Protocol Number: CA2099TM
IND Number: 119,382
EUDRACT Number: 2017-002676-87
Date: 15-Aug-2017
Revised Protocol Date: 16-Nov-2018

CLINICAL PROTOCOL CA2099TM

A Randomized, Double-blind, Placebo-controlled, Phase 3 Study of Nivolumab or Nivolumab plus Cisplatin, in Combination with Radiotherapy in Participants with Cisplatin Ineligible and Cisplatin Eligible Locally Advanced Squamous Cell Carcinoma of the Head and Neck (SCCHN).

Revised Protocol Number: 03

Medical Monitor
Peng Sun, MD, PhD

promptly destroy it. All other rights reserved. References to BMS in this protocol may apply to partners to which BMS has transferred obligations, eg, a Contract Research Organization (CRO).

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

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 03	16-Nov-2018	• Enrollment in the study was closed as of 15-Oct-2018. Revised Protocol 03 covers the changes implemented to the protocol post study enrollment closure: study treatment unblinding, removal of placebo treatment, and removal of analysis of efficacy end-points and efficacy follow-up.
Revised Protocol 02	21-Feb-2018	• Added exclusion of participants with active interstitial lung disease (ILD) / pneumonitis or with a history of ILD / pneumonitis requiring steroids. • Aligned thyroid testing to study visits. • Added guidance for premedications for cetuximab if necessary.
Revised Protocol 01	01-Nov-2017	Update to questionnaire administration updated to align with dosing cycles. Outcome research assessment and endpoints redefined updated to align with analysis planned. TNM Staging clarified for high and intermediate risk definition. Other minor corrections, clarifications
Original Protocol	15-Aug-2017	Not applicable

TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title: A randomized, double blind, placebo controlled, Phase 3 study of nivolumab or nivolumab plus cisplatin, in combination with radiotherapy in participants with cisplatin ineligible and cisplatin eligible locally advanced squamous cell carcinoma of the head and neck (SCCHN).

Study Phase: Phase 3

[redacted]

Study Population:

Per Revised Protocol 03, enrollment in the current study was closed as of 15-Oct-2018. Participants that have signed an informed consent as of that date will be permitted to be randomized. Participants already on study will be re-consented under the modified Revised Protocol 03.

Key Inclusion Criteria:

- Histologically proven SCCHN from one of the following primary sites: oral cavity, oropharynx, hypopharynx, and larynx
- Locally advanced disease which is un-resectable, or resectable but suitable for an organ sparing approach
- No previous radiotherapy or systemic treatment for SCCHN
- Eastern cooperative oncology group (ECOG) score of 0-1
- Age ≥ 18 years or age of majority
- Measurable disease by RECIST 1.1 criteria, and tumor assessment performed prior to randomization
- Sufficient sample of fresh or archival (< 3 months from informed consent date) formalin-fixed, paraffin-embedded (FFPE) tissue block, or unstained tumor tissue sections, with an associated pathology report, must be submitted for biomarker evaluation for PD-L1 status. Central lab must provide Interactive Response Technology (IRT) with confirmation of receipt of evaluable tumor tissue prior to randomization. Biopsy should be excisional, incisional or core needle. Fine needle or aspiration is unacceptable for submission. PD-L1 status must be available prior to randomization.

- HPV p16 test result available (performed locally or centrally) for participants with oropharyngeal disease
- Patients must be of intermediate or high risk categories*:
- **High risk:**

Oral cavity, hypopharynx, larynx, oropharynx (p16 negative): Stage III/ IV

Oropharynx (p16 positive): Stage III (T4 any N or T1-3 N3) - irrespective of smoking status.

- **Intermediate risk:**
  - Oropharynx (p16 positive): T3 N0-2 or T1-3 N2 disease if smoking > 20 pack year history.

*TNM clinical staging according to AJCC version 8

Cohort 1 (cisplatin-ineligible participants) Specific Inclusion Criteria (Arm A and Arm B)

- Physician assesses participant to be non-eligible for treatment with platinum based combined CRT. This must be **for one or more** of the following reasons:
  - Age ≥ 70 years at enrolment
  - Creatinine clearance < 60mL/min and > 30mL/min (using the Cockcroft and Gault formula– see below**)
  - Severe hearing loss (minimal hearing threshold of 80 dB or more in either ear)

Cohort 2 (cisplatin-eligible participants) Specific Inclusion Criteria (Arm C and Arm D)

- Adequate renal function within 28 days prior to randomization as follows:
  - Creatinine clearance ≥ 60 mL/min. as determined by 24 hour collection or estimated by Cockcroft-Gault formula:

$$C_{Cr}=\{((140–\text{age in years}) \times \text{weight in Kg})/(72 \times \text{serum creatinine in mg/dL})\}$$

(for females, multiply the result by 0.85)**

**Participants aged ≥ 70 years may enter either Cohort 1 or 2 dependent on whether the physician's assessment is that the participant is eligible for cisplatin (Cohort 2) or ineligible for cisplatin (Cohort 1) based on their age. It is anticipated that in the majority of cases, patients aged ≥ 70 years will be considered ineligible for cisplatin and enter cohort 1. If the subject has poor renal function as one of the acceptable inclusion criteria, the subject will be enrolled under inclusion criteria 3) ii) and must meet the requirement for Creatinine clearance < 60 mL/min and > 30mL/min (using the Cockcroft and Gault formula).

Key Exclusion Criteria:

- Carcinoma originating in the nasopharynx or paranasal sinus, squamous cell carcinoma that originated from the skin and salivary gland or non-squamous histology (eg, mucosal melanoma), squamous cell carcinoma of unknown primary
- Clinical or radiological evidence of metastatic disease
- Prior radiotherapy that overlaps with radiation fields

- Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the participant to receive protocol therapy, or interfere with the interpretation of study results
- Active unstable angina and/or congestive heart failure
- Myocardial infarction within 6 months prior to randomization
- Participants who have a weight loss of > 10% of body weight between screening and randomization will be considered a screen failure.
- 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.
- 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.
- Participants with active interstitial lung disease (ILD) / pneumonitis or with a history of ILD / pneumonitis requiring steroids.

Objectives and Endpoints: Not Applicable per Revised Protocol 03

Overall Design: Study CA2099TM was a randomized, double-blinded, placebo-controlled, phase 3 study of nivolumab or nivolumab plus cisplatin, in combination with radiotherapy in participants with cisplatin ineligible and cisplatin eligible locally advanced squamous cell carcinoma of the head and neck (LAD SCCHN).

As of 15-Oct-2018, enrollment into the study was closed. At implementation of Revised Protocol 03, the study will be unblinded. Placebo treatments will no longer be given.

Participants will be stratified by risk group (intermediate versus high risk SCCHN).

- Intermediate risk participants will be defined as those with p16-positive oropharyngeal cancer with T3 N0-2 or T1-3 N2 disease if smoking > 20 pack year history.
- High risk participants are defined as participants with tumors arising in the oral cavity, larynx, hypopharynx, or p16-negative oropharynx and Stage III/IV or Oropharynx (p16 positive): Stage III (T4 any N or T1-3 N3) - irrespective of smoking status.

All staging will be according to AJCC 8 guidelines.

See study design schematic below.

Number of Participants: Per Revised Protocol 03, sample size will be limited to participants that have signed an informed consent as of 15-Oct-2018.

Number of Events and Power: Not applicable per Revised Protocol 03. No analyses of efficacy will be conducted.

Treatment Arms and Duration:

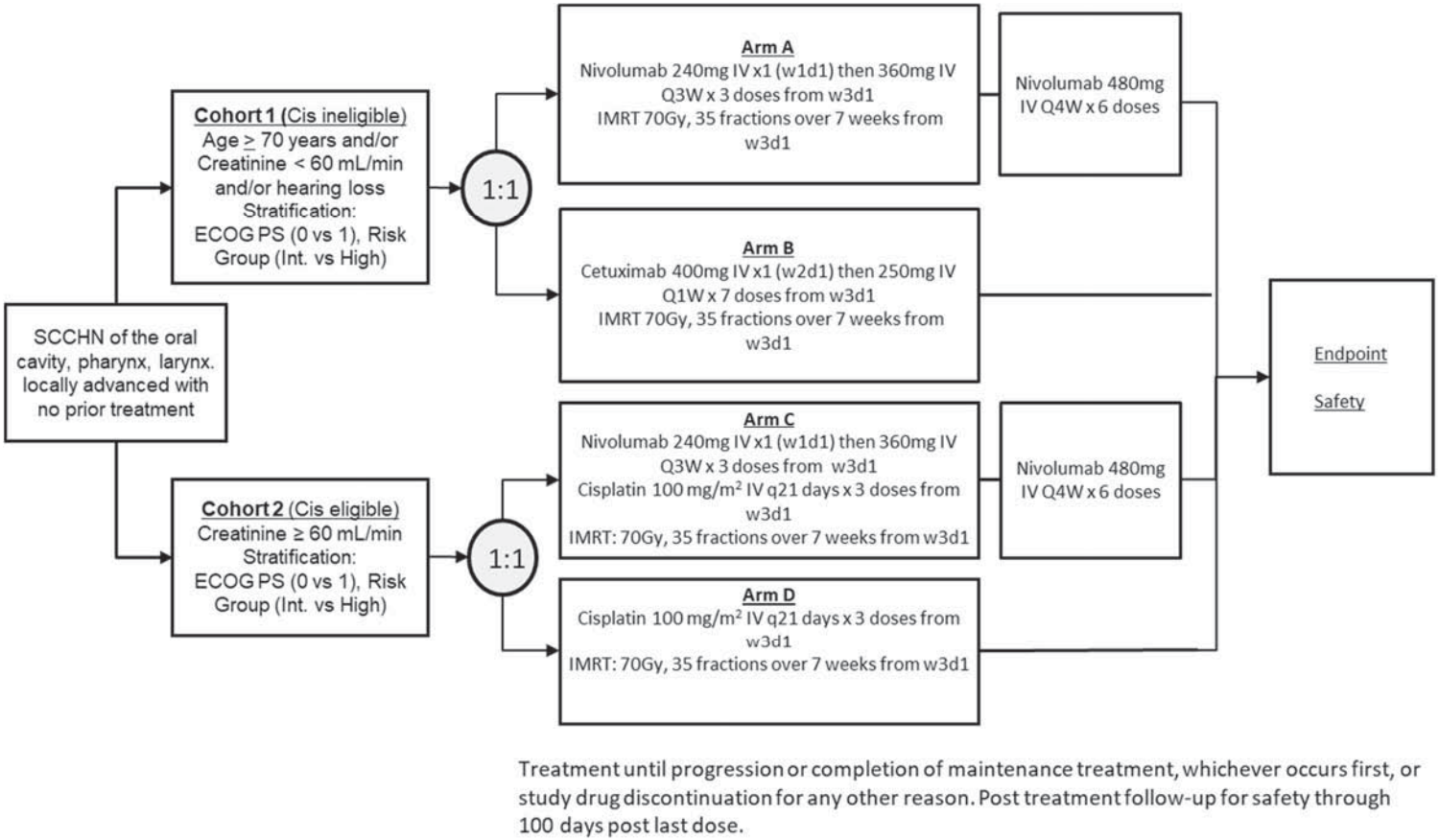
Study treatment:

Study Drug for CA2099TM		
Product Description / Class and Dosage Form	**Potency**	**IP/Non-IP**
Nivolumab Solution for Injection[a]	10 mg/mL – 100 mg fill volume	IP
Cetuximab Solution for Infusion[b]	5 mg/mL - 500 mg fill volume	IP
Cisplatin Concentrate for Solution for infusion[b]	1 mg/mL – 100 mg fill volume	IP

[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) or according to institutional standards.

Study Design Schematic for CA2099TM:



*As of 15-Oct-2018, enrollment in the study is closed. Participants with signed informed consent as of that date will be permitted to be randomized, and participants currently on treatment may continue. All participants should be reconsented under the current Revised Protocol 03. Only safety assessments will be conducted.

Upon approval and implementation of Revised Protocol 03, placebo treatments will no longer be given.

Abbreviations: C=cycle; Cis=cisplatin; CRCL=creatinine clearance; d=day; ECOG PS= Eastern Cooperative Oncology Group performance status; IMRT= Intensity-modulated radiation therapy; Int.=Intermediate; IV=intravenous; PD-L1= Programmed death-ligand 1; Q1W=every week; Q2W=every 2 weeks; q21 days=every 21 days; Q3W=every 3 weeks, Q4=every 4 weeks; SCCHN= squamous cell carcinoma of the head and neck; w or W=week

Participants in **Cohort 1** (cisplatin ineligible) will be randomized 1:1 to either Arm A or Arm B:

- **Arm A** will be administered nivolumab 240 mg for a single dose at w1d1 (C1 of cohort 1) then nivolumab 360 mg every 3 weeks for a total of 3 doses starting at w3d1 (C3, C6, C9 of cohort 1). Then, participants will be administered nivolumab 480 mg every 4 weeks for a total of 6 doses.
- **Arm B** will be administered cetuximab 400 mg/m^2 as a single dose at w2d1 (C2 of cohort 1) then 250 mg/m^2 IV every week for a total of 7 doses starting at w3d1 (C3 to C9 of cohort 1) with IMRT.

Participants in **Cohort 2** (cisplatin eligible) will be randomized 1:1 to either Arm C or Arm D.

- **Arm C** will be administered nivolumab 240 mg for a single dose at w1d1 (C1 of cohort 2) then nivolumab 360 mg every 3 weeks for a total of 3 doses starting at w3d1 (C2, C3, C4 of cohort 2). In addition, participants will be administered cisplatin 100 mg/m^2 every 21 days for 3 doses starting at w3d1 (C2 of cohort 2) with IMRT. Then, participants will be administered nivolumab 480 mg every 4 weeks for a total of 6 doses.
- **Arm D** will be administered cisplatin 100 mg/m^2 every 21 days for 3 doses starting at w3d1 (C2 of cohort 2) with IMRT.

Participants in Cohort 1 (cisplatin ineligible) and Cohort 2 (cisplatin eligible) will receive RT to a total dose of 70 Gy in 35 fractions which will be administered in daily doses of 2 Gy, typically on a 5 days on / 2 days off schedule as appropriate, over 7 weeks by Intensity Modulated Radiation Therapy (IMRT) starting at w3d1. Alternate fractionation schemes are not allowed.

Participants who are randomized to a placebo arm do not need to delay the start of radiotherapy. For subjects randomized to Cohort 1 Arm B, cetuximab may be administered at w1d1 and radiotherapy at w2d1. For participants randomized to Cohort 2 Arm B, cisplatin and radiotherapy may begin at w1d1.

Imaging will occur at baseline (within 28 days prior randomization. Per Revised Protocol 03, subsequent imaging assessments should be performed according to the timing of local standard of care.

The Follow-up stage begins when protocol specific treatment with nivolumab is completed or the decision to discontinue a participant from study therapy is made (no further treatment with study therapy). Participants will have the first follow-up visits (FU1 and FU2) approximately 30 days and 100 days, respectively, from the last dose of study therapy or coinciding with the date of discontinuation and AEs will be followed until the toxicities resolve, return to baseline, or are deemed irreversible.

All participants should continue to have tumor scans per local standards of care. .

A Data Monitoring Committee (DMC) will be utilized to provide general study oversight, to monitor safety on an on-going basis.

