Statistical Analysis Plan for

Official Title of Study

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).

NCT03349710

19-Oct-2019

STATISTICAL ANALYSIS PLAN
FOR DOCUMENT

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 3 STUDY OF NIVOLUMAB OR NIVOLUMAB PLUS CISPLATIN, IN COMBINATION WITH RADIOTHERAPY IN SUBJECTS WITH CISPLATIN INELIGIBLE AND CISPLATIN ELIGIBLE LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (SCCHN)

PROTOCOL CA209-9TM

VERSION # 1.0

DATE: 19-OCT-2019

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[redacted]

2 STUDY DESCRIPTION

2.1 Study design

CA209-9TM was a randomized, double-blinded, placebo-controlled, phase 3 study of nivolumab or nivolumab plus cisplatin, in combination with radiotherapy in subjects 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 and placebo treatments will no longer be given. All enrolled subjects must be re-consented prior to continuing treatment on the study.

The study consists of two independent cohorts:

- **Cohort 1** will randomize subjects who are ineligible for cisplatin chemotherapy to receive nivolumab in combination with radiotherapy **(Arm A)** or cetuximab in combination with radiotherapy **(Arm B)**.
- **Cohort 2** will randomize subjects who are eligible to receive cisplatin-based therapy to receive nivolumab in combination with cisplatin and radiotherapy **(Arm C)** or cisplatin and radiotherapy **(Arm D)**.

In each cohort subjects will be randomized to the two treatment arms in a 1:1 ratio and stratified

by risk group (intermediate vs. high), PD-L1 tumor expression (≥1% vs. < 1% or indeterminate), and ECOG PS (0 vs. 1).

Cohort 1 (cisplatin ineligible):

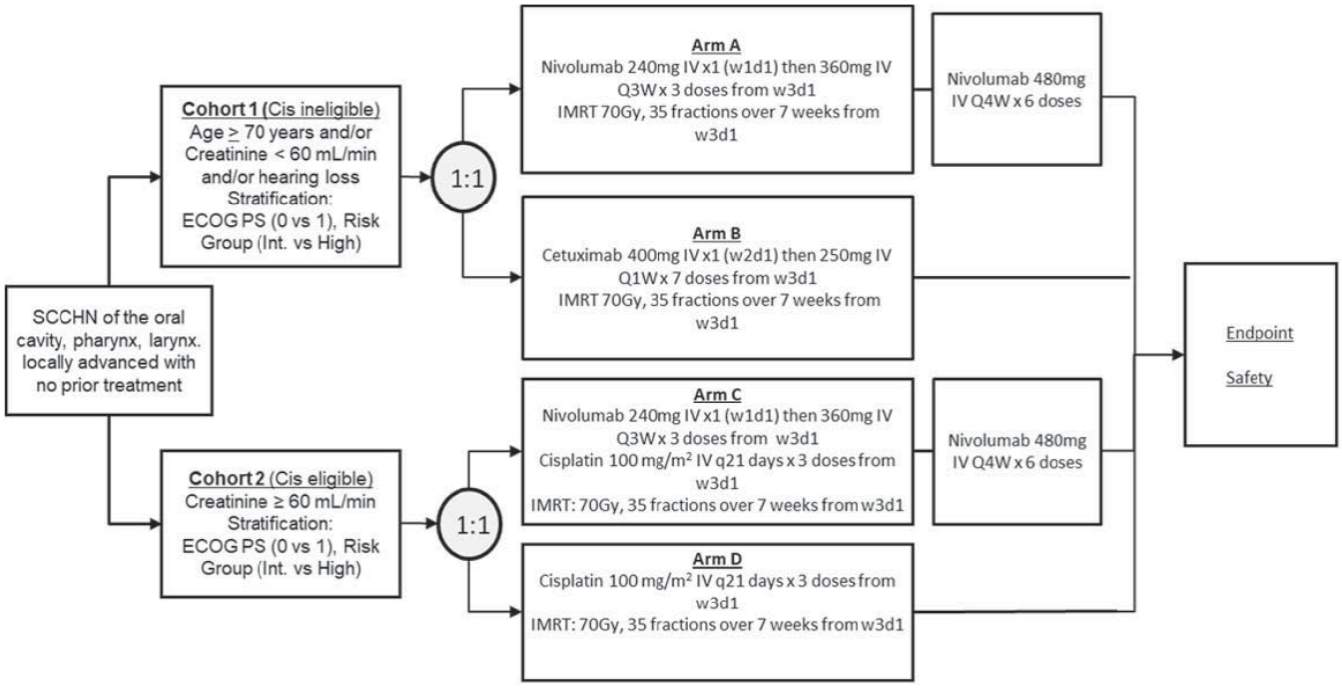
- **Arm A** subjects will be administered Nivolumab in combination with intensity-modulated radiation therapy (IMRT).
  1. Nivolumab 240 mg single dose will be administered at w1d1 followed by 360 mg every 3 weeks for a total of 3 doses starting at w3d1 followed by 480 mg every 4 weeks for a total of 6 doses.
  2. IMRT 70 Gy will be administered as 35 fractions starting from w3d1 over 7 weeks.
- **Arm B** subjects will be administered cetuximab in combination with IMRT.
  1. cetuximab 400 mg/m2 single dose will be administered at w2d1 followed by 250 mg/m2 every week for a total of 7 doses starting at w3d1.
  2. IMRT 70 Gy will be administered as 35 fractions starting from w3d1 over 7 weeks.

