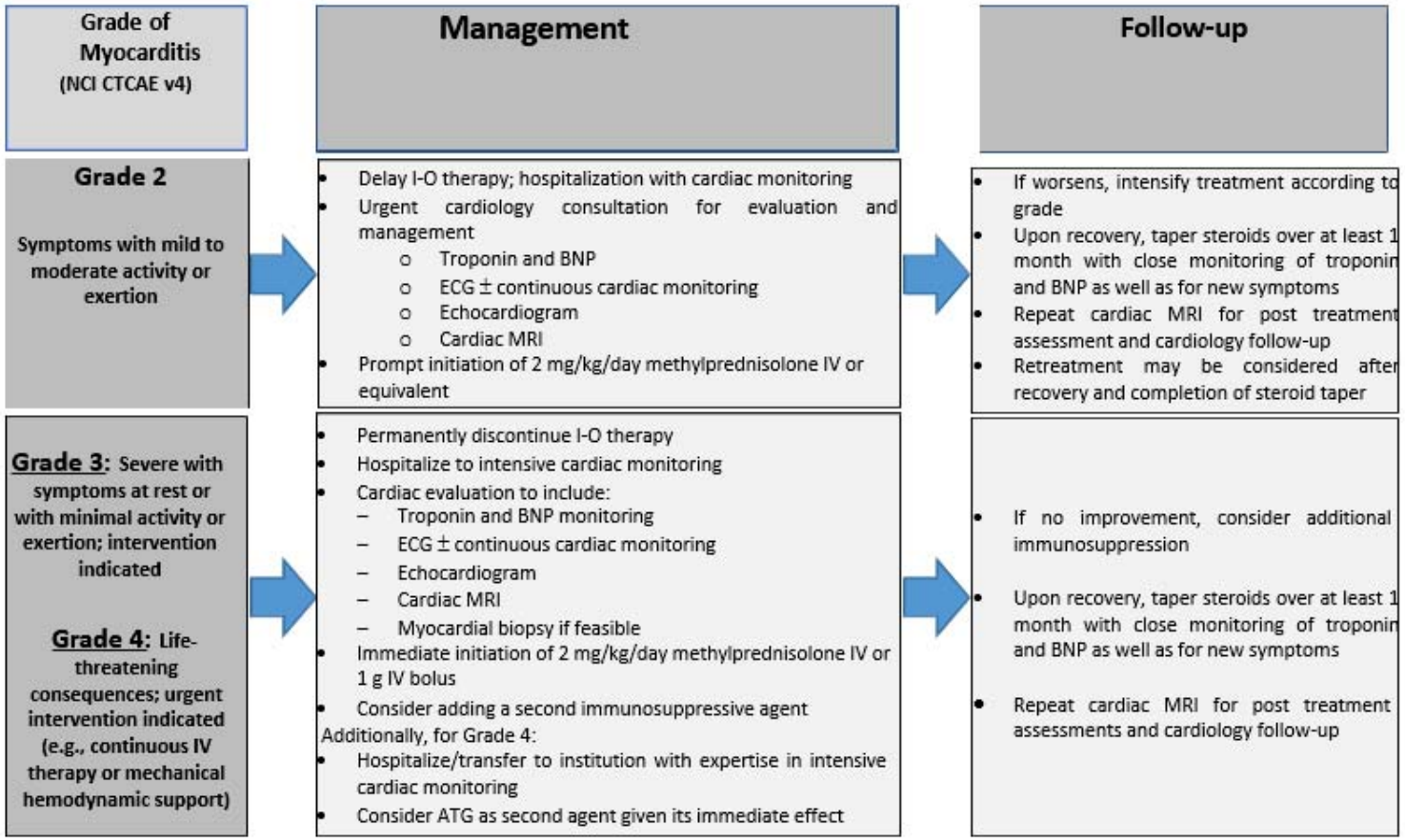
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