Participants MUST discontinue study treatment for 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.

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CA2099TM)

Effective as of 15-Oct-2018, enrollment in the study is closed. Participants who have already signed an informed consent as of 15-Oct-2018 will have the option to begin treatment (see Section 3.1.1)		
Procedure	**Screening Visit[a]**	**Notes**
Eligibility Assessments		
Informed Consent	X	A participant is considered enrolled only when a protocol specific informed consent is signed.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed and confirmed prior to randomization.
Medical History	X	Include any history (e.g., toxicities, allergies, tobacco use, pre-study testing, and documented hearing loss as applicable) relevant to the participant's current state of health and the disease under study. Also, any history related to previous treatments.
Abbreviated Comprehensive Geriatric Assessment (aCGA) –G-8 (**for Cohort 1 only**)	X	For cohort 1 only. Prior to randomization. See Section 5.1.
Tumor Tissue Sample (for stratification by PD-L1 tumor expression and HPV p16)	X	A tumor sample prior to therapy is mandatory for PD-L1 testing (to be shipped to central lab) and HPV p-16 testing for participants with oropharyngeal CA (sample either tested locally or shipped to Central Lab). If a recent tumor sample (obtained within 3 months of enrollment) is not available at screening, a fresh biopsy will be taken prior to randomization. Sufficient tumor tissue should be submitted - either two full block or minimum of 25 slides preferred, obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen. Biopsies of bone lesions that do not have a soft tissue component are unacceptable for submission. See Section 9.8.2. As of 15-Oct-2018, and approval and implementation of Revised Protocol 03, tumor samples will not be collected from any participant still in the screening period.
Radiological Tumor Assessment (i.e., neck, chest, abdomen, pelvis)	X	Performed within 28 days prior to randomization. See Section 9.1.1. TNM staging according to AJCC version 8 (Appendix 6).
Brain Imaging	X	Performed at screening for all participants to rule out brain metastasis. See Section 9.1.1.
Head and Neck Examination	X	For larynx, hypopharynx, and base of tongue primaries, a laryngopharyngoscopy (mirror and/or fiber optic and/or direct procedure) prior to randomization is required, unless the participant cannot tolerate or refuses.

Table 2-1: Screening Procedural Outline (CA2099TM)

Effective as of 15-Oct-2018, enrollment in the study is closed. Participants who have already signed an informed consent as of 15-Oct-2018 will have the option to begin treatment (see Section 3.1.1)		
Procedure	**Screening Visit[a]**	**Notes**
Multidisciplinary Case Evaluation	X	Multidisciplinary case evaluation, should include radiation oncology, medical oncology and ENT/head and neck surgeon or equivalent functions prior to randomization.
Creatinine Clearance Assessment	X	Using Cockroft and Gault formula within 28 days prior to randomization See Section 9.4.1.
Safety Assessments		
Physical Examination	X	Includes height, weight, and ECOG Performance Status (Appendix 7) within 14 days prior to randomization.
Vital Signs	X	Temperature, blood pressure and heart rate within 14 days prior to randomization.
ECG **(for Cohort 1 only)**	X	For cohort 1 only. Within 14 days prior to randomization.
Assessment of Signs and Symptoms	X	Within 14 days prior to randomization.
Concomitant Medication Use	X	Within 14 days prior to randomization.
Serious Adverse Events Assessment	X	Begins at the time of consent. See Section 9.2.1.
Laboratory Tests	X	See Section 9.4.1 for additional details on tests required. Must be performed within 14 days prior to randomization: • Complete Blood Cell (CBC) with differential • Chemistry panel • Thyroid panel including TSH, free T4, free T3
Hepatitis B and C Testing	X	See Section 9.4.1 for additional details on tests required. Hepatitis B surface antigen (HBV sAg), hepatitis C antibody (HCV Ab) or Hepatitis C RNA (HCV RNA) within 28 days prior to randomization.
HIV Testing	X	Testing for HIV must be performed at sites where mandated locally. See Section 9.4.1 and Appendix 8.
Pregnancy Test	X	WOCBP only: Serum or urine test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done at screening visit and repeated within 24 hours of first dose. See Section 9.4.1.

[a] 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.

Table 2-2: On Treatment Procedural Outline for Cohort 1 Arms A and B (CA2099TM)

Effective as of 15-Oct-2018, enrollment in the study is closed. Participants who have already signed an informed consent as of 15-Oct-2018 will have the option to begin treatment. Per Revised Protocol 03, placebo treatment will no longer be given.									
Procedure[a]	**Cycles 1 to 9 each = 1 week[b]**							**C10 to C15[b] (each cycle=4 weeks) Visit at the start of the cycle**	**Notes Procedures must be done within 72 hrs. prior to dosing unless otherwise specified Study visits to occur at the start of each cycle, weekly up to and including C9 for cohort 1 (± 3 days) then every 4 weeks from C10 to C15 for cohort 1 (± 7 days). C10 for cohort 1 to start 3 weeks after the start of C9. Cycles will differ between Cohorts.**
	C1	**C2**	**C3**	**C4 - C5**	**C6**	**C7 - C8**	**C9**		
Safety Assessments									
Informed Consent	Following study closure, participants already enrolled in the study will require re-consent upon implementation of Revised Protocol 03.								
Targeted Physical Examination	X	X	X	X	X	X	X	X	Should be performed by a qualified professional guided by the examiner's observations and/or participant complaints on new or changed conditions, symptoms, or concerns. Includes height, weight and ECOG performance status (Appendix 7). 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.
Vital Signs	X	X	X	X	X	X	X	X	Temperature, blood pressure and heart rate
Assessment of Signs and Symptoms	X	X	X	X	X	X	X	X	
Concomitant Medication Use	X	X	X	X	X	X	X	X	
Serious Adverse Events Assessment	X	X	X	X	X	X	X	X	
Adverse Events Assessment	X	X	X	X	X	X	X	X	

Table 2-2: On Treatment Procedural Outline for Cohort 1 Arms A and B (CA2099TM)

Effective as of 15-Oct-2018, enrollment in the study is closed. Participants who have already signed an informed consent as of 15-Oct-2018 will have the option to begin treatment. Per Revised Protocol 03, placebo treatment will no longer be given.									
Procedure[a]	**Cycles 1 to 9 each = 1 week[b]**							**C10 to C15[b] (each cycle=4 weeks) Visit at the start of the cycle**	**Notes Procedures must be done within 72 hrs. prior to dosing unless otherwise specified Study visits to occur at the start of each cycle, weekly up to and including C9 for cohort 1 (± 3 days) then every 4 weeks from C10 to C15 for cohort 1 (± 7 days). C10 for cohort 1 to start 3 weeks after the start of C9. Cycles will differ between Cohorts.**
	C1	**C2**	**C3**	**C4 - C5**	**C6**	**C7 - C8**	**C9**		
Laboratory Tests	X	X	X	X	X	X	X	X	CBC with differential and Chemistry panel. See Section 9.4.1 for additional details on tests required.
Thyroid Function Testing	To be performed C1 of cohort 1 then every 3 weeks (± 7 days) through C9, then every 4 weeks (± 7 days) through the treatment period.							X (see notes)	Thyroid panel including TSH with reflexive free T3 and free T4 if TSH is abnormal. See Section 9.4.1 for additional details on tests required.
Pregnancy Test	X								WOCBP only: Serum or urine within 24 hours prior to first dose and then every 4 weeks (± 7 days) regardless of dosing schedule.
[redacted]									
[redacted]	[redacted]								
[redacted]									
[redacted]	[redacted]								

Table 2-2: On Treatment Procedural Outline for Cohort 1 Arms A and B (CA2099TM)

Effective as of 15-Oct-2018, enrollment in the study is closed. Participants who have already signed an informed consent as of 15-Oct-2018 will have the option to begin treatment. Per Revised Protocol 03, placebo treatment will no longer be given.

Procedure[a]	Cycles 1 to 9 each = 1 week[b]							C10 to C15[b] (each cycle=4 weeks) Visit at the start of the cycle	Notes
	C1	C2	C3	C4 - C5	C6	C7 - C8	C9		
Whole Blood for Gene Expression									Procedures must be done within 72 hrs. prior to dosing unless otherwise specified Study visits to occur at the start of each cycle, weekly up to and including C9 for cohort 1 (± 3 days) then every 4 weeks from C10 to C15 for cohort 1 (± 7 days). C10 for cohort 1 to start 3 weeks after the start of C9. Cycles will differ between Cohorts.
Whole Blood for SNP									
Peripheral blood mononuclear cells (PBMCs)									
Tumor Tissue Sample									
Saliva, Oral Microbiome									
Stool, Gut Microbiome									
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									

Table 2-2: On Treatment Procedural Outline for Cohort 1 Arms A and B (CA2099TM)

Effective as of 15-Oct-2018, enrollment in the study is closed. Participants who have already signed an informed consent as of 15-Oct-2018 will have the option to begin treatment. Per Revised Protocol 03, placebo treatment will no longer be given.									
Procedure[a]	**Cycles 1 to 9 each = 1 week[b]**							**C10 to C15[b] (each cycle=4 weeks) Visit at the start of the cycle**	**Notes Procedures must be done within 72 hrs. prior to dosing unless otherwise specified Study visits to occur at the start of each cycle, weekly up to and including C9 for cohort 1 (± 3 days) then every 4 weeks from C10 to C15 for cohort 1 (± 7 days). C10 for cohort 1 to start 3 weeks after the start of C9. Cycles will differ between Cohorts.**
	C1	**C2**	**C3**	**C4 - C5**	**C6**	**C7 - C8**	**C9**		
[redacted]									
[redacted]									
[redacted]									
[redacted]	[redacted]								
Study Treatment									
Randomize	X								Only for participants with signed informed consent prior to 15-Oct-2018.
Administer Nivolumab	X		X		X		X	X	See Section 7 for details. At the start of the cycle, administer nivolumab 240 mg x 1 dose in C1 for cohort 1 then nivolumab 360 mg for a total of 3 doses at C3, C6, and C9 for cohort 1, then after 3 weeks from the start of C9 for cohort 1, nivolumab 480 mg for a total of 6 doses will be administered starting at C10 through C15 for cohort 1 (each cycle = 4 weeks).
Administer Cetuximab **(for Cohort 1 only)**		X	X	X	X	X	X		For cohort 1 only, administer cetuximab 400 mg/m^2 IV x 1 dose in C2 for cohort 1, then cetuximab 250 mg/m^2 IV Q1W x 7 doses in C3 to C9 for cohort 1. See Section 7.

Table 2-2: On Treatment Procedural Outline for Cohort 1 Arms A and B (CA2099TM)

Effective as of 15-Oct-2018, enrollment in the study is closed. Participants who have already signed an informed consent as of 15-Oct-2018 will have the option to begin treatment. Per Revised Protocol 03, placebo treatment will no longer be given.

Procedure[a]	Cycles 1 to 9 each = 1 week[b]							C10 to C15[b] (each cycle=4 weeks) Visit at the start of the cycle	Notes Procedures must be done within 72 hrs. prior to dosing unless otherwise specified Study visits to occur at the start of each cycle, weekly up to and including C9 for cohort 1 (± 3 days) then every 4 weeks from C10 to C15 for cohort 1 (± 7 days). C10 for cohort 1 to start 3 weeks after the start of C9. Cycles will differ between Cohorts.
	C1	C2	C3	C4 - C5	C6	C7 - C8	C9		
Radiotherapy (RT)			X	X	X	X	X		IMRT: 70 Gy, 35 fractions over 7 weeks from w3d1 (C3 for cohort 1). Alternate Fractionation Schemes are not permitted. The first fraction of RT should be delivered on a Monday or Tuesday, but this may vary according to local treatment plan. Five fractions should be delivered a week. Randomization and dosing should be timed such that the first dose of nivolumab occurs 14 days ± 3 days prior to the start of RT. See Section 7.1.4.

Abbreviations: c or C=cycle; d or D=day; IV=intravenous; Q1W=every week; Q3W=every 3 weeks; Q4W=every 4 weeks; w or W=week

[a] 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.

[b] If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs.

Table 2-3: On Treatment Procedural Outline for Cohort 2 Arms C and D (CA2099TM)

Procedure[a]	Cycle 1 (C1) (cycle=2 weeks)	C2 - C4 [b] (each cycle= 3 weeks)	C5 to C10[b] (each cycle=4 weeks)	Notes Procedures must be done within 72 hrs. prior to dosing unless otherwise specified Study visits to occur at the start of each cycle [i.e., for C2 to C4 for cohort 2 (± 3 days) and for C5 to C10 for cohort 2 (± 7 days). Cycles will differ between Cohorts.
Effective as of 15-Oct-2018, enrollment in the study is closed. Participants who have already signed an informed consent as of 15-Oct-2018 will have the option to begin treatment. Per Revised Protocol 03, placebo treatment will no longer be given.				
Safety Assessments				
Informed Consent	Following study closure, participants already enrolled in the study will require re-consent upon implementation of Revised Protocol 03.			
Targeted Physical Examination	X	X	X	Should be performed by a qualified professional guided by the examiner's observations and/or subject complaints on new or changed conditions, symptoms, or concerns. Includes height, weight and ECOG performance status (Appendix 7). 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.
Vital Signs	X	X	X	Temperature, blood pressure and heart rate
Assessment of Signs and Symptoms	X	X	X	
Concomitant Medication Use	X	X	X	
Serious Adverse Events Assessment	X	X	X	
Adverse Events Assessment	X	X	X	
Laboratory Tests	X	X	X	CBC with differential and Chemistry panel. See Section 9.4.1 for additional details on tests required.

Table 2-3: On Treatment Procedural Outline for Cohort 2 Arms C and D (CA2099TM)

Procedure[a]	Cycle 1 (C1) (cycle=2 weeks)	C2 - C4 [b] (each cycle= 3 weeks)	C5 to C10[b] (each cycle=4 weeks)	Notes Procedures must be done within 72 hrs. prior to dosing unless otherwise specified Study visits to occur at the start of each cycle [i.e., for C2 to C4 for cohort 2 (± 3 days) and for C5 to C10 for cohort 2 (± 7 days). Cycles will differ between Cohorts.
Thyroid Function Testing	To be performed C1 then every 3 weeks (± 7 days) through treatment period. After C5 every 4 weeks (± 7 days).			Thyroid panel including TSH with reflexive free T3 and free T4 if TSH is abnormal. See Section 9.4.1 for additional details on tests required.
Pregnancy Test	X			WOCBP only: Serum or urine within 24 hours prior to first dose and then every 4 weeks (± 7 days) regardless of dosing schedule.
[redacted]				
[redacted]	[redacted]			
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]	[redacted]			
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]	[redacted]			
[redacted]				

Table 2-3: On Treatment Procedural Outline for Cohort 2 Arms C and D (CA2099TM)

Procedure[a]	Cycle 1 (C1) (cycle=2 weeks)	C2 - C4 [b] (each cycle= 3 weeks)	C5 to C10[b] (each cycle=4 weeks)	Notes Procedures must be done within 72 hrs. prior to dosing unless otherwise specified Study visits to occur at the start of each cycle [i.e., for C2 to C4 for cohort 2 (± 3 days) and for C5 to C10 for cohort 2 (± 7 days). Cycles will differ between Cohorts.
[redacted]				
Study Treatment				
Randomize	X			Only for patients with signed informed consent as of 15-Oct-2018.
Administer Nivolumab	X	X	X	At the start of the cycle, administer nivolumab 240 mg x 1 dose in C1 (cycle= 2 weeks) then nivolumab 360 mg for a total of 3 doses starting at C2 through C4 for cohort 2 (each cycle = 3 weeks), then nivolumab 480 mg for a total of 6 doses starting at C5 through C10 for cohort 2 (each cycle = 4 weeks). See Section 7.