Cohort 2 (cisplatin eligible):

- **Arm C** subjects will be administered Nivolumab in combination with Cisplatin and IMRT.
  1. Nivolumab 240 mg single dose will be administered at w1d1 followed by 360 mg every 3 weeks for a total of 3 doses starting at w3d1 followed by 480 mg every 4 weeks for a total of 6 doses.
  2. Cisplatin 100 mg/m2 will be administered every 21 days starting at w3d1 for a total of 3 doses.
  3. IMRT 70 Gy will be administered as 35 fractions starting from w3d1 over 7 weeks.
- **Arm D** subjects will be administered Cisplatin and IMRT.
  1. Cisplatin 100 mg/m2 will be administered every 21 days starting at w3d1 for a total of 3 doses.
  2. IMRT 70 Gy will be administered as 35 fractions starting from w3d1 over 7 weeks.

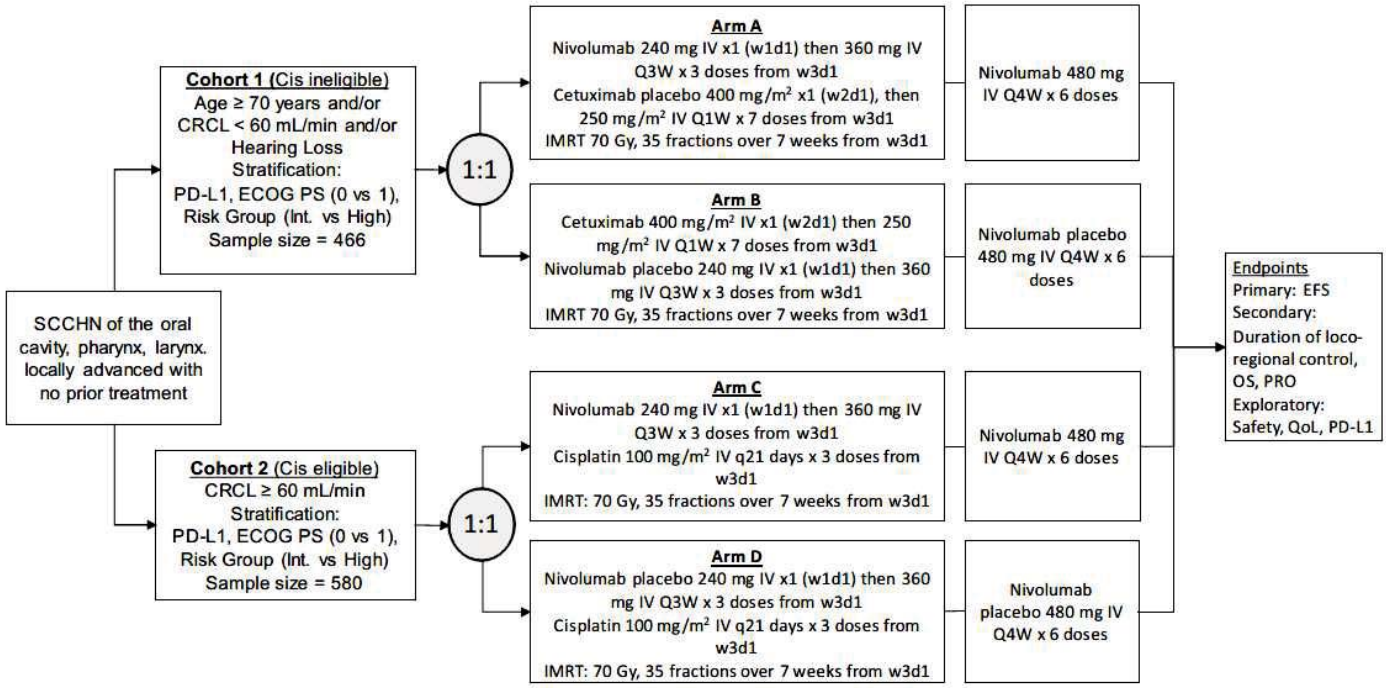
The current study design schematic after unblinding is presented in Table 2.1-1

