Official Title of Study:

Non-Comparative, Open-Label, Multiple Cohort, Phase 1/2 Study of Nivolumab Monotherapy and Nivolumab Combination Therapy in Subjects With Virus-Positive and Virus-Negative Solid Tumors

NCT Number: NCT02488759

Document Date (Date in which document was last revised): Sep 7, 2021

STATISTICAL ANALYSIS PLAN FOR CLINICAL STUDY REPORT

NON-COMPARATIVE, OPEN-LABEL, MULTIPLE COHORT, PHASE 1/2 STUDY OF NIVOLUMAB MONOTHERAPY AND NIVOLUMAB COMBINATION THERAPY IN SUBJECTS WITH VIRUS-POSITIVE AND *VIRUS-NEGATIVE* SOLID TUMORS

PROTOCOL CA209358

VERSION # 4.0

DOCUMENT HISTORY

Version Number	Author(s)	Description
1.0	[redacted]	Initial version
1.1	[redacted]	• Add the definition of Relative Dose Intensity (%) Table 7.4.1-1 • Changed "sum of product diameters" to "sum of diameters" on page 23 and 26
2.0	[redacted]	• Add the analysis for metastatic nivo and ipi combo cohort. • Update the definition of PFS regarding No baseline tumor assessment.
2.1	[redacted]	• Added the analysis for metastatic nivo and BMS-986016 combo cohort and metastatic nivo and daratumumab combo cohort. • Added definition of PFS after surgery for neoadjuvant subjects.
2.2	[redacted]	• Removed metastatic combination gastric cohort. • Revised combo C cohorts • Updated naming of tumor types from "HPV associated tumors" to "Anogenital Cancers. • Updated Table 4.3.3-1 • Updated section 7.3.2 • Updated section 7.3.4 • Updated Table 7.4.1-1 • Updated section 7.5.1.2
3.0	[redacted]	• Added cervical combo B expansion cohort. • Replaced exploratory endpoint for neoadjuvant cohort "PFS after surgery/biopsy" with "RFS" in section 4.3.1 and related analyses sections. • Moved secondary endpoint for neoadjuvant cohorts to exploratory endpoints section. • Added biomarker analysis for CPS. • Removed AE analysis by PD-L1 status.

Version Number	Author(s)	Description
4.0	[redacted]	• Clarified the timing of the primary analysis for metastatic cohort. • Updated the description of PK analysis and Immunogenicity sections that previously referenced CORE safety SAP. • Added final analysis at study closure. • Added summary of continuous % residual viable tumor (%RVT) results and summary of surgery for neoadjuvant cohort. • Clarified the derivation of completion rate in Outcome research analysis that it will be calculated using subjects assessed at assessment time point and it does not use outcome research analysis population.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 BACKGROUND AND RATIONALE

Study CA209358 is an open label, multiple-cohort, Phase 1/2 trial to investigate the safety and efficacy of nivolumab as a single agent and in combination with other therapy (ipilimumab, BMS-986016, or daratumumab) in viral positive and viral negative tumor types - Epstein Barr Virus (EBV) positive gastric cancer, EBV positive and negative nasopharyngeal cancer (NPC), Human Papilloma Virus (HPV) positive squamous cell cancer of the head and neck (SCCHN), HPV positive and negative cervical and other anogenital HPV associated cancers (vaginal, vulvar, anal canal, penile) and Polyomavirus positive merkel cell cancer.

There is a significant unmet medical need for subjects with virus positive tumors including nasopharyngeal carcinoma, gastric, Merkel cell carcinoma, cervical/vulvar/vaginal, or SCCHN as outlined in protocol (Protocol Section 1.1). Virus positive tumors may have distinct patterns of immune responses and tumor immune microenvironments (Protocol Section 1.1); therefore, a strong rationale exists to support blocking the PD-1 signaling pathway with the goal of improving patient outcomes in the metastatic/recurrent settings.

One of the primary objectives of this protocol is to assess the safety and tolerability of administering 2 doses of nivolumab in the neoadjuvant setting, prior to surgical resection of disease. Based on the safety/tolerability profile as described in the protocol (Protocol Section 1.1.3), it is unlikely that subjects in the neoadjuvant cohort receiving 2 doses of nivolumab will experience a significant delay in surgery. CA209-358 will provide preliminary safety and biomarker data utilizing nivolumab in the neoadjuvant setting prior to surgery.