Table 2-3: On Treatment Procedural Outline for Cohort 2 Arms C and D (CA2099TM)

Procedure[a]	Cycle 1 (C1) (cycle=2 weeks)	C2 - C4 [b] (each cycle= 3 weeks)	C5 to C10[b] (each cycle=4 weeks)	Notes Procedures must be done within 72 hrs. prior to dosing unless otherwise specified Study visits to occur at the start of each cycle [i.e., for C2 to C4 for cohort 2 (± 3 days) and for C5 to C10 for cohort 2 (± 7 days). Cycles will differ between Cohorts.
Administer Cisplatin (**for Cohort 2 only**)		X		For cohort 2 only, administer cisplatin 100 mg/m^2 every 21 days x 3 doses in C2, C3, and C4. See Section 7.
Radiotherapy (RT)		X		IMRT: 70 Gy, 35 fractions over 7 weeks from w3d1 (C2). Alternate Fractionation Schemes are not permitted). The first fraction of RT should be delivered on a Monday or Tuesday, but this may vary according to local treatment plan. Five fractions should be delivered a week. Randomization and dosing should be timed such that the first dose of nivolumab occurs 14 days ± 3 days prior to the start of RT. See Section 7.1.4.

Abbreviations: c or C=cycle; d or D=day; IV=intravenous; Q1W=every week; Q3W=every 3 weeks; Q4W=every 4 weeks; w or W=week

[a] 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.

[b] If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs.

Table 2-4: Follow-Up Procedural Outline for Both Cohorts (CA2099TM)

Procedure[a]	Follow-Up Visits [b]	Notes:
Safety Assessments		
Informed Consent	Following study closure, participants already enrolled in the study will require re-consent upon implementation of Revised Protocol 03.	
Targeted Physical Examination	X	To assess for potential late emergent study drug related issues. Also, includes head and neck examination and at the discretion of the investigator, also fiber optic examination.
Vital Signs	X	
Assessment of Signs and Symptoms	X	At least 100 days form the last dose of therapy, participants must be followed for ongoing drug-related AEs until resolved, return to baseline or deemed irreversible, or until lost to follow-up, withdrawal of study consent, or start of subsequent therapy.
[redacted]	[redacted]	[redacted]
Serious Adverse Events Assessment	X	In survival follow-up period only to include toxicities from study therapy
Laboratory Tests	X	See Section 9.4.1 for additional details on tests required. • CBC with differential, Chemistry panel, and Thyroid function testing
Pregnancy Test	X	WOCBP only: Serum or urine. Approximately every 4 weeks for 5 months after the last dose of nivolumab.
[redacted]		
[redacted]	[redacted]	
[redacted]		
[redacted]	[redacted]	
[redacted]		
[redacted]		

Table 2-4: Follow-Up Procedural Outline for Both Cohorts (CA2099TM)

Procedure[a]	Follow-Up Visits [b]	Notes:
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]	[redacted]	

Abbreviations: c or C=cycle; d or D=day; FU=follow up; Q12W=every 12 weeks; w or W=week.

[a] 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.

[b] Participants must be followed for at least 100 days after last dose of study treatment. Follow-up visit #1 should occur 30 days from the last dose (± 7 days) or can be performed on the date of discontinuation if that date is great than 42 days from the last dose. Follow-up visit #2 occurs approximately 100 days (±7 days) from last dose of study treatment. Both follow-up visits should be conducted in person.

3 INTRODUCTION

CA2099TM was a randomized, double blind, placebo controlled, Phase 3 study of nivolumab or nivolumab plus cisplatin, in combination with radiotherapy in participants with cisplatin ineligible and cisplatin eligible locally advanced squamous cell carcinoma of the head and neck (SCCHN).

The study consists of two independent cohorts:

- Cohort 1 will randomize participants who are ineligible for cisplatin chemotherapy based either on age (≥ 70 years), and/or poor renal function (Creatinine clearance < 60 mL/min), and/or have documented hearing loss (minimal hearing threshold of 80 dB or more in either ear) to receive nivolumab in combination with radiotherapy (RT) or cetuximab in combination with RT.
- Cohort 2 will randomize participants who are eligible to receive cisplatin based therapy to receive nivolumab or placebo in combination with cisplatin and RT.

As of 15-Oct-2018, enrollment into the study was closed (see Section 3.1.1). Participants who have signed an informed consent as of 15-Oct-2018 and are in the screening period will be able to be randomized. All participants receiving treatment will have the option to continue treatment under the updated Revised Protocol 03. At approval and implementation of Revised Protocol 03, all enrolled participants must be re-consented prior to continuing treatment on the study. Under Revised Protocol 03 only safety assessments will be conducted as part of study procedures. Participants will be monitored until 100 days post-last dose.

3.1.2 Research Hypothesis

Not Applicable per Revised Protocol 03.

pembro dose-limiting AEs and immune related AEs (irAEs). Of the 27 treated participants, 21

Overall, the safety profile of nivolumab monotherapy is manageable and generally consistent

[redacted]

4 OBJECTIVES AND ENDPOINTS

Not applicable per Revised Protocol 03. Only safety assessments will be conducted. No collections of efficacy, quality of life/patient-reported outcomes, pharmacokinetics, or health resource utilization are planned. Previously collected biomarker samples may be analyzed, but no further sample collections are planned.

5 STUDY DESIGN

5.1 Overall Design

See Section 3.1.1 for updated on Study Design per Revised Protocol 03.

The original design of study CA2099TM was a randomized, double blinded, placebo controlled, phase 3 study of nivolumab or nivolumab plus cisplatin, in combination with radiotherapy in

participants with cisplatin ineligible and cisplatin eligible locally advanced squamous cell carcinoma of the head and neck (LAD SCCHN).

As of 15-Oct-2018, enrollment into the study was closed. At implementation of Revised Protocol 03, the study will be unblinded. Placebo treatments will no longer be given.

For Cohort 1 (cisplatin ineligible), participants must be either age ≥ 70 years, and/or have creatinine clearance < 60 mL/min, and/or have documented hearing loss (minimal hearing threshold of 80 dB or more in either ear). There is no minimum or maximum number of participants that must fulfill any of these criteria. For Cohort 2 (cisplatin eligible), participants eligible for cisplatin based CRT must have cisplatin eligible disease.

Participants will be stratified as follows:

- Cohort 1 (cisplatin ineligible), participants will be stratified by PD-L1 tumor expression (≥1% vs < 1% or indeterminate), risk category (intermediate vs. high risk), and Eastern Cooperative Oncology Group performance status (ECOG PS [0 vs 1]) and randomized in a 1:1 ratio to one of the study arms (Arms A or B).
- Cohort 2 (cisplatin eligible), participants will be stratified by PD-L1 tumor expression (≥1% vs < 1% or indeterminate) and risk category (intermediate vs. high risk), and ECOG PS [0 vs 1]) and randomized in a 1:1 ratio to one of the study arms (Arms C or D).

HPV p16 testing can be performed locally or centrally and is required for entry into the study for participants with oropharyngeal disease. For subjects with oropharyngeal cancer, sites are defined in Appendix 11.

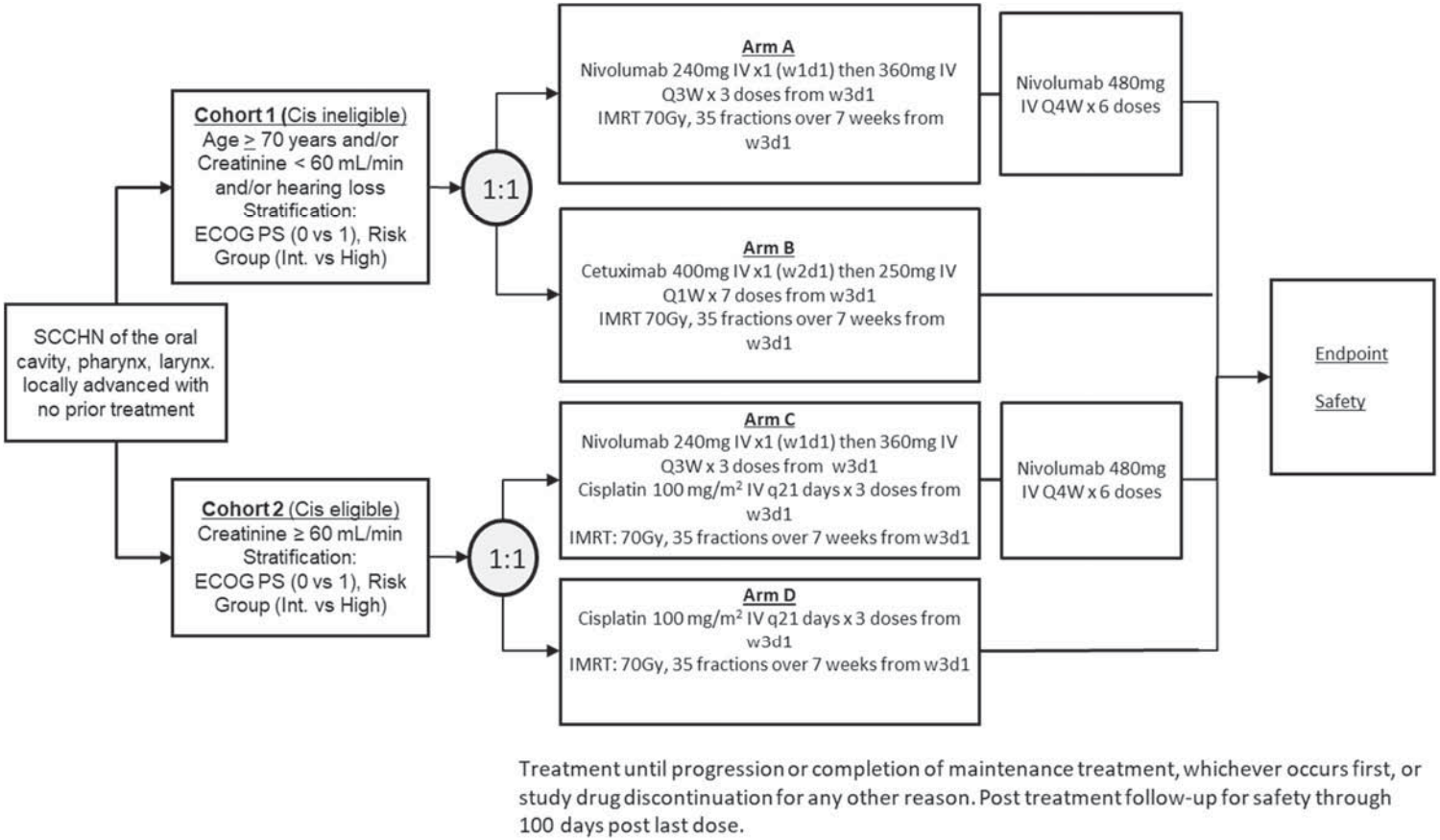
After participants sign an informed consent, a tumor sample collection is mandatory for PD-L1 testing (shipped to a central lab). Sufficient, recent tumor tissue obtained within < 3 months prior to enrollment from a primary tumor lesion which has not been previously irradiated (formalin-fixed paraffin-embedded block or minimum of 25 slides preferred, obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen) must be received by a central lab. If the archival tissue is > 3 months old, a fresh biopsy must be obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen to obtain sufficient tissue sample for PD-L1 testing (two block or minimum of 25 slides preferred). Fine needle aspiration cytology is not acceptable. Biopsies of bone lesions that do not have a soft tissue component are unacceptable for submission. Participants should not have received any systemic anticancer therapy after the date that the submitted tumor tissue was obtained. The PD-L1 analysis must be processed with an available result prior to randomization..

A multidisciplinary case evaluation, including input from radiation oncology, medical oncology and ENT/head and neck surgeon or equivalent functions is required prior to randomization (patients should have been seen by each of these groups or discussed at a multidisciplinary tumor board meeting). For larynx, hypopharynx, and base of tongue primaries, a laryngopharyngoscopy (mirror and/or fiber optic and/or direct procedure) prior to randomization is required unless the participant cannot tolerate or refuses. [redacted]

[redacted]

The study design schematic is presented in Figure 5.1-1.

Figure 5.1-1: Study Design Schematic for CA2099TM*



*As of 15-Oct-2018, enrollment in the study is closed. Participants who have signed an informed consent as of that date will be permitted to be randomized, and participants currently on treatment may continue. All participants should be re-consented under the current Revised Protocol 03. Only safety assessments will be conducted.

Upon approval and implementation of Revised Protocol 03, placebo treatments will no longer be given.

Abbreviations: C=cycle; Cis=cisplatin; CRCL=creatinine clearance; d=day; ECOG PS= Eastern Cooperative Oncology Group performance status; IMRT= Intensity-modulated radiation therapy; Int.=Intermediate; IV=intravenous; PD-L1= Programmed death-ligand 1; Q1W=every week; Q2W=every 2 weeks; q21 days=every 21 days; Q3W=every 3 weeks, Q4=every 4 weeks; SCCHN= squamous cell carcinoma of the head and neck; w or W=week

Participants in **Cohort 1** (cisplatin ineligible) will be randomized 1:1 to either Arm A or Arm B:

- **Arm A** will be administered nivolumab 240 mg for a single dose at w1d1 (C1 of cohort 1) then nivolumab 360 mg every 3 weeks for a total of 3 doses starting at w3d1 (C3, C6, C9 of cohort 1). Then, participants will be administered nivolumab 480 mg every 4 weeks for a total of 6 doses.
- **Arm B** will be administered cetuximab 400 mg/m^2 as a single dose at w2d1 (C2 of cohort 1) then 250 mg/m^2 IV every week for a total of 7 doses starting at w3d1 (C3 to C9 of cohort 1) with IMRT.

Participants in **Cohort 2** (cisplatin eligible) will be randomized 1:1 to either Arm C or Arm D.

- **Arm C** will be administered nivolumab 240 mg for a single dose at w1d1 (C1 of cohort 2) then nivolumab 360 mg every 3 weeks for a total of 3 doses starting at w3d1 (C2, C3, C4 of cohort 2). In addition, participants will be administered cisplatin 100 mg/m^2 every 21 days for 3 doses starting at w3d1 (C2 of cohort 2) with IMRT. Then, participants will be administered nivolumab 480 mg every 4 weeks for a total of 6 doses.
- **Arm D** will be administered cisplatin 100 mg/m^2 every 21 days for 3 doses starting at w3d1 (C2 of cohort 2) with IMRT.