Table 2.1-1: Study Design Schematic



The original study design schematic is presented in Table 2.1-2

Table 2.1-2: Original Study Design Schematic



2.2 Treatment assignment

After protocol specific informed consent is signed subject will be registered into the Interactive Response Technology (IRT). Randomization begins with call to IRT, in order to be randomized to a treatment subject must have an evaluable PD-L1 and HPV p16 result from the central lab.

In each of the two cohorts subjects will be randomized in 1:1 ratio using three stratification factors:

- Risk group (intermediate vs. high).
- PD-L1 tumor expression (≥1% vs. < 1% or indeterminate),
- ECOG PS (0 vs. 1).

As of 15-Oct-2018 and Per revised protocol 03, the following are effective:

- Enrollment for new subjects is closed, the IRT system is closed to enroll new patients.
- Subjects who have signed an informed consent as of 15-Oct-2018 and are currently undergoing screening procedures, may be permitted to be randomized to the study.
- Subjects currently being treated in the study will have the option to continue treatment under the Revised Protocol 03. These subjects will be re-consented by signing a revised informed consent document.

2.3 Blinding and Unblinding

Per original design CA209-9TM was a double-blind placebo-controlled study. Per Revised Protocol 03 and as of 15-Oct-2018 study will be unblinded, placebo treatment removed.

2.4 Protocol Amendments

Table 2.4-1: Protocol Revision History

Document	Date of Issue	Summary of change
Original Protocol	15-Aug-2017	Not applicable
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.
Revised Protocol 02	21-Feb-2018	Added exclusion of subjects 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 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.

3 OBJECTIVES

Not Applicable per Revised Protocol 03.

4 ENDPOINTS

4.1 Safety Endpoints

The assessment of safety will be based on the incidence of adverse events (AEs), serious adverse events (SAEs), adverse events leading to discontinuation, adverse events leading to dose modification, select adverse events (select AEs), immune-mediated AEs (IMAEs), time to onset and time to resolution of immune-related AEs, and deaths. In addition, clinical laboratory tests will be analyzed.

[redacted]

5 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

5.1 Study Periods

- Baseline period:
  - Baseline evaluations or pre-treatment events will be defined as evaluations or events that occur before the date and time of the first dose of study treatment.

    Evaluations on the same date and time of the first dose of study treatment will be considered baseline evaluations.

    Events (AEs) on the same date and time of the first dose of study treatment will not be considered as pre-treatment events.
  - In cases where the time (onset time of event or evaluation time and dosing time) is missing or not collected, the following definitions will apply:
    - Pre-treatment AEs will be defined as AEs with an onset date prior to but not including the day of the first dose of study treatment;
    - Baseline evaluations will be defined as evaluations with a date on or prior to the day of first dose of study treatment.
  - If there are multiple valid observations on or prior to the first dose of study treatment, then the latest non missing observation on or before first dose date (and time if collected) will be used as the baseline in the analyses. If multiple observations exist on the latest collection date (and time if collected), the record with the latest data entry date and time will be used. If multiple observations exist on the latest collection date (and time if collected) and data entry date and time, then the first observation is used as baseline, unless otherwise specified.
    - For Eastern Cooperative Oncology Group (ECOG) performance status (PS), the latest ECOG PS value prior to or on the first dose date (and time if collected) will be used as the baseline in the analyses. If multiple records fall on the last date then the record with the highest value of ECOG PS will be considered as baseline.
    - For PD-L1, among the records prior to or on first dose date (and time if collected), identify first those with quantifiable test result. If there are no records with quantifiable test result, then select those with indeterminant result ("INDETERMINATE"). If there

are no records with indeterminant test result, then select those with unavailable result ("NOT EVALUABLE). If there are no records with unavailable test result, then select those with not reported or not available result (all other records). The latest record will be used as the baseline in the analyses. If there is more than one record for the latest date, then choose the one with the greatest specimen ID.