In the metastatic setting, subjects with virus-positive tumors generally have limited treatment options with high mortality rates, and NCCN guidelines recommend clinical trials as an option for each of the tumor types in this trial.

This document contains descriptions of the statistical analyses that will be conducted for the Clinical Study Report (CSR) of study CA209358. This document also refers to Core Safety Statistical Analysis Plan[1] that contains program level safety analyses descriptions.

Research Hypothesis:

Research Hypothesis (A): Nivolumab, in the neo-adjuvant setting, will be safe and tolerable in subjects with select virus positive and virus-negative tumors.

Research Hypothesis (B): Treatment with nivolumab alone or in combination with other therapy (ipilimumab, BMS-986016, or daratumumab) will lead to clinically meaningful tumor reductions, as measured by objective response rate and duration of response, in subjects with metastatic or unresectable tumors.

Schedule of Analyses:

Final analyses will be conducted by tumor types in each cohort

Neoadjuvant Cohort:

Analysis of PFS after surgery/biopsy will be conducted after a minimum of twelve months after the last subject's surgery or biopsy in this cohort on each tumor type

Metastatic Cohorts:

Primary endpoint for the metastatic cohorts is the investigator-assessed objective response rate (ORR) per RECIST 1.1. The primary analysis will be conducted after one year follow up for the last subject's first dose of study treatment. The timing of the primary analysis will allow to have mature OS data and will not affect the ORR results. In addition, safety analyses will be performed on each tumor type. Depending on enrollment rate, combination cohort could have a final analysis at the same time with monotherapy cohorts or later.

The final closure analysis will be conducted when a last subject is followed up for 122 days post last treatment dose for safety in accordance with the minimum safety follow up defined in the protocol. Updated safety analysis will be conducted. No subsequent survival analysis will be performed after a post-treatment safety follow-up is completed and the study will be considered as closed.

2 STUDY DESCRIPTION

2.1 Study Design

This is an open label, multiple-cohort, phase 1/2 trial to investigate the safety and efficacy of nivolumab as a single agent or in combination therapy in virus-positive and virus-negative solid tumors.

The tumor types for the neoadjuvant cohort are:

(N-1): HPV positive SCCHN
(N-2): HPV negative SCCHN
(N-3): GYN (Cervical, Vaginal, or Vulvar) Carcinoma
(N-4): Merkel Cell Carcinoma

The diseases or tumor types for the recurrent/metastatic monotherapy cohort are

(M-1): EBV positive related Gastric cancer,
(M-2): HPV positive SCCHN
(M-3): GYN (Cervical, Vaginal, or Vulvar) Carcinoma
(M-4): Merkel Cell carcinoma
(M-5): Nasopharyngeal Carcinoma (NPC)

The diseases or tumor types for the recurrent/metastatic combination therapy cohort are

(MC-1a): HPV positive Squamous Cell cancer of the Head and Neck (SCCHN) PD-1/PD-L1 naive: combo A
(MC-2a): Cervical Carcinoma: combo A
(MC-2b): Cervical Carcinoma: combo B

(MC-exp): Squamous Cell Cancer of the Cervix: combo B expansion

(MC-3a): Other anogenital HPV associated cancers (vaginal, vulvar, anal canal, penile): combo A

(MC-3b): Other anogenital HPV associated cancers (vaginal, vulvar, anal canal, penile): combo B

(MC-4a): Merkel Cell Carcinoma: combo A

(MC-5a): Nasopharyngeal carcinoma (NPC): combo A

(MC-6c): HPV positive Squamous Cell cancer of the Head and Neck (SCCHN) Prior PD-1/PD-L1: combo C