Participants in Cohort 1 (cisplatin ineligible) and Cohort 2 (cisplatin eligible) will receive RT to a total dose of 70 Gy in 35 fractions which will be administered in daily doses of 2 Gy, typically on a 5 days on / 2 days off schedule as appropriate, over 7 weeks by Intensity Modulated Radiation Therapy (IMRT) starting at w3d1. Alternate fractionation schemes are not allowed. Sites must be equipped and qualified to deliver standard of care radiotherapy in combination to the specified systemic agents. Radiotherapy will be subject to a Quality Assurance (QA) process. This will involve site qualification/credentialization and real time review of radiotherapy plans with real time feedback to sites. On completion of radiotherapy all data must be submitted for final analysis. The radiotherapy requirements and QA processes will be the subject of a separate manual. QA services will be provided by an external vendor.

After randomization, participants must commence systemic treatment within 3 days. Participants should not delay starting systemic treatment in order to complete radiotherapy QA. Following initial systemic treatment, sites have 14 days to complete radiotherapy planning and QA before starting RT at w3d1.

Participants who are randomized to a placebo arm do not need to delay the start of radiotherapy. For subjects randomized to Cohort 1 Arm B, cetuximab may be administered at w1d1 and radiotherapy at w2d1. For participants randomized to Cohort 2 Arm B, cisplatin and radiotherapy may begin at w1d1.

Imaging will occur at baseline (within 28 days prior randomization. Per Revised Protocol 03, subsequent imaging assessments should be performed according to the timing of local standard of care.

The Follow-up stage begins when protocol specific treatment with nivolumab is completed or the decision to discontinue a participant from study therapy is made (no further treatment with study therapy). Participants will have the first follow-up visits (FU1 and FU2) approximately 30 days and 100 days, respectively, from the last dose of study therapy or coinciding with the date of discontinuation and AEs will be followed until the toxicities resolve, return to baseline, or are deemed irreversible.

All participants should continue to have tumor scans per local standards of care. .

5.1.1 Data Monitoring Committee and Other External Committees

5.1.1.1 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be utilized to provide general oversight and safety considerations for this study, CA2099TM. The DMC will provide advice to the Sponsor regarding actions the committee deems necessary for the continuing protection of subjects enrolled in this study. The DMC will be charged with assessing such actions in light of an acceptable safety profile for nivolumab. The DMC will act in an advisory capacity to BMS and will monitor subject 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.

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

5.1.2 Radiotherapy Quality Assurance

Radiation Therapy (RT) QA for this study consists of 3 components.

1) Sites will undergo radiation therapy credentialing prior to enrolling patients on study.
2) The RT treatment plans for all patients will have a pre-treatment central review prior to the start of radiation therapy. Feedback will be provided to the treating site within 72 hours of receipt of the treatment plan.
3) At the completion of radiation therapy documentation of the course of treatment delivered will be submitted for central review. A summary of the delivered radiation therapy and compliance with protocol requirements will be provided to BMS for the participant record.

Qualification of site for delivery of radiotherapy will be based on ongoing radiation quality assurance activities, including site credentialing and rapid review of radiotherapy plans. The RT QA data submission requirements and protocol compliance criteria are detailed in the RT QA Manual.

5.2 Number of Participants

Per Revised Protocol 03, enrollment in this study was closed as of 15-Oct-2018.

5.3 End of Study Definition

The start of the trial is defined as the first visit for the first participant screened. End of trial is defined as the last visit or scheduled procedure shown in the Schedule of Activities (SOA) for the last participant. Study completion is defined as the final date on which data is collected for this study. The total duration of the study will be determined by the last safety follow-up visit for the last participant after stopping treatment (i.e. 100 days from the last dose of study treatment).

[redacted]

[redacted]

6 STUDY POPULATION

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

6.1 Inclusion Criteria

Per Revised Protocol 03, enrollment in the current study was closed as of 15-Oct-2018. Participants that have signed an informed consent as of that date will be permitted to be randomized. All study participants must be re-consented at implementation of Revised Protocol 03.

1) Signed Written Informed Consent

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

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

2) Type of Participant and Target Disease Characteristics

a) Histologically proven squamous cell carcinoma of the head and neck (SCCHN) from one of the following primary sites: oral cavity, oropharynx, hypopharynx, and larynx

b) Locally advanced disease which is unresectable, or resectable but suitable for an organ sparing approach

c) No previous radiotherapy or systemic treatment for SCCHN

d) Eastern cooperative oncology group (ECOG) score of 0-1 (Appendix 7)

e) Measurable disease by RECIST1.1 (Appendix 10) criteria, and tumor assessment performed prior to randomization

f) Sufficient sample of fresh or archival (< 3 months from informed consent date) formalin-fixed, paraffin-embedded (FFPE) tissue block, or unstained tumor tissue sections, with an associated pathology report, must be submitted for biomarker evaluation for PD-L1 status. Central lab must provide Interactive Response Technology (IRT) with confirmation of receipt of evaluable tumor tissue prior to randomization. Biopsy should be excisional, incisional or core needle. Fine needle or aspiration is unacceptable for submission. PD-L1 status must be available prior to randomization. Not applicable after 15-Oct-2018.

g) HPV p16 test result available (performed locally or centrally) for participants with oropharyngeal disease

h) Patients must be of intermediate or high risk categories*:

i) High risk:

(1) Oral cavity, hypopharynx, larynx, oropharynx (p16 negative): Stage III/IV

(2) Oropharynx (p16 positive): Stage III (T4 any N or T1-3 N3) - irrespective of smoking status.

ii) Intermediate risk:

(1) Oropharynx (p16 positive): T3 N0-2 or T1-3 N2 disease if smoking > 20 pack year history

*TNM clinical staging according to AJCC version 8 (Appendix 6).

3) Cohort 1 (cisplatin ineligible) Specific Inclusion Criteria (Arms A and Arm B)

a) Physician assesses participant to be non-eligible for treatment with platinum based combined CRT. This must be for one or more of the following reasons:

i) Age ≥ 70 years at enrolment

ii) Creatinine clearance < 60mL/min and > 30mL/min (using the Cockcroft and Gault formula– see below**)

iii) Severe hearing loss (minimal hearing threshold of 80 dB or more in either ear)

4) Cohort 2 (cisplatin eligible) Specific Inclusion Criteria (Arm C and Arm D)

a) Adequate renal function within 28 days prior to randomization as follows:

i) Creatinine clearance ≥ 60 mL/min. as determined by 24 hour collection or estimated by Cockcroft-Gault formula:

$$C_{Cr}=\{((140–\text{age in years}) \times \text{weight in Kg})/(72 \times \text{serum creatinine in mg/dL})\}$$

(for females, multiply the result by 0.85)**

**Participants aged ≥ 70 years may enter either Cohort 1 or 2 dependent on whether the physician's assessment is that the participant is eligible for cisplatin (Cohort 2) or ineligible for cisplatin (Cohort 1) based on their age. It is anticipated that in the majority of cases, patients aged ≥ 70 years will be considered ineligible for cisplatin and

enter cohort 1. If the subject has poor renal function as one of the acceptable inclusion criteria, the subject will be enrolled under inclusion criteria 3) ii) and must meet the requirement for Creatinine clearance < 60 mL/min and > 30mL/min (using the Cockcroft and Gault formula)

5) Age and Reproductive Status

a) Males and Females ≥ ages 18 or age of majority

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

c) Women must not be breastfeeding

d) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of study treatment with nivolumab and 5 months after the last dose of study treatment {i.e., 30 days (duration of ovulatory cycle) plus the time required for the investigational drug to undergo approximately five half-lives.}.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of study treatment with nivolumab and 7 months after the last dose of study treatment {i.e., 90 days (duration of sperm turnover) plus the time required for the investigational drug to undergo approximately five half-lives.}.

f) Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section.

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

6.2 Exclusion Criteria

Per Revised Protocol 03, enrollment in the current study was closed as of 15-Oct-2018. Participants that have signed an informed consent as of that date will be permitted to begin treatment.

1) Medical Conditions

a) Carcinoma originating in the nasopharynx or paranasal sinus, squamous cell carcinoma that originated from the skin and salivary gland or non-squamous histology (e.g., mucosal melanoma), squamous cell carcinoma of unknown primary

b) Clinical or radiological evidence of metastatic disease

c) Prior radiotherapy that overlaps with radiation fields

d) Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the participant to receive protocol therapy, or interfere with the interpretation of study results

e) Active unstable angina and/or congestive heart failure

f) Myocardial infarction within 6 months prior to randomization

g) Participants who have a weight loss of > 10% of body weight between start of screening period and randomization will be considered a screen failure

h) 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.

i) Participants with active interstitial lung disease (ILD) / pneumonitis or with a history of ILD / pneumonitis requiring steroids.

[redacted]

3) Physical and Laboratory Test Findings

a) Screening laboratory values should be obtained within 14 days prior to first dose, the below values are exclusionary:

i) Neutrophils < 1500/μL

ii) Platelets < 100 $x10^3/\mu L$

iii) Hemoglobin < 9.0 g/dL

iv) AST/ALT: > 3.0 x ULN

v) Total bilirubin > 1.5 x ULN (except participants with Gilbert Syndrome who must have a total bilirubin level of < 3.0 x ULN)

b) Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, e.g., hepatitis B surface antigen (HBsAg, Australia antigen) positive, or hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative).

c) Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated locally.

4) Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to 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 (e.g., infectious disease) illness

Eligibility criteria for this study have been carefully considered to ensure the safety of the study participants and that the results of the study can be used. It is imperative that participants fully meet all eligibility criteria.

6.3 Lifestyle Restrictions

Not applicable. No restrictions are required

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized in the study/included in the analysis population. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs.

6.4.1 Retesting During Screening or Lead-In Period

As of 15-Oct-2018, enrollment in this study was closed, as of enrollment closure this section is not applicable.

This study permits the re-enrollment of a participant that has discontinued the study as a pre-treatment failure (i.e., participant has not been randomized). If re-enrolled, the participant must be re-consented.

Retesting of laboratory parameters and/or other assessments within any single Screening or Lead-in period will be permitted (in addition to any parameters that require a confirmatory value).

The most current result prior to Randomization is the value by which study inclusion will be assessed, as it represents the participant's most current, clinical state.

Laboratory parameters and/or assessments that are included in Table 2-1, 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.

7 TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo or medical device intended to be administered to a study participant according to the study randomization or treatment allocation.

Study treatment includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following (see Table 7-1 for additional details):

- BMS-936558-01 (Nivolumab) Solution for Injection
- Cetuximab solution for Infusion
- Cisplatin solution for Infusion

Note: At the approval and implementation of Revised Protocol 03 study treatments will be unblinded, and no further placebo medication will be given.

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

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

Table 7-1: Study Treatments for CA2099TM

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Nivolumab Solution for Injection[a]	10 mg/mL – 100 mg fill volume	IP	Open Label[b]	Vials	Refer to the label or container and/or pharmacy manual
Cetuximab Solution for Infusion[c]	5 mg/mL - 500 mg fill volume	IP	Open Label[b]	Vials	Refer to the label or container and/or pharmacy manual
Cisplatin Concentrate for Solution for Infusion[c]	1 mg/mL – 100 mg fill volume	IP	Open Label[b]	Vials	Refer to the label or container and/or pharmacy manual.

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

[b] The term "open label" refers to the medication as it is upon receipt at the pharmacy. Per Revised Protocol 03, the study will be unblinded, and placebo treatment will no longer be administered.

[c] 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) or according to institutional standards.

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

7.1 Treatments Administered

The selection and timing of dose for each participant is as follows in Table 7.1-1. Dosing schedule by cycle for Cohort 1 and 2 are shown in Table 7.1-2and Table 7.1-3, respectively.

Table 7.1-1: Selection and Timing of Dose

Arm	Study Treatment	Dosage level(s) and Formulation	Frequency of Administration	Route of Administration
A	Nivolumab	240 mg IV x 1 dose then 360 mg IV x 3 doses then 480 mg IV x 6 doses	Single dose at w1d1 (C1 of cohort 1) then every 3 weeks (Q3W) for 3 doses starting w3d1 then every 4 weeks (Q4W) for 6 doses	IV
B	Cetuximab	400 mg/m^2 IV x 1 dose then 250 mg/m^2 IV x 7 doses	Single dose at w2d1 (C1 of cohort 1) then every week (Q1W) for 7 doses	IV
C	Nivolumab	240 mg IV x 1 dose then 360 mg IV x 3 doses then 480 mg IV x 6 doses	Single dose at w1d1 (C1 of cohort 2) then every 3 weeks (Q3W) for 3 doses starting w3d1 then every 4 weeks (Q4W) for 6 doses	IV
	Cisplatin	100 mg/m^2 IV x 3 doses	Every 21 days (q21days) starting at w3d1	IV
D	Cisplatin	100 mg/m^2 IV x 3 doses	Every 21 days (q21days) starting at w3d1	IV

Abbreviations: C=cycle; d=day; IV=intravenous; Q1W=every week; q21 days= every 21 days; Q3W=every 3 weeks; Q4W=every 4 weeks; w=week

Table 7.1-2: Dosing Schedule by Cycle for Cohort 1 Arms A and B

	Drug	Cycle 1 (cycle=1 week)	Cycle 2 (cycle=1 week)	Cycle 3 (cycle=1 week)	Cycle 4 and Cycle 5 (cycle=1 week)	Cycle 6 (cycle=1 week)	Cycle 7 and Cycle 8 (cycle=1 week)	Cycles 9 (cycles=1 week)	Cycles 10 to 15[a] (cycles=4 weeks)
Cohort 1 Arm A	**Nivolumab**	Nivolumab 240 mg IV x 1	--	Nivolumab 360 mg IV	--	Nivolumab 360 mg IV	--	Nivolumab 360 mg IV	Nivolumab 480 mg IV at the start of the cycle
	Per Revised Protocol 03, no placebo will be administered.								
Cohort 1 Arm B	**Per Revised Protocol 03, no placebo will be administered.**								
	Cetuximab	--	Cetuximab 400 mg/m^2 IV x 1	Cetuximab 250 mg/m^2 IV	Cetuximab 250 mg/m^2 IV each cycle	Cetuximab 250 mg/m^2 IV	Cetuximab 250 mg /m^2 IV each cycle	Cetuximab 250 mg/m^2 IV	--

Abbreviations: C=cycle; IV=intravenous

[a] Cycle 10 to start after 2 weeks off after the end of Cycle 9.

Table 7.1-3: Dosing Schedule by Cycle for Cohort 2 Arms C and D

	Cycle 1 (cycle=**2** weeks)	**Cycle 2** (cycle=**3** weeks)	**Cycle 3** (cycle=**3** weeks)	**Cycle 4** (cycle=**3** weeks)	**Cycles 5 to 10** (cycles=**4** weeks)
Cohort 2 Arm C	Nivolumab 240 mg IV	Nivolumab 360 mg IV + Cisplatin 100 mg/m^2 IV	Nivolumab 360 mg IV + Cisplatin 100 mg/m^2 IV	Nivolumab 360 mg IV + Cisplatin 100 mg/m^2 IV	Nivolumab 480 mg IV at the start of the cycle
Cohort 2 Arm D		Cisplatin 100 mg/m^2 IV	Cisplatin 100 mg/m^2 IV	Cisplatin 100 mg/m^2 IV	

Abbreviations: C=cycle; IV=intravenous

The infusion duration of nivolumab is 30 minutes and for cetuximab is infusion duration is over 2 hours for 400 mg/m^2 and 1 hour for the 250 mg/m^2, see Section 7.1.2. The start and stop times of the infusions should be documented.