27-Jun-2019

Myocarditis Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

27-Jun-2019

APPENDIX 3 RECIST 1.1 GUIDELINES

1 EVALUATION OF LESIONS

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

1.1 Measurable

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

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

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

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

1.2 Non-Measurable

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

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

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

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

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

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

3 RESPONSE CRITERIA

3.1 Evaluation of Target Lesions

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

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

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

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

3.1.1 Special Notes on the Assessment of Target Lesions

3.1.1.1 Lymph nodes

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

3.1.1.2 Target lesions that become 'too small to measure'

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

3.1.1.3 Lesions that split or coalesce on treatment

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

3.2 Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

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

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

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

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

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

3.2.1.1 When the patient also has measurable disease

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

3.2.1.2 When the patient has only non-measurable disease

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

it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

3.2.2 New Lesions

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

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

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

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

3.3 Response Assessment

3.3.1 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and

will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement.

3.3.2 Time Point Response

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

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

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

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

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

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

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

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

3.3.3 Best Overall Response

Best response determination of complete or partial response requires confirmation: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of ≥ 4 weeks later. In this circumstance, the best overall response can be interpreted as in Table 3.3.3-1.

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

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

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

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

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

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

3.3.4 Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive repeat assessments that should be performed no less than 28 days after the criteria for response are first met. For this study, the next scheduled tumor assessment can meet this requirement.

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

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

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation (These methods of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)[b] – oral (birth control pills) – intravaginal (vaginal birth control suppositories, rings, creams, gels) – transdermal

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

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

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

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

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

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

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

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 6.4.

APPENDIX 5 HEAD AND NECK SQUAMOUS CELL CARCINOMAS CLASSIFIED AS FOLLOWS:

- oral cavity:
  - anterior two thirds of the tongue
  - tongue unspecified,
  - lip
  - gum
  - floor of the mouth
  - hard palate
  - palate unspecified
  - other oral cavity—including buccal mucosa and retromolar area
  - oral cavity unspecified

- oropharynx:
  - base of the tongue
  - soft palate
  - tonsil
  - uvula
  - other parts of the oropharynx
  - Waldeyer's ring
  - oropharynx unspecified

- larynx:
  - glottis
  - supraglottis
  - subglottis
  - other and unspecified larynx subsites
  - Hypopharynx cases are classified as belonging to the larynx, including pyriform sinus

APPENDIX 6 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for the Revised Protocol 04, 20-Jun-2018

Evolving data in SCCHN in the recent years suggest that PD-L1 combined positive score (PD-L1 CPS) is a more appropriate PD-L1 measure for selecting participants who derive the best benefit for immunotherapy. Additionally, recent data demonstrate the potential for nivolumab + ipilimumab to benefit a broader SCCHN patient population than PD-L1 expressers alone. The primary end-points of the current study (CheckMate 651) will be revised to compare: (a) OS of participants with PD-L1 CPS ≥ 20 who are receiving nivolumab combined with ipilimumab to those receiving EXTREME regimen (changed from tumor cell PD-L1 ≥ 1%) and (b) OS of all study participants (irrespective of PD-L1 expression) who are receiving nivolumab combined with ipilimumab to those receiving EXTREME regimen. Additionally, OS for nivolumab + ipilimumab versus EXTREME regimen in participants with PD-L1 CPS ≥ 1 will be added as a key secondary end-point. The primary end-point of PFS for nivolumab + ipilimumab versus EXTREME regimen will be removed as evolving data suggest that PFS is not an appropriate end-point for immunotherapy in SCCHN.