- Post baseline period:
  - On-treatment AEs will be defined as AEs with an onset date and time on or after the date and time of the first dose of study treatment (or with an onset date on or after the day of first dose of study treatment if time is not collected or is missing). For subjects who are off study treatment, AEs will be included if event occurred within a safety window of 30 days (or 100 days depending on the analysis) after the last dose of study treatment. No "subtracting rule" will be applied when an AE occurs both pre-treatment and post-treatment with the same preferred term and grade.
  - On-treatment evaluations (laboratory tests, pulse oximetry and vital signs) will be defined as evaluations taken after the day (and time, if collected and not missing) of first dose of study treatment. For subjects who are off study treatment, evaluations should be within a safety window of 30 days (or 100 days depending on the analysis) after the last dose of study treatment.
- For subjects who are off study treatment safety assessments will only be collected through 100 days post last dose.

5.2 Treatment Regimens

Treatment group "as randomized" corresponds to the treatment group assigned by the Interactive Response Technology (IRT) system.

Treatment group "as treated" will be same as the treatment group "as randomized" by IRT unless a subject received the incorrect study treatment for the entire period of treatment, in which case the subject's treatment group "as treated" will be defined as the incorrect study treatment.

All analyses will be performed using the treatment group "as randomized", except for dosing and safety for which analyses will be performed using treatment group "as treated".

All analyses for cisplatin ineligible cohort and cisplatin eligible cohort will be presented separately unless specified otherwise.

5.3 Populations for Analyses

- Enrolled subjects: All subjects who signed the informed consent no later than 15-Oct-2018.
- Randomized subjects: All enrolled subjects as defined above who were randomized through the IRT.
- Treated subjects: All randomized subjects who received at least one dose of any study drug (Nivolumab, Nivolumab-Placebo, Cetuximab, Cetuximab-Placebo, Cisplatin).

6 SAMPLE SIZE AND POWER

Per Revised Protocol 03, sample size will be limited to the patients enrolled as of October 15, 2018. Accordingly no efficacy analyses will be performed and no power is considered.

7 STATISTICAL ANALYSES

7.1 General Methods

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

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

Analyses will be performed for each cohort separately.

7.1.1 Adverse Events, Serious Adverse Events, Multiple events, Select Adverse Events, Other Events of Special Interest and Immune-Mediated Adverse Events

Drug-related AEs are those events with relationship to study drug "Related", as recorded on the CRF. If the relationship to study drug is missing, the AE will be considered as drug-related.

Serious adverse events consist of AEs deemed serious by the Investigator and flagged accordingly in the CRF and clinical database.

Adverse events leading to study drug discontinuation are AEs with action taken regarding study drug(s) = "Drug was discontinued".

Adverse events leading to dose delay are AEs with action taken regarding study drug(s) = "Drug was delayed".

Adverse events leading to dose reduction are AEs with action taken regarding study drug(s) = "Dose was reduced".

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and the most recent version of the dictionary at the time of the database lock will be used. Adverse event results will be graded for severity using the NCI Common Terminology Criteria for Adverse Events (CTCAE) and the version of the criteria specified in the protocol will be used.

In the AE summary tables, unless otherwise specified, subjects will be counted only once at the Preferred Term (PT), only once at the System Organ Class (SOC), and only once at subject level for the counting of total number of subjects with an AE. The AE tables will be sorted by the SOCs and then PTs. SOC will be ordered by descending frequency overall and then alphabetically. PTs will be ordered within SOC by descending frequency overall and then alphabetically. The sorting

will be done based on the 'Any Grade' column of the experimental arm when arms are presented side-by-side.

Unless otherwise specified, the AE summary tables will be restricted to on-treatment events regardless of the causality.

Analyses that take into account the multiple occurrences of a given adverse event will be conducted (see Section 7.6.9). To prepare these analyses, the CRF data will be processed according to standard BMS algorithms[1] in order to collapse adverse event records into unique records based on the preferred term. These data will be presented as the rate per 100 person-years of exposure. These analyses will take into account all on-treatment events (allowing more than 1 event per subject) and the total exposure time. The person-year exposure will be computed as the sum over the subjects' exposure expressed in years where the exposure time is defined as

- (Date of last dose of study treatment - date of first dose of study treatment + 31 days (or 101 days, depending on the analysis))/365.25, for subject who are off study treatment and were followed for at least 30 days (or 100 days, depending on the analysis) after last dose of study treatment. Exposure time calculation will be based on all study therapy including administration of placebo drugs.
- (Last known alive date - date of first dose of study treatment +1)/365.25, for subjects who are still on-treatment or who are off study treatment and were followed less than 30 days (or 100 days depending on the analysis) after last dose of study treatment.

7.1.1.1 Select Adverse Events

The select Adverse Events (select AEs) consist of a list of preferred terms grouped by specific category. AEs that may differ from or be more severe than AEs caused by non-immunotherapies and AEs whose early recognition and management may mitigate severe toxicity are included as select AEs. Categories of select AEs may include subcategories.