7.1.1 Nivolumab Dosing

Participants should begin study treatment within 3 calendar days of treatment assignment. Participants should receive nivolumab as a 30-minute infusion starting on Day 1 Cycle 1 at 240 mg, then after 2 weeks (-2/+3 days) 360 mg for 3 doses Q3W (± 3 days), then at 480 mg for 6 doses Q4W. Cycles differ between Cohorts. Refer to Table 7.1-2 for Cohort 1 and Table 7.1-3 for Cohort 2 when nivolumab is administered by cycle.

There will be no dose escalations or reductions of nivolumab allowed. Participants may be dosed no less than 12 days from the previous dose during Q2W cycles. For the Q3W (360 mg nivolumab) dosing, participants may be dosed no less than 18 days from the previous dose. For Q4W dosing cycles, participants may be dosed within a ± 7 day window. Premedications are not recommended for the first dose of nivolumab. Refer to Table 7.1-2 for details on dosing schedule for administration of nivolumab in Cohort 1 and Table 7.1-3 for Cohort 2.

Participants should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.7.

Doses of nivolumab may be interrupted, delayed (Section 7.4.1), or discontinued (Section 8.1.1) depending on how well the participant tolerates the treatment.

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) and 40 mg/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 (i.e., 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 (e.g., 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 a saline flush 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.

On cycles where nivolumab and cetuximab or cisplatin needs to be administered on the same day, nivolumab should be administered first using separate infusion bags and filters. The infusion of cetuximab or cisplatin should occur no earlier than 30 minutes after the completion of the nivolumab infusion.

7.1.2 Cetuximab

For countries in which BMS is providing packaged/labeled cetuximab, please refer to package insert, summary of product characteristics (SmPC), or similar document for details regarding drug preparation, administration and use time.

For countries where local sourcing of cetuximab is permitted, product should be stored, prepared and administered in accordance to the package insert, summary of product characteristics (SmPC) or similar document.

For participants in Cohort 1, cetuximab initial dose of 400 mg/m^2 (over 2 hour infusion) is given on Day 1 Cycle 2, then weekly (± 3 days) at 250 mg/m^2 (over 1 hour infusion) for 7 weeks (C3 to C9 in cohort 1). Refer to Table 7.1-2 for when cetuximab is administered by cycle.

7.1.2.1 Cetuximab supportive care

CAUTION: Infusion reactions may occur during or following cetuximab administration. Most infusion reactions occur with the first infusion of cetuximab, but some patients' first infusion reactions have been reported following subsequent doses. The infusion reaction may occur during the infusion or be delayed until any time after the infusion.

All patients will be premedicated with diphenhydramine hydrochloride, 50 mg, (or an equivalent antihistamine) by IV 30-60 minutes prior to the first dose of cetuximab in an effort to prevent an infusion reaction. For the initial dose of cetuximab of 400 mg/m^2, the dose may be split to observe for signs of an infusion reaction. An initial dose of 100 mg/m^2 may be given and if no signs of an infusion reaction are observed 30 minutes after the end of the infusion, the remaining 300 mg/m^2 may be given.

The routine use of systemic steroids for premedication is not necessary and may interfere with anti PD-1 activity. If considered absolutely necessary, systemic high dose steroids are allowed as premedication for the first dose of cetuximab and only as clinically indicated for the subsequent doses. Topical steroids are acceptable.

For cetuximab, the recommended premedication is with an H1 antagonist (e.g., 50 mg 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 of practice.

It is recommended that the medical staff closely observe participants for treatment-related adverse events, especially infusion reactions (see Section 7.4.2.4 for management) during the cetuximab infusion per local institutional standards.

For subsequent infusions, it is recommended that the participants be observed for 1 hour post-infusion.

Doses of cetuximab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. For more details see Sections dose delays (7.4.2), dose reductions (7.4.2), resuming treatment (7.4.4), and 8.1 discontinuation.

Participants should be carefully monitored for infusion reactions. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.2.4.

7.1.3 Cisplatin

For participants in Cohort 2, cisplatin (100 mg/m^2 IV) will begin dosing on Day 1 Cycle 2 and then every 21 days (± 3 days); participants are expected to receive 3 doses but must have minimum 2 doses. Individual investigators may use institutional guidelines for the administration of cisplatin. Refer to Table 7.1-3 to when cisplatin is administered by cycle.

Doses of cisplatin may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. For more details, see Sections 7.4.3 (dose delays), 7.4.3.1 (dose reductions), 7.4.4 (resuming treatment), and 8.1 (discontinuation).

7.1.3.1 Cisplatin supportive care

Institutional or National Comprehensive Cancer Network (NCCN) guidelines or local guidance should be followed for cisplatin supportive care. 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 participants 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 investigator, 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 mcg/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 an aprepitant is not given. On the day of chemotherapy administration, the dose of dexamethasone must be reduced by 50%, if an aprepitant is given.

For cisplatin, the recommended premedications 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.

7.1.4 Radiotherapy

All participating institutions must be credentialed for head and neck IMRT prior to enrolling participants in this study. See Section 5.1.2 for details.

Intensity Modulated Radiation Therapy (IMRT) is mandatory for this study. Proton therapy is not permitted.

IMRT will be given in 35 fractions over 7 weeks beginning at Day 1 Cycle 3 for Cohort 1 or Day 1 Cycle 2 for Cohort 2, 5 fractions per week (both corresponding to (w3d1).

Full details of radiation therapy are provided in an accompanying radiation therapy manual.

The first fraction of RT should be delivered on a Monday or Tuesday, but this may vary according to local treatment plan. Five fractions should be delivered a week. Randomization and dosing should be timed such that the first dose of nivolumab occurs 14 ± 3 days prior to the start of radiotherapy.

7.2 Method of Treatment Assignment

All participants will be assigned to treatment using an Interactive Response Technology (IRT). Users will receive log in information and directions on how to access the IRT. Study treatment will be dispensed at the study visits as listed in Schedule of Activities (Section 2).

As of 15-Oct-2018, enrollment in the study is closed. Participants with signed informed consent as of the 15-Oct-2018 may be randomized to treatment.

7.3 Blinding

Per approval and implementation of Revised Protocol 03, the study will be unblinded.

7.4 Dosage Modification

7.4.1 Nivolumab Dose Delay

If adverse events prevent the administration of nivolumab, the participant should continue to receive other study therapies.

Nivolumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related adverse event, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related adverse event
- 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 8.1.1)
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

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.

In case of RT delay due to technical issues (instrument breakdown), continue systemic treatment as planned.

7.4.1.1 Rescheduling Nivolumab Treatment After Dose Delay

- **If nivolumab is delayed during the combined radiotherapy phase, radiotherapy should continue unless there is a specific reason to discontinue both nivolumab and radiotherapy. It is anticipated that the majority of immune related AEs that require nivolumab delay or discontinuation will not require delay or discontinuation of radiotherapy**
- If nivolumab is delayed, the criteria for restarting nivolumab should be adhered to independent of whether the participant is receiving concurrent radiotherapy
- In the event of delay of nivolumab dosing during combined radiotherapy/nivolumab treatment, participants should receive 480 mg Q4W as soon after completion of radiotherapy as possible (at the earliest week 10), i.e., patients may receive fewer than 3 doses of 360 mg Q3W
- In the event of dose delay during nivolumab maintenance dosing, all 6 doses of nivolumab 480 mg Q4W should be given, up to a maximum duration of 40 weeks
- In the event of delay to radiotherapy requiring radiotherapy beyond week 11, 480 mg IV Q4 dosing should be substituted with 240 mg IV Q2 dosing until the radiotherapy is complete

7.4.2 Cetuximab Dose Modifications and Delay

If adverse events prevent the administration of cetuximab, the participant should continue to receive radiation therapy.

In the event of cetuximab treatment delay, there will be no reloading cetuximab infusion. Resume at the appropriate dose as indicated in Table 7.4.2-1.

Table 7.4.2-1: Cetuximab Dose Levels

	Starting Dose	Dose Level–1	Dose Level–2
Cetuximab	400 mg/m^2 (first week only)		
Cetuximab	250 mg/m^2 (weekly)	200 mg/m^2 (weekly)	150 mg/m^2 (weekly)

Note: If a weight change of ≥ 10% occurs, the cetuximab dose should be adjusted.

7.4.2.1 Cetuximab Dose Modifications for Hematologic Adverse Events

Cetuximab will not be dose reduced or held for hematologic adverse events, such as neutropenia, neutropenic fever, or thrombocytopenia.

7.4.2.2 Cetuximab Dose Modifications for Non-Hematologic Adverse Events

See Table 7.4.2.2-1.

See Section 7.4.2.5 for instructions for rash.

Table 7.4.2.2-1: Cetuximab Dose Modifications for Non-Hematologic Adverse Event

Toxicity Grade (CTCAE, v. 4)	**Cetuximab Dose[a]**
Renal-Calculated Creatinine Clearance*	
≥ 50 mL/min	Maintain dose levels
< 50 mL/min	Maintain dose levels
Fatigue (Asthenia) ≥ Grade 3	Maintain dose levels
Nausea/Vomiting ≤ Grade 2 with maximal medical management	Maintain dose levels
≥ Grade 3 with maximal medical management	Hold drug until ≤ grade 2, then resume at same dose level
Other Non-hematologic Adverse Events[b,c]	
Grade 3- 4, if possibly related to cetuximab, or likely to be exacerbated by continuation of cetuximab, e.g., diarrhea, except for weight loss or mucositis	Hold drug until < grade 3, then resume at 1 dose level reduction
Any grade 1-2	Maintain dose levels

[a] Dose levels are relative to the previous dose. Dose reductions of cetuximab below the –2 dose level will not be allowed. If a dose reduction below the -2 dose is mandated by the toxicity grade, cetuximab will be permanently discontinued. In any case of cetuximab treatment delay, there will be no re-loading infusion, and all subsequent treatment will be at the assigned dose level.

[b] With the exception of infusion reaction;

[c] For depressed K or Mg, administer replacement therapy. Chemotherapy should continue at the discretion of the treating physician (see table below for management of hypomagnesemia).

*For subjects with normal renal function.

7.4.2.3 Cetuximab Dose Modifications for Hypomagnesemia

Table 7.4.2.3-1: Cetuximab Dose Modifications for Hypomagnesemia

CTCAE, v. 4 Grade	Serum Magnesium		Guidelines for management	Action
	mg/dL	mmol/L		
1	< LLN – 1.2	< LLN – 0.5	Consider replacement with IV magnesium sulfate 2-5 g in normal saline or D5W. Infusion schedule based on institutional guidelines.	Maintain dose and schedule
2	< 1.2 – 0.9	< 0.5 – 0.4	As above for grade 1 and consider prophylactic weekly infusion of magnesium and/or oral magnesium supplementation (e.g., magnesium oxide) if grade 2 of higher hypomagnesemia persists.	Maintain dose and schedule
3	< 0.9 – 0.7	< 0.4 – 0.3	As above for grades 1 and 2	Hold cetuximab until recovery to ≤ grade 2, then resume at same dose level
4	< 0.7	< 0.3	As above for grades 1 and 2	Hold cetuximab until recovery to ≤ grade 2, then reduce by 1 dose level

7.4.2.4 Cetuximab Infusion Reaction Management

See Section 7.1.2.1 for additional information on cetuximab supportive care.

Table 7.4.2.4-1: Cetuximab Infusion Reaction Management

CTCAE, v. 4 Adverse Event Grade	Treatment Guidelines[a]
Grade 1: Mild transient reaction; infusion interruption not indicated; intervention not indicated	For mild infusion reactions, slow the infusion rate for cetuximab by 50% when the drug is restarted. For reactions manifesting only as delayed drug fever, consider administering prophylactic antihistamine medications for subsequent doses. Maintain the cetuximab dose. Acetaminophen or a non-steroidal anti-inflammatory drug (NSAID) may be administered prior to subsequent cetuximab infusions, if not otherwise contraindicated in participants.
Grade 2: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs	For moderate infusion reactions, slow the infusion rate for cetuximab by 50% when the drug is restarted and consider administering antihistamine medications and/or steroidal medications. Maintain the cetuximab dose. Acetaminophen or a non-steroidal anti-inflammatory drug (NSAID) may be administered prior to subsequent cetuximab infusions, if not otherwise contraindicated in participants.

Table 7.4.2.4-1: Cetuximab Infusion Reaction Management

CTCAE, v. 4 Adverse Event Grade	Treatment Guidelines[a]
Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	NO FURTHER STUDY DRUG THERAPY. Severe infusion reactions require immediate interruption of cetuximab infusion and permanent discontinuation from further treatment with cetuximab. Appropriate medical therapy including epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Patients should be carefully observed until the complete resolution of all signs and symptoms.

[a] Study Therapy Retreatment Following Infusion Reactions: Once a cetuximab infusion rate has been decreased due to an infusion reaction, it will remain decreased for all subsequent infusions. If the participant has a second infusion reaction > grade 2 with the slower infusion rate, the infusion should be stopped, and the patient should receive no further cetuximab treatment. If a patient experiences a Grade 3 or 4 infusion reaction at any time, the patient should receive no further cetuximab treatment. If there is any question as to whether an observed reaction is an infusion reaction of Grades 1-4, the Study Director and Medical Monitor should be contacted immediately to discuss and grade the reaction.

7.4.2.5 Cetuximab Related Rash

Manifestations: Rash associated with EGFR-inhibitors is a relatively new dermatologic condition. It appears to be "acneiform" but it is NOT considered a form of acne; rather, it is a form of folliculitis. Skin changes may be manifested in a number of ways: erythema; follicle based papules, which may ulcerate; pain; itching; cosmetic disturbance; and/or nail disorders. The rash may become infected and transform into cellulitis.

Grading of Cetuximab-induced Rash: According to physician judgment, if a participant experiences ≥ Grade 3 rash (according to either the "outside of the radiation field" or the "inside of the radiation field" definitions below), cetuximab treatment adjustments should be made according to the Cetuximab Dose Modification tables (Table 7.4.2.5-1 and Table 7.4.2.5-2). In participants with mild and moderate skin adverse events, cetuximab should continue without adjustment.

NOTE: Rash intensity (i.e., the size and number of papules or the level of discomfort and extent of erythema) may be an important consideration. However, the absolute number of lesions, **without associated physical discomfort**, does not necessarily constitute a basis for a dose reduction or delay. Rash considered "intolerable" (because of pain, itching, or appearance) or that has failed to respond to symptomatic management may be considered Grade 3 and thus prompt dose reduction or delay of cetuximab. **The clinical judgment of the treating physician is critical to grading and will ultimately dictate dose modification.**

Acute Skin Changes:

- Rash Occurring Outside of the Radiation Field: Should be graded using the following CTCAE, v. 4 terms. A rash complicated by secondary infection or cellulitis should be graded per additional CTCAE terms (see Table 7.4.2.5-1).
- Rash Occurring Inside the Radiation Field: Acute radiation dermatitis may be exacerbated by cetuximab or chemotherapy. The severity of such rash should be graded using CTCAE, v. 4 criteria for radiation dermatitis (see Table 7.4.2.5-2).
- Late Skin Changes: A potential late change of interest is consequential scarring/pock marking in or out of the radiation field. This may be reported by using the MedDRA code, "Skin and subcutaneous tissue disorders - Other, specify" with the following protocol-specific grading scale as guidance:
  - Grade 1: Mild (seen only on close inspection)
  - Grade 2: Moderate (scarring, intervention or cosmetic coverage/intervention indicated)
  - Grade 3: Severe (significant disfigurement, deep scarring, or ulceration)
  - Grade 4: Deep cratering/scarring, skin necrosis, or disabling

Table 7.4.2.5-1: Rash Occurring Outside of the Radiation Field

	1	2	3	4
Pruritus*	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	-
Rash/acneiform*	Papules and/or pustules covering < 10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADLI	Papules and/or pustules covering > 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self -care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life threatening consequences

Table 7.4.2.5-1: Rash Occurring Outside of the Radiation Field

	1	2	3	4
Paronychia*	Nail fold edema or erythema; disruption of the cuticle	Localized intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Surgical intervention or IV antibiotics indicated; limiting self care ADL	-

*Onset of grade 3 will require modification. See the Table 7.4.2.5-3, Cetuximab Dose Modification Guidelines for Dermatologic Changes.