Summary of key changes for Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1.2: Rationale for revised protocol 04	Updated section with emerging data (CheckMate 141, KeyNote-040, and KeyNote-048)	Emerging data from multiple studies in the recent years demonstrated long-term OS benefit with PD-1 inhibitor (nivolumab and pembrolizumab) therapy compared to standard of care in R/M SCCHN population. These studies while suggesting OS benefit in all study participants also showed with a trend towards better efficacy in participants who express PD-L1 in either their tumor or immune cells.
[redacted]		

Summary of key changes for Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 1.2.6: Rationale for 24 Months Maximum Treatment Duration	Updated literature references in this section	Literature references in this section was updated to support rationale for 24 months maximum treatment duration
Section 1.4.1: Primary Objective	The following changes were made to the primary objectives: (a) Modify: Compare OS for participants who are receiving nivolumab + ipilimumab versus EXTREME regimen in participants with PD-L1 CPS ≥ 20 (changed from tumor PD-L1 ≥ 1) and (b) Add: OS for nivolumab + ipilimumab versus EXTREME regimen in all study participants (irrespective of PD-L1 expression). (c) Remove: The primary end-point of PFS for nivolumab + ipilimumab versus EXTREME regimen.	In all of the recent studies of PD-1 inhibitors in SCCHN, PFS did not capture the benefit of PD-1 therapy versus standard of care therapy in both biomarker selected and unselected population. Emerging data from multiple studies in the recent years (CheckMate141, KeyNote-040, KeyNote-048) demonstrated long term OS benefit with PD-1 inhibitor (nivolumab and pembrolizumab) therapy in R/M SCCHN population. [redacted] These studies while suggesting OS benefit in all study subjects also showed with a trend towards better efficacy in participants who express PD-L1 in either their tumor or immune cells. Summary of this data also suggest that CPS is a more appropriate PD-L1 measure for selecting participants who derive the best benefit for immunotherapy. Additionally, recent data demonstrate the potential for nivolumab + ipilimumab to benefit a broader SCCHN patient population than tumor cell PD-L1 expressers alone.

Summary of key changes for Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1.4.2: Secondary Objective	The key secondary objective was changed to OS in subject with CPS ≥ 1	Emerging data in the last year demonstrates long-term OS benefit with PD-1 inhibitor (nivolumab and pembrolizumab) therapy in R/M SCCHN population, with a trend towards better efficacy in subjects who express PD-L1 in either their tumor or immune cells. Study KeyNote-048 demonstrated improved efficacy benefit for pembrolizumab at CPS > 1. The summary of this data suggests that Nivolumab + Ipilimumab may benefit the population selected based on PDL-1 CPS cut-off ≥ 1
Section 1.4.3: Exploratory Objective	(1) Efficacy evaluation based on biomarker subgroups were added (2) Exploratory objectives for PROs were changed PD-L1+ positive participant to participants with PD-L1 CPS ≥ 20	To investigate biomarkers (PD-L1, TMB, GEP etc.) which may be predictive of efficacy. Align with primary analysis population
Section 1.6: Overall Risk/Benefit Assessment	Updated overall risk-benefit with data from CheckMate 141, CheckMate 012, [redacted] and KeyNote-048.	More data from recent studies were added as a reference to have better understanding about Risk/Benefit.
Section 2	Updated section with new language	Section 2 was updated to align with current standards for BMS clinical studies.
Section 2.1.1: Good Clinical Practice	Updated section with new language	Section 2.1 was updated to align with current standards for BMS clinical studies
Section 3.1:Study Design and Duration	Updated schema to reflect the changes in end point	The study schema was updated to reflect the changes in end points

Summary of key changes for Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.4.1: Prohibited and/or Restricted Treatments	Added "Any live / attenuated vaccine (eg varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella (MMR) during treatment and until 100 days post last dose." Added guidance for the use of marijuana and its derivatives	To align with current standards for BMS studies
Section 4.5.4.1: Criteria to Resume Nivolumab Dosing (Arm A)	Added criteria to clarify that participants 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.	To align with current standards for BMS clinical studies
Section 6: Adverse Events	Added criteria for meeting or not meeting AE definition.	To align with current standards for BMS clinical studies
Section 6.1: Serious Adverse Events	Added text for evaluating AEs and SAEs	To align with current standards for BMS clinical studies
Section 6.1: Overdose	Updated overdose reporting criteria	To align with current standards for BMS clinical studies
Section 8.4.2.1: Analysis Methods for Primary Endpoints	Updated testing hierarchy in Figure 8.4.2.1-1 for the endpoints to be tested in this study.	Align with updated objectives/endpoints.
Section 8.4.2.2: Analysis Methods for Secondary Endpoints	Updated analysis methods for Secondary endpoints was changed.	Align with updated secondary objectives.
Section 8.4.6: Outcomes Research Analyses	Changed PD-L1+ positive population to randomized subjects with PD-L1 CPS ≥ 20	Based on new endpoints, study population was changed.