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

In addition to the frequency and worst severity of select AEs, time-to onset, time-to resolution, and time-to resolution where immune modulating medication was initiated will be analyzed for each specific category/subcategory of drug-related select AEs when applicable.

7.1.1.2 Other Events of Special Interest

Other events of special interest (OEOSI) consist of a list of preferred terms grouped by specific category. The list of MedDRA preferred terms used to identify OEOSI is revisited quarterly and updated accordingly. The preferred terms used for the selection at the time of the database lock by categories will be provided.

7.1.1.3 Immune-Mediated Adverse Events

In order to further characterize AEs of special clinical interest, analysis of immune-mediated AEs (IMAE) will be conducted. IMAEs are specific events (or groups of PTs describing specific events) considered as potential immune-mediated events by investigator that meet the definition summarized below:

- those occurring within 100 days of the last dose,
- regardless of causality,
- treated with immune-modulating medication (of note, endocrine AEs are considered IMAEs regardless of immune-modulating medication use, since endocrine drug reactions are often managed without immune-modulating medication).
- with no clear alternate etiology based on investigator assessment, or with an immune-mediated component

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

7.1.2 Laboratory Tests

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

Laboratory tests will be graded using the NCI Common Terminology Criteria, and the most recent version of the criteria at the time of the database lock will be used.

Clinical laboratory data will be analyzed using International System of Units (SI) and repeated using US conventional units.

In the laboratory summary tables, unless otherwise specified, subjects will be counted only once for each lab parameter according to their worst on treatment CTC grade (worst being the highest CTC grade). The laboratory tables and listings will be sorted by laboratory category, laboratory subcategory and laboratory test code sequence number.

7.2 Study Conduct

7.2.1 Accrual

By subject listing of informed consent (and re-consent if available), randomization date, first dosing date, country, investigational site will be provided.

7.2.2 Relevant Protocol Deviations

Not Applicable.

7.3 Study Population

Analyses in this section will be tabulated for all randomized subjects by treatment group as randomized, unless otherwise specified. Analyses will be performed separately for cisplatin ineligible and cisplatin eligible cohorts.

7.3.1 Subject Disposition

Number of subjects who discontinued study treatment along with corresponding reason will be tabulated by treatment group as treated. Reason for discontinuation will be derived from subject status CRF page. This analysis will be performed only on the all treated subjects population.

A by-subject listing for all treated subjects will be provided showing the subject's off treatment date and whether the subject continue in the treatment period/study along with the reason for going off treatment period/study.

7.3.2 Demographics and Other Baseline Disease Characteristics

The following demographic and baseline disease characteristics will be summarized and listed by treatment group as randomized:

- Age (continuous)
- Age categorization (< 65, ≥ 65 and < 75, ≥ 75 and < 85, ≥ 85, ≥ 75, ≥ 65)
- Sex (Male vs. Female)
- Race (White, Black or African American, Asian, Other)
- Asian race subgroups (Asian Indian, Chinese, Japanese, Korean, Taiwanese, Malay, Other Asian)
- Ethnicity (Hispanic/Latino and Not Hispanic/Latino) *
  * Required for US subjects only
- Region (US/Canada, Europe, Asia, Rest of the World)
- ECOG PS (0 vs. 1 vs. >1)
- CNS metastasis at Baseline (Yes, No) - per radiographic tumour screening assessment
- Smoking Status (Current/Former, Never, Unknown)
- Smoking History (<= 20 pack year history vs. > 20 pack year history)
- PD-L1 (>=1%, <1%, indeterminate, non-evaluable)
- Creatinine clearance (< 60mL/min vs. >= 60mL/min)
  Creatinine clearance is estimated by Cockcroft-Gault formula:
  CCr={((140 age in years) x weight in Kg)/(72 x serum creatinine in mg/dL)}
  (for females, multiply the result by 0.85)
- Disease stage at initial diagnosis (stage III, IV)
- TNM Classification at initial diagnosis
- Time from Initial Disease Diagnosis to Randomization (< 1 year, 1 - < 2 year, 2 - < 3 year, 3 - < 4 year, 4 - < 5 year, ≥ 5 year).
- SCCHN risk of tumor recurrence (Intermediate vs High).
- Sites of diseases (all lesions) at baseline per Investigator
- Number of disease sites per subject (all lesions) at baseline per Investigator
- Number of target lesions, non-target lesions and disease sites at baseline per Investigator
- Tumor burden: sum of the diameters of target lesions at baseline per Investigator

A listing of randomization scheme presenting randomized treatment group and as treated treatment group will be provided for all randomized subjects.

7.3.3 Medical History

Not Applicable.