Table 7.4.2.5-2: Rash Occurring Inside the Radiation Field

	1	2	3	4
Radiation recall reaction (dermatologic); Dermatitis radiation	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated

Table 7.4.2.5-3: Cetuximab Dose Modification Guidelines for Dermatologic Changes (≥ Grade 3)

	Cetuximab	**Outcome**	**Cetuximab Dose Modification**
1st occurrence	Delay infusion 1 to 2 weeks	Improvement to ≤ Grade 2	Resume at 250 mg/m^2
		No Improvement; remains grade 3	Discontinue cetuximab
2nd occurrence	Delay infusion 1 to 2 weeks	Improvement to ≤ Grade 2	Resume at Dose Level-1 (200 mg/m^2)
		No Improvement; remains grade 3	Discontinue cetuximab

Table 7.4.2.5-3: Cetuximab Dose Modification Guidelines for Dermatologic Changes (≥ Grade 3)

	Cetuximab	Outcome	Cetuximab Dose Modification
3rd occurrence	Delay infusion 1 to 2 weeks	Improvement to ≤ Grade 2	Resume at Dose Level-2 (150 mg/m^2)
		No Improvement; remains grade 3	Discontinue cetuximab
4th occurrence	Discontinue cetuximab		

Drug-Related Rash Management: Participants developing dermatologic adverse events while receiving cetuximab should be monitored for the development of inflammatory or infectious sequelae, and appropriate treatment of these symptoms initiated. Below are suggestions for managing cetuximab-induced rash[75]:

- **Antibiotics**: The benefit of routine antibiotics in uncomplicated (uninfected) rash is unclear, though the early use of tetracycline based antibiotics early is encouraged. Prophylactic used is also permissible. Rash complicated by cellulitis should be treated with appropriate antibiotics based on clinical judgment or microbial sensitivity analysis.
- **Antihistamines**: Benadryl or Atarax may be helpful to control itching.
- **Topical Steroids**: The benefit of topical steroids is unclear.
- **Retinoids**: No data to support use. Use is not advised.
- **Benzoyl peroxide**: Should NOT be used as this may aggravate rash.
- **Makeup**: Rash can be covered with makeup; this should not make it worse (use a dermatologist-approved cover-up, e.g., Dermablend®, or any other type of foundation). Remove makeup with a skin-friendly liquid cleanser, e.g., Neutrogena®, Dove®, or Ivory Skin Cleansing Liqui-Gel®.
- **Moisturizers**: Use emollients to prevent and alleviate the skin dryness, e.g., Neutrogena® Norwegian Formula Hand Cream® or Vaseline Intensive Care Advanced Healing Lotion®.
- **Sunlight**: It is recommended that participants wear sunscreen and hats and limit sun exposure while receiving cetuximab as sunlight can exacerbate any skin reactions that may occur.
- **Over-the-counter medications**: Over-the-counter acne vulgaris medications (e.g., benzoyl peroxide) are not advised. This rash is not like acne vulgaris and these treatments could make it worse.

7.4.2.6 Treatment Of Isolated Drug Fever

In the event of isolated drug fever, the investigator must use clinical judgment to determine if the fever is related to the study drug or to an infectious etiology.

If a participant experiences isolated drug fever, for the next dose, pre-treat with acetaminophen or non-steroidal anti-inflammatory agent (investigator discretion), repeat antipyretic dose 6 and 12 hours after cetuximab infusion. The infusion rate will remain unchanged for future dose. If a

participant experiences recurrent isolated drug fever following pre-medication and post-dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be 50% of previous rate. If fever recurs following infusion rate change, the investigator should assess the participant's level of discomfort with the event and use clinical judgment to determine if the patient should receive further cetuximab.

7.4.2.7 Rescheduling Cetuximab Treatment After Dose Delay

Weekly cetuximab will continue if radiation therapy is being held. If cetuximab is omitted for more than 4 consecutive infusions for adverse events due to cetuximab, or for an intercurrent illness (e.g., infection) requiring interruption of therapy, the participant should be discontinued from further cetuximab therapy. If adverse events prevent the administration of cetuximab, the participant may continue to receive nivolumab/placebo and radiation therapy.

If a dose of cetuximab is omitted, it will not be made up or added to the end of treatment. The omitted dose and the reason for the omission should be recorded in the site's source documentation.

7.4.3 Dose Modifications And Delay For Cisplatin

Note: If adverse events prevent the administration of cisplatin, the participant should continue to receive nivolumab and radiation therapy.

Cisplatin 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 $\geq$ 2 non-skin, drug-related adverse event, except for alopecia, fatigue or laboratory abnormalities
- 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 7.4.3.1. 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.

7.4.3.1 Dose Reductions for cisplatin

A maximum of 2 dose reductions are permitted; if additional reductions are required, cisplatin 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. Participants who

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

Recommendations for dose modifications for cisplatin should be considered with local institutional standards. The dose levels for cisplatin are listed in Table 7.4.3.1-1.

Table 7.4.3.1-1: Dose Levels for Cisplatin

Toxicity Grade (CTCAE, v. 4)	Cisplatin Dose
Stating Dose	100 mg/m^2
Dose Level -1	75 mg/m^2
Dose Level -2	56 mg/m^2

7.4.3.2 Recommended Cisplatin 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 7.4.3.2-1.

Table 7.4.3.2-1: Cisplatin Dose Modifications for Hematologic Toxicity[a]

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

7.4.3.3 Recommended Dose Modifications for Non-Hematologic Toxicity

Dose adjustments for non-hematologic toxicity during treatment are described in Table 7.4.3.3-1. All dose modifications should be made based on the worst grade toxicity per CTCAE v4.0.

Table 7.4.3.3-1: Cisplatin Dose Modifications for Non-hematologic Toxicity[a]

Drug Related Toxicity	Cisplatin
Nausea/vomiting ≥ Grade 3 despite optimal medical treatment	Decrease 1 dose level
Stomatitis ≥ Grade 3	Decrease 1 dose level
Diarrhea ≥ Grade 3 despite optimal medical treatment	Decrease 1 dose level
Neuropathy (sensory or motor), Grade 2 lasting > 7 days OR Grade 3 lasting < 7 days	Decrease 2 dose level
Ototoxicity Grade 2	Decrease 1 dose level
Nephrotoxicity (Creatinine Clearance 40-59mL/min or Grade 3 Creatinine)	Decrease 2 dose level
Creatinine clearance < 40 mL/min	Discontinue
Neuropathy Grade 4 (sensory or motor)	Discontinue
Mucositis Grade 4	Decrease 1 dose level
Other Grade ≥ 3 toxicities (except fatigue and transient arthralgia and myalgia)	Decrease 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 the cytotoxic.

7.4.3.4 Rescheduling Cisplatin Treatment After Dose Delay

Three-weekly cisplatin will continue if radiation or nivolumab/placebo is being held. If cisplatin is delayed for more than 6 weeks for an AE due to cisplatin, or for an intercurrent illness (e.g. infection) requiring interruption of therapy, the participant should be discontinued from further cisplatin therapy. If AEs prevent the administration of cisplatin, the participant may continue to receive nivolumab/placebo and radiation therapy. The omitted dose and the reason for the omission should be recorded in the site's source documentation.

7.4.4 Criteria to Resume Cisplatin or Cetuximab Dosing

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 ≥ 100,000 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 8.1) 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 Section 7.4.2.5 above.

For cetuximab, if the criteria to resume treatment are met, the participant should restart treatment at the next scheduled time-point per protocol. For cisplatin, if treatment is delayed > 6 weeks, participant must be discontinued from the study therapy. Delays of > 6 weeks are allowed for extended steroid tapers or after consultation with the BMS medical monitor.

7.4.5 Dose Delay: Radiotherapy

Dose delay of nivolumab will be based upon standard nivolumab protocol requirements. The decision to delay nivolumab should be made separately from the decision to delay radiotherapy, and in the majority of cases of nivolumab delay, radiotherapy should be continued unless there is a medically justified reason to delay both nivolumab and radiotherapy simultaneously.

For details of delay to radiotherapy treatment, please refer to the accompanying radiotherapy manual.

7.4.6 Management Algorithms For Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab is considered an immuno-oncology agent 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 Appendix 5 and in the nivolumab Investigator Brochure.

7.4.7 Treatment of Nivolumab Related Infusion Reactions

As nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if a reaction occurs, it may manifest as fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Study Medical Monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 4) 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 administration.

For Grade 2 symptoms: (moderate reaction required therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids); prophylactic medications indicated for ≤ 24 hours):

- Stop the nivolumab 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 nivolumab will be not be administered at that visit.
- 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 infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

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

- Immediately discontinue infusion of nivolumab. 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. Study drug 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 (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine or corticosteroids).

7.5 Preparation/Handling/Storage/Accountability

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

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

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

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

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

Please refer to the current version of the Investigator Brochure (IB) and/or pharmacy manual for complete storage, handling, dispensing, and infusion information for nivolumab, cetuximab, cisplatin, and matching placebo. The pharmacy manual will refer to the current SmPC for non-BMS investigational products. These products may be obtained by the investigational sites as local commercial product in countries where it is allowed by local regulations. Non-BMS investigational products should be prepared/stored/administered in accordance with the package insert or summary of product characteristics (SmPC) or according to institutional standards.

Further guidance and information for final disposition of unused study treatment are provided in Appendix 2.

7.6 Treatment Compliance

Study treatment compliance will be periodically monitored by drug accountability. Drug accountability should be reviewed by the site study staff at each visit to confirm treatment compliance. Sites should discuss discrepancies with the participant at each on-treatment study visit.

[redacted]

7.7.2 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.

7.7.2.1 Permitted Therapies

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 (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

7.7.2.2 Imaging Restriction and Precautions

Per Revised Protocol 3, imaging will be performed according to local standard of care.

It is the local imaging facility's responsibility to determine, based on participant attributes (e.g., 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 (i.e., estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this participant population. Certain surgically-implanted devices (pacemaker, deep brain stimulator, metallic implants, etc.) are incompatible with MRI imaging. The local imaging facility and investigator should determine the appropriate precautions or guidelines that should be instituted for participants with tattoos, body piercings or other body art.

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.

[redacted].

7.8 Treatment After the End of the Study

At the conclusion of the study, participants who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study treatment **for the maximum treatment duration specified in protocol Section 7.1**. Study treatment will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS.

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

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

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

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws

consent for any further contact with him/her or persons previously authorized by participant to provide this information
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by 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.)
- Documented investigator-assessed progression by RECIST v1.1

Refer to the Schedule of Activities (Table 2-4) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In the event a normal healthy female participant becomes pregnant during a clinical trial, the study treatment must be discontinued immediately. In most cases, the study treatment will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for participant safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

All participants who discontinue study treatment should comply with protocol specified follow-up procedures as outlined in Section 2. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

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

8.1.1 Nivolumab Dose Discontinuation

Nivolumab treatment should be permanently discontinued for 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 adverse event lasting > 7 days or recurs, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, 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
  - 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 drug(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug(s), 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 lasting ≤ 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.

Prior to re-initiating 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. 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.

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.

8.1.2 Criteria to Resume Nivolumab Treatment

Participants may resume treatment with study drug when the drug-related AE(s) resolve 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
- 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.
- Participants with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 8.1.1) should have treatment permanently discontinued.
- 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 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. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

8.1.3 Nivolumab Treatment Beyond Disease Progression

Treatment beyond investigator assessed progression will not be permitted on this study. The radiotherapy given in combination with nivolumab/cisplatin/cetuximab are intended to be definitive treatment and any recurrence is likely to represent genuine progression of the disease, if that recurrence/progression is non equivocal. In cases where progression is equivocal based on imaging findings, it is recommended that a biopsy is performed to further investigate radiological findings.

8.1.4 Cetuximab Dose Discontinuation

Specific details of AEs requiring discontinuation can be found in section 8.1 and Section 7.4.2.

8.1.5 Cisplatin Dose Discontinuation

See Section 8.1 and Section 7.4.3 for criteria for discontinuation of study treatment.

8.1.6 Post Study Treatment Study Follow-up

Per Revised Protocol 03, overall survival follow up is not required. Participants will be followed for assessment of safety through 100 days post last dose of study treatment.

BMS may request that survival data be collected on all treated/randomized participants outside of the protocol defined window (Section 2). At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contacts or is lost to follow-up.

8.2 Discontinuation from the Study

Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.

- Participants should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible.
- The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study treatment only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page.
- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-Up

After 15-October-2018, follow-up is restricted to safety assessments through the 100 days after the last day of dosing.

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

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities.
- Protocol waivers or exemptions are not allowed.

- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities (Section 2).
- Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (e.g., 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.
- If a participant shows pulmonary-related signs (hypoxia, fever) or symptoms (e.g.. dyspnea, cough, fever) consistent with possible pulmonary adverse events, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in the BMS-936558 (nivolumab) Investigator Brochure.
- 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.

9.1 Efficacy Assessments

9.1.1 Imaging Assessment for the Study

Per Revised Protocol 03, imaging assessments will be conducted per the schedule of local standard of care. Tumor imaging assessments for ongoing study treatment decisions will be completed by the investigator using RECIST v1.1 criteria (see Appendix 10)

Screening (baseline) tumor assessments of neck, chest, abdomen, and pelvis are to be performed within 28 days prior to randomization.

If the investigator assesses there to be progression, study treatments must discontinue; treatment beyond progression is not permitted in this protocol.

[redacted]

9.2 Adverse Events

The definitions of an AE or serious adverse event (SAE) can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

Immune-mediated adverse events are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (e.g., infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the participant's case report form.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue before completing the study.

Contacts for SAE reporting specified in Appendix 3

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study treatment and continue during the treatment period and for a minimum of 100 days following discontinuation of study treatment, at the time points specified in the Schedule of Activities (Section 2). Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the participants.

All SAEs must be collected that occur during the screening period and within 100 days of the last dose of study treatment. For participants randomized/assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of randomization.

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.

If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the eCRF section.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of this being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

The method of evaluating, and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 3.

9.2.2 Method of Detecting AEs and SAEs

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

Every adverse event must be assessed by the investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the participant's case report form.

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.

9.2.3 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 3).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.
- All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 9.2 will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 3.

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will file it along with

the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Sponsor or designee will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

All SAEs must be collected that occur during the screening period and within 100 days of the last dose of study treatment. For participants randomized/assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of randomization.