Summary of key changes for Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.1.2: Financial disclosure	Added statement to compliance section	To align with current standards for BMS clinical studies
Section 9.2.2: Study Drug Records	Added statement to compliance section regarding records for study treatments	To align with current standards for BMS clinical studies
Section 9.2.4: Clinical Study Report and Publications	Section updated with new language	To align with current standards for BMS clinical studies
Section 9.2.4.1: Scientific Publications	Section updated with new language	To align with current standards for BMS clinical studies
Throughout the document	Term "subject" changed to "participant"	To align with current standards for BMS clinical studies
Appendix 4	Updated "Highly Effective Methods That Are User Independent"	To align with current standards for BMS clinical studies

Overall Rationale for the Revised Protocol 03, 01-May-2018

The rationale for the key changes is based on the recent data from the 2-year survival update of CheckMate 141 (CA209141) study of nivolumab versus standard of care chemotherapy in recurrent or metastatic SCCHN patients post platinum therapy. The data from this update showed that, in the overall study population, nivolumab demonstrated 32% reduction in risk of death compared to chemotherapy (HR = 0.68 [95% CI: 0.54, 0.86]). Furthermore, in patients whose tumors expressed PD-L1 ≥ 1% (PD-L1 expressors), nivolumab demonstrated a 45% reduction in risk of death versus chemotherapy (HR = 0.55 [95% CI: 0.39, 0.78]). This recent data, while confirming the long-term survival benefit of check-point inhibitors in the over-all SCCHN population (irrespective of baseline biomarker status), also demonstrates a relatively better efficacy in PD-L1 expressors. Based on the summary of the above data, the current Phase 3 CA209651 study will compare the co-primary end-points of PFS and OS between study arms in PD-L1 expressor population. The PFS and OS in over-all study population will be evaluated as secondary end-points.

It has been shown that approximately 60% of the SCCHN tumors may express PD-L1. Therefore, the required number of events and sample size were increased to allow adequate power to analyze the co-primary end-points of PFS and OS in this biomarker-selected group. The primary objective, endpoints, sample size and statistical analysis sections of the protocol were revised accordingly.

Summary of key changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Primary Objectives; Section 1.3.1	The primary objectives were changed from PFS and OS in all randomized subjects to PFS and OS in subjects with PD-L1 expressing tumors.	CheckMate 141 compared nivolumab monotherapy to investigator choice monotherapy in platinum refractory SCCHN subjects. The updated analysis of CheckMate 141 (2-year OS update) provided evidence of efficacy in both the tumor PD-expressor and PD-L1non-expressor (<1%) groups. However, the efficacy was greatest in the PD-L1 expressor group. Based on these results, the primary comparisons of PFS and OS will be conducted in the subjects with PD-L1 expressing tumors. Comparisons of these endpoints in all study subjects will become secondary objectives.
Synopsis, Study Design; Statistical Considerations, Sample Size; Section 8.1	Sample Size determination was updated with sample size increased from 700 to 930.	Based on the 2-year survival update of CheckMate 141 study, subjects with PD-L1 expressing tumors had a relatively better efficacy with nivolumab treatment. Hence, the primary analysis population was changed from all study subjects to subjects with PD-L1 expressing tumors. The required number of events and sample size were increased in order to provide adequate power in this biomarker-selected group. Power was provided for the primary comparisons of PFS and OS and for the secondary comparisons of these endpoints in all subjects.
Section 8.4.2.1, Analysis Methods for Co-primary Endpoints	Indicated that the primary analyses would be in PD-L1 expressors rather than in the entire study population.	In line with the change in the primary objectives.