7.3.4 Prior Therapy Agents

Prior systemic cancer therapy, prior radiotherapy, and prior surgery will be summarized by treatment group and overall and listed by subject.

7.3.5 Physical Examinations

Not Applicable.

7.3.6 Baseline Physical Measurements

Not Applicable.

7.4 Extent of Exposure

Analyses will be performed by treatment group "as treated". Listings will include all available exposure data.

7.4.1 Administration of Study Therapy

A by-subject listing of study drug dosing will be provided.

7.4.2 Modifications of Study Therapy

No additional analysis will be provided.

7.4.2.1 Dose Delays

Each Nivolumab, Cetuximab, and Cisplatin infusion including corresponding placebo drugs may be delayed. A dose will be considered as actually delayed if the delay is exceeding 3 days (i.e. greater than or equal to 4 days from scheduled dosing date). Reason for dose delay will be retrieved from CRF dosing pages.

7.4.2.2 Infusion Interruptions and Rate Changes

Each Nivolumab, Cetuximab, and Cisplatin infusion including corresponding placebo drugs may be interrupted and/or the IV infusion rate can be reduced. This information will be retrieved from CRF dosing pages.

7.4.2.3 Dose Escalations

Dose escalations are not allowed for any of the study drug.

7.4.2.4 Dose Reductions

Nivolumab dose reductions are not allowed.

Cetuximab and Cisplatin dose may be reduced up to two times, need for further reduction will require drug discontinuation. Once a dose has been decreased, it should remain reduced for all

subsequent dosing unless dose is further reduced. Dose reduction information will be retrieved from CRF dosing pages.

7.4.2.5 Dose Omissions

For Cetuximab and Cisplatin omitted dose and the reason for the omission should be recorded in the site's source documentation.

[redacted]

7.4.3.1 Immune modulating medication

Not Applicable.

7.4.3.2 Subsequent Cancer Therapy

Not Applicable.

[redacted]

7.6 Safety

Analyses in this section will be tabulated for all treated subjects by treatment group "as treated".

7.6.1 Deaths

Deaths will be summarized by treatment group:

- All deaths, reasons for death.
- Deaths within 30 days of last dose received, reasons for death.
- Deaths within 100 days of last dose received, reasons for death.

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

7.6.2 Serious Adverse Events

Serious adverse events will be summarized by treatment group:

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

All analyses will be conducted using the 30-day safety window.

A by-subject SAE listing will be provided for the "enrolled subjects" population.

7.6.3 Adverse Events Leading to Discontinuation of Study Therapy

AEs leading to discontinuation will be summarized by treatment group:

- Overall summary of AEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.
- Overall summary of drug-related AEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.

The analyses will be conducted using the 30-day safety window.

A by-subject AEs leading to discontinuation listing will be provided.

7.6.4 Adverse Events Leading to Dose Modification

AEs leading to dose delay/reduction will be summarized by treatment group:

- Overall summary of AEs leading to dose delay/reduction by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.
- Overall summary of related AEs leading to dose delay/reduction by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.

The analysis will be conducted using the 30-day safety window.

A by-subject AEs leading to dose delay/reduction listing will be provided.

7.6.5 Adverse Events

Adverse events will be summarized by treatment group.

The following analyses will be conducted using the 30 days safety window only:

- Overall summary of any AEs by worst CTC grade (1, 2, 3, 4, 5, not reported, total) presented by SOC/PT.
- Overall summary of any AEs presented by worst CTC grade (any grade, grade 3-4, grade 5) by SOC/PT. This table will be restricted to events with an incidence greater or equal to 5% in any treatment group.
- Overall summary of drug-related AEs by worst CTC grade (1, 2, 3, 4, 5, not reported, total) presented by SOC/PT.

A by-subject AE listing will be provided. A by-subject listing of any AE requiring immune modulating medications will also be provided.

7.6.6 Select Adverse Events

Analyses will be performed by select AE category.

7.6.6.1 Incidence of Select AE

Select AEs will be summarized by treatment group for each category/subcategory.

The following analyses will be conducted using the 30-day safety window only:

- Overall summaries of any select AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory/PT.
- Overall summaries of any drug-related select AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category or Subcategory/PT.

A by-subject select AE listing will be provided.

7.6.6.2 Time-to Onset of Select AE

Not Applicable.

7.6.6.3 Time-to Resolution of Select AE

Not Applicable.

7.6.7 Immune-Mediated Adverse Events

IMAEs will be summarized by treatment group for each immune-mediated category / PT using the 100-day safety window:

- Overall summary of non-endocrine IMAEs by worst CTC grade (any grade, grade 3-4, grade 5) where immune modulating medication was initiated presented by Category / PT.
- Overall summary of endocrine IMAEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by Category / PT.