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

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

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to Sponsor or designee. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form electronic, as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the participant to have study treatment discontinued or interrupted
- Any laboratory test result abnormality that required the participant to receive specific corrective therapy

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

9.2.7 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 9.2 and Appendix 3 for reporting details).

Potential drug induced liver injury is defined as:

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

AND

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

AND

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

9.2.8 Other Safety Considerations

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

9.3 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important.

In the event of an overdose, the investigator should:

1) Contact the Medical Monitor immediately
2) Closely monitor the participant for AEs/SAEs and laboratory abnormalities
3) Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant/

For details of regarding overdose with cetuximab or cisplatin can be found in the local product information.

Overdoses meeting the regulatory definition of an SAE must be reported as an SAE (see Appendix 3).

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities in Section 2.

9.4.1 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report.

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin (T Bili) Alkaline phosphatase (ALP) Lactate dehydrogenase (LDH) Creatinine Blood Urea Nitrogen (BUN) or serum urea level Glucose	Albumin (Screening only) Sodium (Na) Potassium (K) Chloride (Cl) Calcium (Ca) Phosphate (P) Magnesium (Mg) Creatinine clearance (CrCl)
Serology	
Hepatitis C antibody (HCV Ab), Hepatitis C RNA (HCV RNA)- screening only Hepatitis B surface antigen (HBV sAg)- screening only HIV, if mandated locally- screening only (See Appendix 8)	
Other Analyses	
Thyroid stimulating hormone (TSH) with free thyroxine (fT3) and free triiodothyronine (fT4)- screening only; TSH with reflexive fT3 and fT4 during study and follow up	
Pregnancy test (WOCBP only)- screening and during study	
Follicle stimulating hormone (FSH)- screening only for women under 55 years old to confirm menopause as needed	

9.4.2 Imaging Safety Assessment

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

9.5 Pharmacokinetics and Immunogenicity

Not applicable per Revised Protocol 03. Samples collected for PK and immunogenicity analysis will be discarded and not analyzed.

[redacted]

Sample Collection and Storage

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 (or designee) to ensure the research supports appropriate and well-defined scientific research activities.

- Residual whole blood (DNA), serum, plasma blood, PBMCs, and tumor biopsy collections (See Table 9.8.1-1) will be retained for additional research purposes.

Samples kept for future research will be stored at the BMS Biorepository in Hopewell, NJ, USA or an independent, BMS-approved storage vendor.

The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than fifteen (15) years after the end of the study or the maximum allowed by applicable law.

Transfers of samples by research sponsor to third parties will be participant to the recipient's agreement to establish similar storage procedures.

Samples will be stored in a coded fashion, and no researcher will have access to the key. The key is securely held by the Investigator at the clinical site, so there is no direct ability for a researcher to connect a sample to a specific individual.

Further details of sample collection and processing will be provided to the site in the laboratory procedure manual.

Table 9.8.1-1: Residual Sample Retention for Additional Research Schedule[a]

Sample Type	Time points for which residual samples will be retained
Serum/Plasma	All
Whole Blood (DNA)	All
PBMC	All
Tumor Biopsy	All

[a] Samples collected prior to 15-Oct-2018, may be retained for additional research.

9.8.2 Tumor Tissue Specimens

Screening Biopsies

The screening tumor biopsy tissue needs to be shipped to the central laboratory and the PD-L1 analysis and HPV p-16 testing (if needed) must be processed with an available result prior to randomization. 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 within 3 months of enrollment
- An archived biopsy (block or slides) must contain tumor tissue
- If archived blocks are not available, ≥ 25 slides (preferred) containing tumor are available for exploratory use.

9.8.2.1 Tumor sample collection details

In revised protocol 03 tumor samples are no longer required to be collected.

A minimum of 5 formalin-fixed paraffin embedded (FFPE) unstained sections (preferred) are required for assessment of PD-L1 status. Specimens should contain a minimum of 100 evaluable tumor cells.

9.9 Medical Resource Utilization and Health Economics HEOR

Not applicable per Revised Protocol 03.

10 STATISTICAL CONSIDERATIONS

Per Revised Protocol 03, efficacy analyses will not be conducted (Section 3.1.1).

10.1 Sample Size Determination

Per Revised Protocol 03, sample size will be limited to the patients enrolled as of October 15, 2018.

This trial is made up of two cohorts, the first comprised of cisplatin ineligible participants and the second of cisplatin eligible participants. Each will be sized and analyzed separately.

The sample size and power calculations that follow were conducted assuming exponential time to even distributions, using East software, version 6.3.1.

[redacted]

[redacted]

10.2 Populations for Analyses

Per Revised Protocol 03 this section is not applicable

Analyses will be done by cohort. Key analysis populations for each cohort are defined as follows:

Table 10.2-1: Analysis Populations

Population	Description
Enrolled	All participants who signed an informed consent form and were registered into the IRT.
Treated	All randomized participants who received at least one dose of study drug. This is the dataset for safety evaluation.

10.3 Endpoints

Per Revised Protocol 03, only safety assessments will be collected.

- 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). Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.
- Time to onset and time to resolution of immune-related AEs

10.4 Statistical Analyses

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

[redacted]

10.4.2 Safety Analyses

Analyses of safety will be conducted by cohort. They will be restricted to treated participants. Adverse events will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, by treatment arm. The frequency and percentage of worst grade AEs, AEs leading to discontinuation and SAEs, without regard to cause and drug-related, will be presented by system organ class and preferred term. On-study lab parameters including hematology, coagulation, chemistry, liver function and renal function will be summarized using worst grade per NCI CCAE v 4.0 criteria.

[redacted]

[redacted]

12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
Ab	Antibody
aCGA	Abbreviated Comprehensive Geriatric Assessment
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALP	Alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HCV	hepatitis C antibody
APM	antigen processing machinery
AR	additional research
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AT	Aminotranferase
BA/BE	bioavailability/bioequivalence
Bcl-xL	B-cell lymphoma-extra large
%BE	percent biliary excretion
BICR	Blinded Independent Central Review
BID, bid	bis in die, twice daily
BLQ	below limit of quantification
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
BRt	Total amount recovered in bile
%BRt	Total percent of administered dose recovered in bile
BTLA	B- and T-lymphocyte attenuator
BUN	blood urea nitrogen
C or C	Cycle
CA	Cancer
Ca	Calcium

Term	Definition
Cavg	average concentration
CBC	Complete Blood Cell
Cexpected-tau	expected concentration in a dosing interval
CD-28	Cluster of Differentiation 28
CFR	Code of Federal Regulations
aCGA	Abbreviated Comprehensive Geriatric Assessment
CI	confidence interval
Cl^-	Chloride
CrCl	creatinine clearance
Cmaxss	steady-state maximum observed concentration
CMH	Cochran-Mantel-Haenszel
CMV	Cytomegalovirus
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form, paper or electronic
eCRF	Electronic Case Report Form
CRT	chemoradiotherapy
CT	computed tomography
CTAg	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
d or D	Day
DILI	Drug induced liver injury
DLRC	Duration of locoregional control
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DMC	Data monitoring committee
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4^{th} Edition)
DLRC	Duration of loco-regional control
EC50	Half maximal effective concentration
ECG	Electrocardiogram

Term	Definition
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Co-operative Oncology Group performance status
EFS	event free survival
Eg	exempli gratia (for example)
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
EORTC	European Organisation for the Research and Treatment of Cancer
EORTC QLQ-H&N35	EORTC head and neck cancer–specific module
FDA	Food and Drug Administration
FDG PET	fluorodeoxyglucose-positron emission tomography
FFPE	formalin-fixed paraffin embedded
FISH	fluorescent in-situ hybridization
FOXp3	forkhead box P3
FSH	follicle stimulating hormone
FU	follow up
GBM	glioblastoma multiforme
Hr	Hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C antibody
HCV RNA	hepatitis C RNA
HIV	Human Immunodeficiency Virus
HLA	human leukocyte antigen
HPV	Human papilloma virus
HR	heart rate
HR	hazard ratio
HRQoL	Health-related quality of life
HSV	herpes simplex virus
IB	Investigator Brochure

Term	Definition
IC	investigator's choice
ICAM	Intercellular Adhesion Molecule 1
ICOS	inducible T-cell costimulator
Ie	id est (that is)
IEC	Independent Ethics Committee
IFN-γ	Interferon gamma
IGRT	Image-Guided Radiation Therapy
IHC	immuno-histochemistry
IL	Interleukin
ILD	Interstitial lung disease
IMP	investigational medicinal products
IMRT	intensity modulated radiotherapy
IND	Investigational New Drug Exemption
IO	Innumo-oncology
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	Intravenous
K^+	Potassium
Kg	Kilogram
L	Liter
LAD	locally advanced
LAD SCCHN	locally advanced squamous cell carcinoma of the head and neck
LDH	lactate dehydrogenase
Mg	Milligram
Mg^{++}	Magnesium
MHC	Major histocompatibility complex
Min	Minute
mL	Milliliter
MLR	mixed lymphocyte reaction

Term	Definition
MNA	Mini Nutritional Assessment
MRI	magnetic resonance imaging
MS	mass spectrometry
MTD	maximum tolerated dose
N	number of subjects or observations
Na^+	Sodium
N/A	not applicable
Ng	Nanogram
nM	Nanomolar
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NIMP	non-investigational medicinal products
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small-cell lung cancer
OPC	Oropharynx
OPSCC	oropharyngeal squamous cell carcinoma
OS	Overall survival
PBMC	peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PD-1	Programmed death-1
PDILI	Potential Drug Induced Liver Injury
PD-L1	Programmed death-ligand 1
pembro	pembrolizumab
PET/CT	positron emission tomography/computed tomography
PFS	Progression free survival
PGIC	patient global impression of change
PGIS	Patient global impression of severity
PK	Pharmacokinetics
PPK	population Pharmacokinetics

Term	Definition
PO	per os (by mouth route of administration)
PRO	patient reported outcomes
PS	Performance status
Q1W	every week
Q2W	Every 2 week
Q3W	every 3 week
Q4W	every 4 week
QA	Quality Assurance
QD, qd	quaque die, once daily
QLQ-C30	Quality of Life Questionnaire–Core 30
QoL	quality of life
RCC	renal cell carcinoma
R&D	Research and development
RNA	ribonucleic acid
RO	Receptor occupancy
RT	Radiation Therapy
RTOG	Radiation Therapy Oncology Group
SAE	serious adverse event
SAP	statistical analysis plan
SCCHN	squamous cell carcinoma of the head and neck
SD	Standard deviation
SNPs	single nucleotide polymorphisms
SmPC	summary of product characteristics
SOA	Schedule of Activities
Subj	Subject
SUSAR	Suspected, Unexpected Serious Adverse Reaction
TCR	T-cell receptor
fT3	free thyroxine
fT4	free thyroxine
TAO	Trial Access Online, the BMS implementation of an EDC capability

Term	Definition
T.Bili	Total bilirubin
T-HALF	Half life
TID, tid	ter in die, three times a day
Tmax, TMAX	time of maximum observed concentration
TMB	Tumor mutation burden
TRAE	treatment-related adverse events
TRSAEs	treatment-related serious adverse events
TSH	Thyroid stimulating hormone
ULN	upper limit of normal
VAS	visual analogue scale
W	Week
WBC	white blood cell
WOCBP	women of childbearing potential
WNOCBP	women **not** of childbearing potential
RT	Radiotherapy

APPENDIX 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 eCRF is intended to refer to a person (Participant) who has consented to participate in the clinical research study.

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

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

The study will be conducted in compliance with the protocol. The protocol and any amendments and the participant 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 Sponsor or designee immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

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

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

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, participant recruitment materials (e.g., 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 (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study subjects.

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

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

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the 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 subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

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

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.

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 participant volunteers to participate.

Sponsor or designee will provide the investigator with an appropriate (i.e., Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for participant or participant's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the participant or the participant's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.

If informed consent is initially given by a participant's legally acceptable representative or legal guardian, and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

Revise the informed consent whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or the participant's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the participant'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 participant records.

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

SOURCE DOCUMENTS

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.

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.

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

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

CASE REPORT FORMS

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

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

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

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

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

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

MONITORING

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

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

RECORDS RETENTION

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

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

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

RETURN OF STUDY TREATMENT

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

If..	Then
Study treatments supplied by BMS (including its vendors	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (e.g., cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors) (examples include study treatments sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, 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. The following minimal standards must be 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, i.e., 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.

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study treatments provided by BMS (or its vendors). Destruction of non- study treatments sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

CLINICAL STUDY REPORT AND PUBLICATIONS

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

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

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Participant recruitment (e.g., among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (e.g., among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW UP AND REPORTING

ADVERSE EVENTS

Adverse Event Definition:
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 treatment 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.
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.

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as 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) 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 (e.g., 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 (e.g., 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)
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 [e.g., 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 9.2.7 for the definition of potential DILI.)

Pregnancy and potential drug induced liver injury (DILI) must follow the same transmission timing and processes to BMS as used for SAEs (see section 9.2.5 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy should be reported as SAE (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

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.

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 treatment 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.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study treatment, and pregnancies must be reported to BMS (or designee) immediately within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.
  - The required method for SAE data reporting is through the eCRF.
  - The paper SAE Report Form is only intended as a back-up option when the electronic data capture (EDC) system is unavailable/not functioning for transmission of the eCRF to BMS (or designee).
    - In this case, the paper form is transmitted via email or confirmed facsimile (fax) transmission
    - When paper forms are used, the original paper forms are to remain on site
- Pregnancies must be recorded on a paper Pregnancy Surveillance Form and transmitted via email or confirmed facsimile (fax) transmission

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

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 weeks after the end of study treatment.

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

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[b] – oral – intravaginal – 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 [b] • Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)[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)

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 9.2.5 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting

APPENDIX 6 TNM STAGING ACCORDING TO AJCC VERSION 8

The American Joint Committee for Cancer (AJCC) TNM Staging System is based on the extent of the tumor (T), the extent of spread to the lymph nodes (N), and the presence of metastasis (M).

Adapted from Amin, M.B., Edge, S., Greene, F., Byrd, D.R., Brookland, R.K., Washington, M.K., et al. (Eds.) (2017). AJCC Cancer Staging Manual, 8th Edition. Switzerland:Springer International Publishing.

LARYNX

Table -1: Supraglottis Tumor Staging (Definition of Primary Tumor)

Supraglottis	
T Category	**T Criteria**
TX	Primary tumor cannot be assessed
Tis	Carcinoma *in situ*
T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic space, paraglottic space, and/or inner cortex of the thyroid cartilage
T4	Moderately advanced or very advanced
T4a	Moderately advanced local disease Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Table -2: Glottis Tumor Staging (Definition of Primary Tumor)

Glottis	
T Category	**T Criteria**
TX	Primary tumor cannot be assessed
Tis	Carcinoma *in situ*
T1	Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
T1a	Tumor limited to one vocal cord
T1b	Tumor involves both vocal cords
T2	Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility
T3	Tumor limited to the larynx with vocal cord fixation and/or invasion of paraglottic space and/or inner cortex of the thyroid cartilage
T4	Moderately advanced or very advanced
T4a	Moderately advanced local disease Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, cricoid cartilage, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Table -3: Subglottis Tumor Staging (Definition of Primary Tumor)

Subglottis	
T Category	**T Criteria**
TX	Primary tumor cannot be assessed
Tis	Carcinoma *in situ*
T1	Tumor limited to the subglottis
T2	Tumor extends to vocal cord(s) with normal or impaired mobility
T3	Tumor limited to larynx with vocal cord fixation and/or invasion of paraglottic space and/or inner cortex of the thyroid cartilage
T4	Moderately advanced or very advanced

Table -3: Subglottis Tumor Staging (Definition of Primary Tumor)

Subglottis	
T Category	**T Criteria**
T4a	Moderately advanced local disease Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Table -4: Definition of Regional Lymph Nodes (N)

Clinical N (cN)	
N Category	**N Criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(-)
N2	Metastasis in a single ipsilateral node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-); *or* metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-)
N2a	Metastasis in a single ipsilateral node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-)
N2b	Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(-)
N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-)
N3	Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE(-); *or* metastasis in any lymph node(s) with clinically overt ENE(+)
N3a	Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE(-)
N3b	Metastasis in any lymph node(s) with clinically overt ENE(+)

Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L).