Summary of key changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 8.4.2.2, Analysis Methods for Secondary Endpoints	Made PFS and OS in all study subjects secondary endpoints. Indicated that PFS in all subjects would be tested hierarchically after PFS in subjects with PD-L1 expressing tumors and that OS in all subjects would be tested hierarchically after OS in subjects with PD-L1 expressing tumors.	Needed to ensure that the familywise type I error rate was controlled and thus needed to pre-specify the testing hierarchy for secondary endpoints.
Section 8.4.5, Biomarker Analyses	Added brief description of how TMB would be analyzed.	Assessment of TMB was introduced as an exploratory objective in revised protocol 02. However, no description of TMB analyses was given at that time.
Nivolumab Dose Discontinuation 4.5.1.1 Nivolumab plus Ipilimumab (Arm A)	Grade 3 drug-related myocarditis was added into nivolumab dose discontinuation criteria.	Rare cases of myocarditis have been reported with nivolumab or nivolumab in combination with ipilimumab. For grade 3 myocarditis, nivolumab or nivolumab in combination with ipilimumab should be permanently discontinued based on nivolumab IB v16.
All	Minor formatting and typographical corrections.	Minor, therefore have not been summarized.

Overall Rationale for the Revised Protocol 02, 26-Oct-2017

The purpose of this revised protocol is to increase the sample size to account for a delay in separation of the Kaplan-Meier (KM) curves for both progression-free survival (PFS) and overall survival (OS) between the 2 treatment arms. Delayed separation of the Kaplan-Meier curves for nivolumab and standard of care chemotherapy was observed in CA209141, the Phase 3 study of nivolumab in platinum-refractory squamous cell carcinoma of the head and neck.

In addition, a maximum duration of nivolumab and ipilimumab treatment of 24 months from the start of treatment was added. Accumulating evidence from different clinical trials in different tumor types with nivolumab or nivolumab combined to ipilimumab indicates that no additional benefit is obtained for subjects treated beyond 24 months, and responses remain durable.

Duration of response has been changed from an exploratory objective to a secondary objective based on the expected improvement in duration of response as seen in other nivolumab trials. Response to first therapy after disease progression was changed to an exploratory endpoint to limit the secondary objectives only to critical endpoints.

Tumor mutational burden has been shown to be a predictive biomarker of efficacy for checkpoint inhibitors in several tumors. Therefore, exploratory biomarker objectives were added in order to evaluate the potential associations between efficacy outcomes (such as objective response rate, PFS, and OS) with select biomarkers, including tumor mutational burden, from tumor tissue and peripheral blood. The amount of tumor tissue required for study entry was increased to allow enough samples for these additional exploratory analyses.

Summary of key changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis, Investigational Product Arm A; Synopsis, Study Design; Section 1.1.4, Rationale for 24 Months Maximum Treatment Duration; Section 3.1, Study Design and Duration; Section 3.2, Post Study Access to Therapy; Section 3.5, Discontinuation of Subjects Following any Treatment with Study Drug; Section 4.5.6, Treatment Beyond Disease Progression	Added the maximum treatment duration of nivolumab and ipilimumab of 24 months from first nivolumab treatment.	Accumulating evidence from different clinical trials in different tumor types with nivolumab or nivolumab combined to ipilimumab indicates that no additional benefit is obtained for subjects treated beyond 24 months, and responses remain durable.
Synopsis, Primary Objectives; Section 1.3.1,	The primary objectives of progression-free survival and	For clarity.