A by-subject listing of IMAEs will be provided. By-subject listings of time-to resolution for longest IMAEs cluster (any grade and grade 3-5 in separate summaries) will also be provided.

7.6.8 Other Events of Special Interest

A by-subject listing of OEOSI will be provided.

7.6.9 Multiple Events

Not applicable.

7.6.10 Laboratory Parameters

The analysis population for each laboratory test is restricted to treated subjects who underwent that laboratory test. Laboratory tests (in addition to the tests specified below) with CTC criteria collected in the specific studies may also be included in the summaries.

7.6.10.1 Hematology

The following will be summarized by treatment group as worst CTC grade on-treatment per subject and as shift table of worst on-treatment CTC grade compared to baseline CTC grade per

subject: hemoglobin (HB), platelets, white blood counts (WBC), absolute neutrophils count (ANC) and lymphocyte count (LYMPH).

The analyses will be conducted using the 30-day safety window.

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

7.6.10.2 Serum Chemistry

The following will be summarized by treatment group as worst CTC grade on-treatment per subject and as shift table of worst on-treatment CTC grade compared to baseline CTC grade per subject: ALT, AST, alkaline phosphatase (ALP), total bilirubin and creatinine.

The analyses will be conducted using the 30-day safety window.

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

7.6.10.3 Electrolytes

The following will be summarized by treatment group as worst CTC grade on-treatment per subject and as shift table of worst on-treatment CTC grade compared to baseline CTC grade per subject: sodium (high and low), potassium (high and low), calcium (high and low), magnesium (high and low), and Glucose Serum (fasting hyperglycemia and hypoglycemia regardless of fasting status).

The analyses will be conducted using the 30-day safety window.

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

7.6.10.4 Additional Analyses

In addition, further analyses on specific laboratory parameters will be performed by treatment group:

Abnormal Hepatic Function Test

The number of subjects with the following laboratory abnormalities from on-treatment evaluations will be summarized by treatment group:

- ALT or AST > 3 x ULN, > 5 x ULN, > 10 x ULN and > 20 x ULN
- Total bilirubin > 2 x ULN
- Concurrent (within 1 day) ALT or AST > 3 x ULN and total bilirubin > 2 x ULN
- Concurrent (within 30 days) ALT or AST > 3 x ULN and total bilirubin > 2 x ULN

The analyses will be conducted using the 30-day safety window.

A by-subject listing of these specific abnormalities will be provided.

Abnormal Thyroid Function Test

The number of subjects with the following laboratory abnormalities from on-treatment evaluations will be summarized by treatment group:

- TSH value > ULN and

- with baseline TSH value ≤ ULN
- with at least one FT3/FT4 test value < LLN within 2-week window after the abnormal TSH test
- with all FT3/FT4 test values ≥ LLN within 2-week window after the abnormal TSH test
- with FT3/FT4 missing within 2-week window after the abnormal TSH test.

- TSH < LLN and
  - with baseline TSH value ≥ LLN
  - with at least one FT3/FT4 test value > ULN within 2-week window after the abnormal TSH test
  - with all FT3/FT4 test values ≤ ULN within 2-week window after the abnormal TSH test
  - with FT3/FT4 missing within 2-week window after the abnormal TSH test

The analyses will be conducted using the 30-day safety window.

A by-subject listing of these specific abnormalities will be provided.

7.6.11 Vital Signs

Not Applicable.

7.6.12 Physical Measurements

Not Applicable.

7.6.13 Non-Protocol Medical Procedures

Not Applicable.

7.6.14 Pregnancy

Not Applicable.

7.6.15 Adverse Events By Subgroup

Not Applicable.

[redacted]

[redacted]

[redacted]

8 CONVENTIONS

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

- For missing and partial adverse event onset dates, imputation will be performed using the Adverse Event Domain Requirements Specification[2]
- For missing and partial adverse event resolution dates, imputation will be performed as follows:
  - If only the day of the month is missing, the last day of the month will be used to replace the missing day. If the imputed date is after the death date or the last known alive date, then the latest known alive date or death date is considered as the resolution date.
  - If the day and month are missing or a date is completely missing, it will be considered as missing.
- Missing and partial non-study medication domain dates will be imputed using the derivation algorithm described in 4.1.3 of BMS Non-Study Medication Domain Requirements Specification[3].
- For death dates, the following conventions will be used for imputing partial dates:
  - If only the day of the month is missing, the 1st of the month will be used to replace the missing day. The imputed date will be compared to the last known alive date and the maximum will be considered as the death date.
  - If the month or the year is missing, the death date will be imputed as the last known alive date.
  - If the date is completely missing but the reason for death is present, the death date will be imputed as the last known date alive.
- For date of progression to prior therapies, the following conventions will be used for imputing partial dates:
  - If only the day of the month is missing, the 1st of the month will be used to replace the missing day.
  - If the day and month are missing or a date is completely missing, it will be considered as missing.
- For other partial/missing dates, the following conventions were used:
  - If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
  - If both the day and the month are missing, "July 1" will be used to replace the missing information.
  - If a date is completely missing, it will be considered as missing.