Similarly, clinical and pathological ENE should be recorded as ENE(-) or ENE(+)

Table -5: AJCC Prognostic Stage Groups

When T is...	And N is...	And M is..	Then the stage group is...
Tis	N0	M0	0
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	III
T1,T2,T3	N1	M0	III
T4a	N0,1	M0	IVA
T1,T2,T3,T4a	N2	M0	IVA
Any T	N3	M0	IVB
T4b	Any N	M0	IVB
Any T	Any N	M1	IVC

LIP AND ORAL CAVITY

Table -6: Tumor Staging (Definition of Primary Tumor)

T Category	T Criteria
TX	Primary tumor cannot be assessed
Tis	Carcinoma *in situ*
T1	Tumor is ≤ 2 cm, ≤ 5 mm depth of invasion (DOI) DOI is depth of invasion and not tumor thickness
T2	Tumor ≤ 2 cm, DOI > 5 mm and ≤ 10 mm *or* tumor > 2 cm but ≤ 4 cm, and ≤ 10 mm DOI
T3	Tumor > 4 cm *or* any tumor > 10 mm DOI
T4	Moderately advanced or very advanced local disease
T4a	Moderately advanced local disease (lip) Tumor invades through cortical bone or involves the inferior alveolar nerve, floor of mouth, or skin of face (i.e., chin or nose) (oral cavity) Tumor invades adjacent structures only (e.g. through cortical bone of the mandible or maxilla, or involves the maxillary sinus or skin of face) Note: Superficial erosion of the bone/tooth socket (alone) by a gingival primary is not sufficient classify a tumor as T4
T4b	Very advanced local disease Tumor invades masticator space, pterygoid plates, or skull base and/or encases the internal carotid artery

Table -7: Definition of Regional Lymph Nodes (N)

Clinical N (cN)	
N Category	**N Criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(-)
N2	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-); *or* in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-)
N2a	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-)
N2b	Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(-)
N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension, and ENE(-)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-); *or* metastasis in any node(s) and clinically overt ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-)
N3b	Metastasis in any node(s) and clinically overt ENE(+)

Note: A designation of "U" or "L" ma be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L).

Similarly, clinical and pathological ENE should be recorded as ENE(-) or ENE(+)

Table -8: AJCC Prognostic Stage Groups

When T is...	And N is...	And M is..	Then the stage group is...
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	III
T1,2,3	N1	M0	III
T4a	N0,1	M0	IVA
T1,2,3,4a	N2	M0	IVA
Any T	N3	M0	IVB
T4b	Any N	M0	IVB
Any T	Any N	M1	IVC

OROPHARYNX (P16+)

Table -9: Tumor Staging (Definition of Primary Tumor)

T Category	T Criteria
T0	No primary identified
T1	Tumor 2 cm or smaller in greatest dimension
T2	Tumor larger than 2 cm but not larger than 4 cm in greatest dimension
T3	Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	Moderately advanced local disease Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond*

*Mucosal extension of lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx.

Table -10: Definition of Regional Lymph Nodes (N)

Clinical N (cN)	
N Category	**N Criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One or more ipsilateral lymph nodes, none larger than 6 cm
N2	Contralateral or bilateral lymph nodes, none larger than 6 cm
N3	Lymph node(s) larger than 6 cm

Table -11: AJCC Prognostic Stage Groups

When T is...	And N is...	And M is...	Then the stage group is...
T0, T1 or T2	N0 or N1	M0	I
T0, T1 or T2	N2	M0	II
T3	N0, N1 or N2	M0	II
T0, T1, T2, T3 or T4	N3	M0	III
T4	N0, N1, N2 or N3	M0	III
Any T	Any N	M1	IV

OROPHARYNX (P16-) AND HYPOPHARYNX

Table -12: Oropharynx (P16-)Tumor Staging (Definition of Primary Tumor)

Oropharynx (P16-)	
T Category	**T Criteria**
TX	Primary tumor cannot be assessed
Tis	Carcinoma *in situ*
T1	Tumor 2 cm or smaller in greatest dimension
T2	Tumor larger than 2 cm but not larger than 4 cm in greatest dimension
T3	Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	Moderately advanced or very advanced local disease
T4a	Moderately advanced local disease Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard plate or mandible*
T4b	Very advanced local disease Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery

*Note: Mucosal extension of lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx

Table -13: Hypopharynx Tumor Staging (Definition of Primary Tumor)

Hypopharynx	
T Category	**T Criteria**
TX	Primary tumor cannot be assessed
Tis	Carcinoma *in situ*
T1	Tumor limited to one subsite of hypopharynx and/or 2 cm or smaller in greatest dimension
T2	Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures larger than 2 cm but not larger than 4 cm in greatest dimension without fixation of hemilarynx
T3	Tumor larger than 4 cm in greatest dimension or with fixation of hemilarynx or extension to esophagus
T4	Moderately advanced or very advanced local disease
T4a	Moderately advanced local disease Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, or central compartment soft tissue*
T4b	Very advanced local disease Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures

*Note: Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat

Table -14: Definition of Regional Lymph Nodes (N)

Clinical N (cN) - Oropharynx(P16-) and Hypopharynx	
N Category	**N Criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(-)
N2	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-); *or* in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-)
N2a	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-)
N2b	Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(-)
N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-); *or* metastasis in any node(s) and clinically overt ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-)
N3b	Metastasis in any node(s) and clinically overt ENE(+)

Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L).

Similarly, clinical and pathological ENE should be recorded as ENE(-) or ENE(+)

Table -15: AJCC Prognostic Stage Groups

When T is...	And N is...	And M is..	Then the stage group is...
Tis	N0	M0	0
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	III
T1,T2,T3	N1	M0	III
T4a	N0,1	M0	IVA
T1,T2,T3,T4a	N2	M0	IVA
Any T	N3	M0	IVB
T4b	Any N	M0	IVB
Any T	Any N	M1	IVC

APPENDIX 7 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

[redacted]

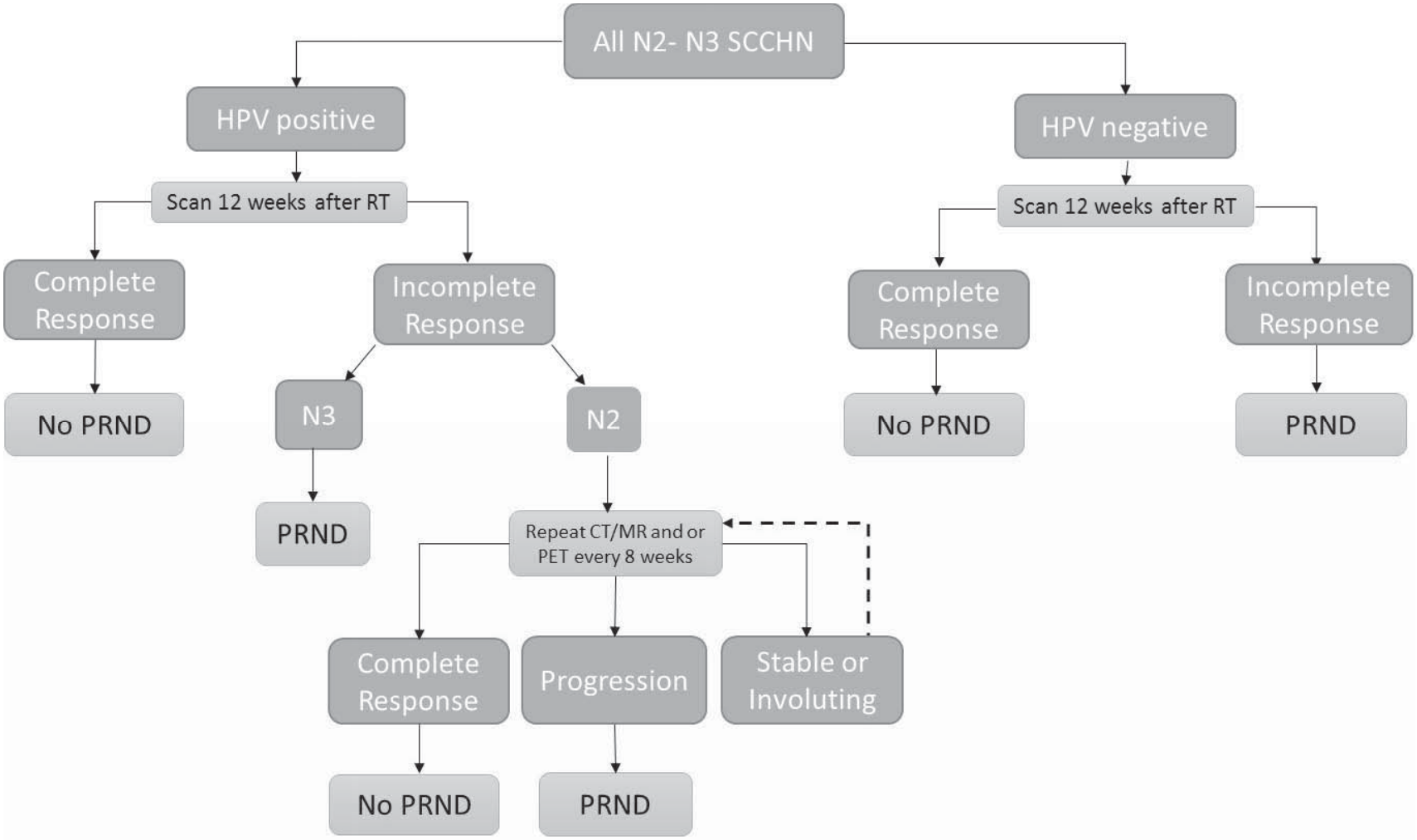
APPENDIX 8 COUNTRY SPECIFIC APPENDIX

Argentina, Czech Republic, France, Germany, Italy, Spain

Criterion to exclude HIV positive participants in countries listed above

	Country-specific language
Section 2 Flow Chart/Time and Events Schedule, Table 2-1: Screening Assessments-Laboratory Tests	Add "HIV" to the list of laboratory tests
Section 6.2 Exclusion Criteria, Exclusion criterion 1.a	"Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)"to be replaced with "Positive test for HIV".

APPENDIX 9 NECK DISSECTION GUIDELINES



Abbreviations: HPV= human papillomavirus; PRND=post radiation neck dissection; RT=Radiotherapy; SCCHN=squamous cell carcinoma of the head and neck

Source: Huang SH, et al. Temporal Nodal Regression and Regional Control After Primary Radiation Therapy for N2-N3 Head-and-Neck Cancer Stratified by HPV Status. International Journal of Radiation Oncology 87, 2013.

APPENDIX 10 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES (VERSION 1.1) WITH BMS MODIFICATIONS

1 EVALUATION OF LESIONS

Solid tumors will be evaluated using Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) guideline with BMS modifications.[1]

At baseline, tumor lesions/lymph nodes will be categorized as 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:

10 mm by CT/MRI scan (scan slice thickness no greater than 5 mm), or ≥2x slice thickness if greater than 5mm.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT/MRI scan (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/MRI 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, sagittal 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.

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

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, 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.

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

1.3 Special considerations regarding lesion measurability

1.3.1 Bone lesions

- Bone scan, PET scan and plain films are ***not*** considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

1.4 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).

Note: A maximum of two lesions can be selected per organ system. For example, a maximum of two lung lesions can be selected (selected from one lung or one lesion from each). A maximum of two lymph nodes can be selected at baseline, as the lymphatic system is considered one organ.

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 non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2 RESPONSE CRITERIA

2.1 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.
- **Not Evaluable (NE):** If one or more target lesions cannot be measured or adequately assessed as either fully resolved or too small to measure (due to missing or poor quality images), and the sum of diameters of the remaining measured target lesions (if any) has not increased sufficiently to meet Progressive Disease as defined above.

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 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.

2.1.1.2 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 as the reference diameter. (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.

2.1.1.3 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'.

2.2 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. 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)
- **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions.

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

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

2.2.1.1 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 A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Pleural effusions, pericardial effusions and ascites will not be followed as target or non-target lesions and will not contribute to response or progression. 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.

2.2.1.2 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 lymphangitic disease from localized to widespread, or may be described 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.

2.2.2 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.

NOTE: Fluid collections (pleural effusions, pericardial effusions, and ascites) will not be considered new lesions and will not contribute to response or progression. In the event a new fluid collection is seen on a post-baseline imaging exam, a comment may be made, but the appearance of a new fluid collection alone should not result in an assessment of Progressive Disease (PD). 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. A lesion identified on Chest X-Ray that was not present in prior CT can be considered a new lesion and will result in Progressive Disease (PD).

If a new lesion is equivocal, for example because of its small size, continued 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.

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until disease progression or the last response recorded, taking into account any requirement for confirmation and censoring rules regarding subsequent therapy. 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.

2.3.2 Time Point Response

At each protocol specified time point, a response assessment occurs. Table 2.3.2-1provides 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 2.3.2-2 is to be used.

Table 2.3.2-1: 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

Table 2.3.2-1: Time Point Response: Patients With Target (± Non-Target) Disease			
Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**
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 2.3.2-2: 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.

2.3.3 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 (28 days) later. In this circumstance, the best overall response can be interpreted as in Table 2.3.3-1. When SD is believed to be best response, it must meet the protocol specified minimum time from the date of first treatment or randomization date.

For example, if the first scheduled follow-up imaging visit is Week 6 (± 7 days) for a particular protocol, a Best Response of SD can only be made after the subject is on-study for a minimum of 6 weeks (42 days) minus 7 days, for an absolute minimum time on-study of 35 days from the reference start date (reference date is considered Day 1 on study). If the subject is not on-study for at least this amount of time, any tumor assessment indicating stable disease before this time period will have a Best Response of NE unless PD is identified.

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 2.3.3-1: Best Overall Response (Confirmation of CR and 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 met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration 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.

2.3.4 Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive or subsequent repeat assessments that should be performed no less than 28 days after the criteria for response are first met. Subsequent documentation of a CR may provide confirmation of a previously identified CR even with an intervening NE or PR (eg, CR NE CR or CR PR CR). Subsequent documentation of a PR may provide confirmation of a previously identified PR even with an intervening NE or SD (eg, PR NE PR or PR SD PR). However, only one (1) intervening time point will be allowed between PR/CRs for confirmation.

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.

[redacted]

APPENDIX 11 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