Summary of key changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Primary Objectives	overall survival were reformatted.	
Synopsis, Secondary Objectives; Section 1.3.2, Secondary Objectives	Moved duration of responses (duration of response) to a secondary objective.	Measuring the durability of response is particularly important with IO agents because some subjects on IO agents have stay in response for an extended period of times. The objective was elevated to a secondary objective.
Synopsis, Exploratory Objectives; Section 1.3.3, Exploratory Objectives	Moved time to symptom deterioration to an exploratory endpoint.	Time to symptom deterioration was moved to an exploratory objective in order to limit the list of secondary objectives focused on critical endpoints.
	Removed response to first subsequent therapy after disease progression objective.	Reliable data cannot be collected on this endpoint. In addition, this endpoint is of limited value.
	Strengthened the objective related to the association between biomarkers and clinical outcomes.	Added exploratory endpoint to support the collection of additional biological samples for biomarker analysis.
	Added an exploratory objective related to the association between tumor mutational burden and clinical outcomes.	Tumor mutational burden has been shown to be a predictive biomarker of efficacy for checkpoint inhibitors in several tumors. Therefore, it is important to elevate this endpoint.
	Added an exploratory objective related to the association between biomarker and clinical outcomes.	It is important to identify the predictive biomarkers of response and prognosis in SCCHN. Therefore, an exploratory objective was added to evaluate select blood and tissue based biomarkers in tumor and blood samples.
Synopsis, Study Design; Synopsis, Statistical Considerations, Sample Size; Section 8.1, Sample	The sample was increased from 490 to 700 subjects.	The sample size calculations were revised to account for the delayed separation of Kaplan-Meier curve observed in PFS and OS in

Summary of key changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Size Determination		CA209141 between nivolumab and standard of care chemotherapy. Increasing the sample size is calculated to compensate for this delayed separation.
Synopsis, Study Population	Adjusted Inclusion Criteria b to match the body of the protocol.	For clarity for sites.
	Adjusted the Exclusion Criteria to match the body of the protocol.	For clarity for sites.
Synopsis, Statistical Considerations, Analyses, Interim Analysis; Section 8.5, Interim Analysis	Added a second interim analysis of OS.	Added an interim analysis of OS at the time of the final PFS analysis.
Section 1.1.1, Rationale for the Combination of Nivolumab and Ipilimumab	Added text to regarding the results of Checkmate 141.	To provide updated data from Checkmate 141.
Section 3.3.1, Inclusion Criteria	Adjusted Criterion 2.c for clarity.	Edited for clarity.
	Revised Criterion 2.h regarding palliative radiotherapy as 2.l.	The window between radiation and study drug administration was modified to allow for patients with recent treatment with radiation based on evolving data on checkpoint inhibitors in combination with or in sequence with radiation that have shown manageable toxicity profile.
	Added criterion 2.j regarding life expectancy of at least 3 months.	To provide guidance to the investigators on proper patient selection.
	Changed the duration of contraception use after the last dose for both male and female subjects	To align with the Prescribing Information in the United States and the Summary of Product Characteristics in the European Union.

Summary of key changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.3.2, Exclusion Criteria	Added a sub-criterion to Criterion 2.d.	Allows for entry into the study for subjects who have a second primary SCCHN.
	Removed Criterion 2.g.	Removes exclusion criteria specific for pulmonary cancers which is not applicable to SCCHN.
	Added Criterion 2.i.	To reduce potential for any drug-drug interactions.
	Revised Criterion 3.c.v to appear as Criterion 3.c.viii.	Updated lower limit of creatinine to reflect clinical standards.
Section 3.4.1, Prohibited and/or Restricted Treatments	Added botanical preparations as prohibited treatments.	To reduce potential for any drug-drug interactions.
Section 3.4.2, Other Restrictions and Precautions	Adjusted exclusion from MRI to adhere to the center's standard of care.	Provided additional guidance for subject contraindicated for contrast agents.
Section 1.1.4, Duration of Treatment	Added section.	Described above.
Section 3.3.1, Inclusion Criteria	Adjusted Criterion 2.c for clarity.	Edited for clarity.
	Added Criterion 2.j and 2.k.	Edited for clarity.
Section 3.4.3, Permitted Therapy	Adjusted requirements for pre-study radiotherapy.	To align with Inclusion Criteria
Section 4.5.1.1, Nivolumab plus Ipilimumab (Arm A)	Added additional dosing details.	To align with the nivolumab program standards.
Section 4.5.1.2, EXTREME Regimen (Arm B)	Adjusted order of this section and added details regarding platinum therapy.	Edited for clarity.
Section 4.5.3.2, Nivolumab and Ipilimumab	Updated the dose delay criteria.	To align with the Summary of Product Characteristics Dose Delay Criteria.
Section 4.5.2.2, EXTREME Regimen	Provided additional guidance regarding dose delays for participants in the EXTREME regimen.	For clarity for the site.