The following conversion factors will be used to convert days to months or years:

1 month = 30.4375 days and 1 year = 365.25 days.

Duration (e.g. time-to onset, time-to resolution) will be calculated as follows:

Duration = (Last date - first date + 1)

Last known alive date will be defined based on all appropriate dates collected on the CRF.

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

9 CONTENT OF REPORTS

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

10 DOCUMENT HISTORY

Table 10-1: Document Revision History

Version Number	Author(s)	Description
1.0	Li Wei	Initial release dated 19-Oct-2019

APPENDIX 1 TIME-TO ONSET AND TIME-TO RESOLUTION DEFINITION AND CONVENTIONS FOR SELECT ADVERSE EVENTS, IMMUNE-MEDIATED ADVERSE EVENTS AND EVENTS OF SPECIAL INTEREST

Time-to onset definition

Time-to onset of AE (any grade) for a specific category is defined as the time between the day of the first dose of study treatment and the onset date of the earliest AE (of any grade) in this category.

The time-to onset of AE (grade 3-5) for a specific category is defined similarly with an onset date corresponding to a grade 3-5 AE.

Time-to onset of drug-related AE (any grade or grade 3-5) for a specific category is defined similarly but restricted to drug-related AE.

Time-to onset for a specific subcategory is defined similarly but restricted to event of this subcategory.

Time-to resolution definition

In order to derive the time-to resolution, overlapping or contiguous AEs within a specific category or subcategory will be collapsed into what will be termed "clustered" AEs. For example, if a subject (without pre-treatment AE) experienced an AE from 1st to 5th January, another AE (with different PT but within same category) from 6th to 11th January and same AE from 10th to 12th January, these will be collapsed into one clustered AE from 1st to 12th January. Appendix Table 1 is summarizing key derivation steps for each type of clustered AEs.

Time-to resolution of AE (any grade) for a specific category is defined as the longest time from onset to complete resolution or improvement to the grade at baseline among all clustered AEs experienced by the subject in this category per adverse event criteria category. Events which worsened into grade 5 events (death) or have a resolution date equal to the date of death are considered unresolved. If a clustered AE is considered as unresolved, the resolution date will be censored to the last known alive date. Improvement to the grade at baseline implies that all different events in the clustered adverse event should at least have improved to the corresponding (i.e. with same preferred term) baseline grade. This measure is defined only for subjects who experienced at least one AE in the specific category.

The time-to resolution of AE (grade 3-5) for a specific category is defined similarly with an onset date corresponding to a grade 3-5 AE.

Time-to resolution of drug-related AE (any grade or grade 3-5) for a specific category is defined similarly but restricted to drug-related AE.

The time-to resolution of AE (any grade or grade 3-5, drug-related or all) where immune modulating medication was initiated is defined similarly. For data presentation not restricted to IMAE, the additional condition that the subject started an immune modulating medication during the longest AE resolution period will be applied.

Time-to resolution for a specific subcategory is defined similarly but restricted to event of this subcategory.

Appendix Table 1: Derivation of Clustered AE

Type of clustered AE	Derivation
Any grade	Collapse any on-treatment AE from the same category
Drug-related of any grade	Collapse any on-treatment drug-related AE from the same category
Grade 3-5	Collapse any on-treatment AE from the same category. Resolution will be based on the onset date of the earliest grade 3-5 records (if no grade 3-5 record, clustered AE is excluded)
Drug-related of Grade 3-5	Collapse any on-treatment drug-related AE from the same category Resolution will be based on the onset date of the earliest grade 3-5 record (if no Grade 3-5 record, clustered AE is excluded)

The algorithm for collapsing adverse event records is using the following conventions:

For each subject and specified category, the corresponding adverse event records will be collapsed when:

1) Multiple adverse event records have the same onset date.
2) The onset date of an event record is either the same day or 1 day later than the resolution date of a preceding event record (contiguous events).
3) The onset date of an event record is after the onset date and prior to or on the resolution date of a preceding event record (overlapping events).

[redacted]