Summary of key changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 4.5.4.1, Criteria to Resume Nivolumab Dosing (Arm A)	Updated the criteria to resume treatment.	To provide clarity and eliminate redundancy with other sections.
Section 4.5.5.1, Nivolumab Dose Discontinuation	Updated the dose discontinuation criteria.	To align with the Summary of Product Characteristics Dose Delay Criteria.
Section 4.5.6, Treatment Beyond Disease Progression	Adjusted the frequency of subsequent scans.	Adjusted scan frequency to same frequency for on study scans.
Section 5.1, Flow Chart/Time and Events Schedule, Table 5.1-1, Screening Procedural Outline (CA209651)	Increased the amount of tissue required.	Provided additional tissue for completion of procedures required during screening period.
	Clarified the imaging requirements for tumor assessments.	Clarified the requirement for obtaining CT or MRI scans with and without contrast.
	Removed whole blood sample and saliva sample assessments, which were not planned for screening.	For clarity for the sites.
Section 5.4, Efficacy Assessments	Tumor assessments were aligned with the Time and Events Tables.	For clarity for the sites.
Section 5.5, Pharmacokinetic Assessment, Table 5.5-1, Pharmacokinetic (PK) and Immunogenicity Sample Collections for Nivolumab and Ipilimumab (Arm A)	Changed collection time for Cycle 1 Day 1.	To decrease subject burden.
Section 5.6, Biomarker Assessments	Added footnote e regarding biopsy at progression.	To provide guidance to the sites on obtaining tumor biopsies after progression.
Section 5.6.1, Exploratory Serum/plasma biomarkers	Added Plasma.	For clarity.
Section 5.6.2, Circulating Free DNA in Plasma	Section added.	Updated biomarker section to explore less invasive emerging technologies.

Summary of key changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.6.3, Tumor Tissue Specimens	Increase the tumor tissue requirements.	The analysis of tumor mutational burden to the biomarker plan requires additional samples to be collected.
Section 5.6.7, Whole Blood for Genomic Analyses	Changed the heading title and added detail regarding genomic testing.	Describes the addition of whole blood genomic testing to the biomarker plan.
Section 5.7, Outcomes Research Assessments	Added an option for subjects not able to vocalize responses on the phone.	Added to accommodate SCCHN subjects with speech impairment alternatives for the completion of questionnaires.
Section 6.1.1, Serious Adverse Event Collection and Reporting	Added the definition of a SUSAR.	For clarity for the sites.
Section 8.3.2, Secondary Endpoints	Added the definition of duration of objective response.	Moved the definition of DOR to the section on secondary endpoints now that it is being considered a secondary objective.
Section 8.4.2.1, Analysis Methods for Co-primary Endpoints	Spelled out the levels to be used for the confidence intervals for the HRs of PFS and OS.	For greater clarity.
Section 8.4.2.2, Analysis Methods for Secondary Endpoints	Spelled out the nominal significance level for comparing ORR between arms and the corresponding level for the confidence interval for the odds ratio.	For greater clarity.
Section 8.4.5, Biomarker Analyses	Added the plan for the analysis of the biomarker endpoints.	Added to support the exploratory endpoint for biomarker analysis.
Section 8.4.6, Outcome Research Analyses	Added analysis for TTSD.	For clarity.

Summary of key changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 4	Updated the Methods of Contraception Appendix to include the definition of women of childbearing potential and provide more detail on the methods of contraception allowed in the study.	To update to the current nivolumab program standards.
All	Minor formatting and typographical corrections.	Minor, therefore have not been summarized.