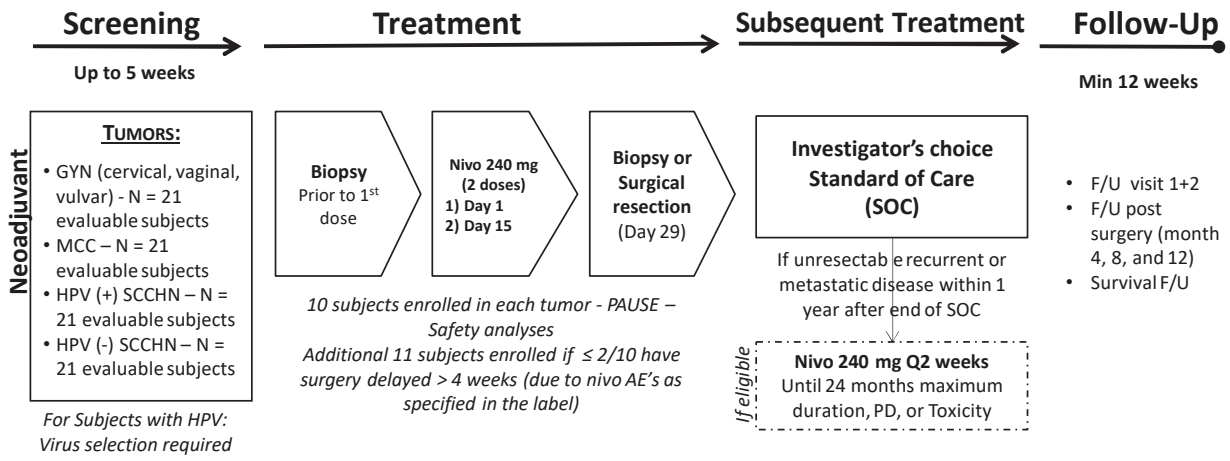
(MC-7d): Squamous Cell cancer of the Head and Neck (SCCHN) I-O naive: combo D

The study design schematic is presented below.

The tumor types for the neoadjuvant cohort and the study design schematic for the neoadjuvant cohort (Figure 2.1-1) are presented below:

- HPV positive SCCHN and HPV negative SCCHN
- Cervical, Vaginal, Vulvar carcinoma
- Merkel Cell Carcinoma

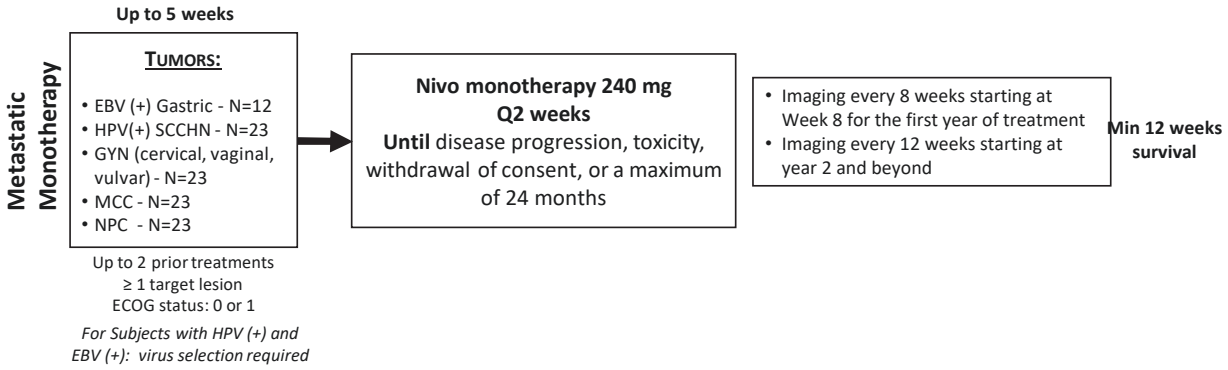
Figure 2.1-1: Study Design Schematic for the Neoadjuvant Cohort:



The diseases or tumor types for the recurrent/metastatic monotherapy cohort and the study design schematic for the recurrent/metastatic monotherapy cohort is presented in (Figure 2.1-2) are presented below:

- EBV positive Gastric cancer,
- HPV positive SCCHN
- Cervical, vaginal, and vulvar carcinoma
- Merkel Cell carcinoma
- Nasopharyngeal Carcinoma (NPC)

Figure 2.1-2: Study Design Schematic for the Metastatic Monotherapy Cohort



The diseases or tumor types for the recurrent/metastatic combination therapy cohorts (Combo A, B and C) are listed below and the study design schematics for the recurrent/metastatic combination therapies A, B, and C are presented in Figure 2.1-3 and Figure 2.1-4.

- HPV positive SCCHN
  - Immuno-Oncology naive (anti-tumor vaccine and any T cell co-stimulation or checkpoint pathways therapy) (Combo A)
  - Prior PD-1/PD-L1 (Combo C)
- Cervical cancer (Combo A and B)
- Anogenital HPV associated tumors (vaginal, vulvar, anal canal, penile) (Combo A and B)
- Merkel Cell Carcinoma (Combo A)
- Nasopharyngeal Carcinoma (NPC) (Combo A)

Figure 2.1-3: Study Design Schematic for the Metastatic Cohort Combination Therapies A and B and Combo B SCC of the Cervix Expansion

;

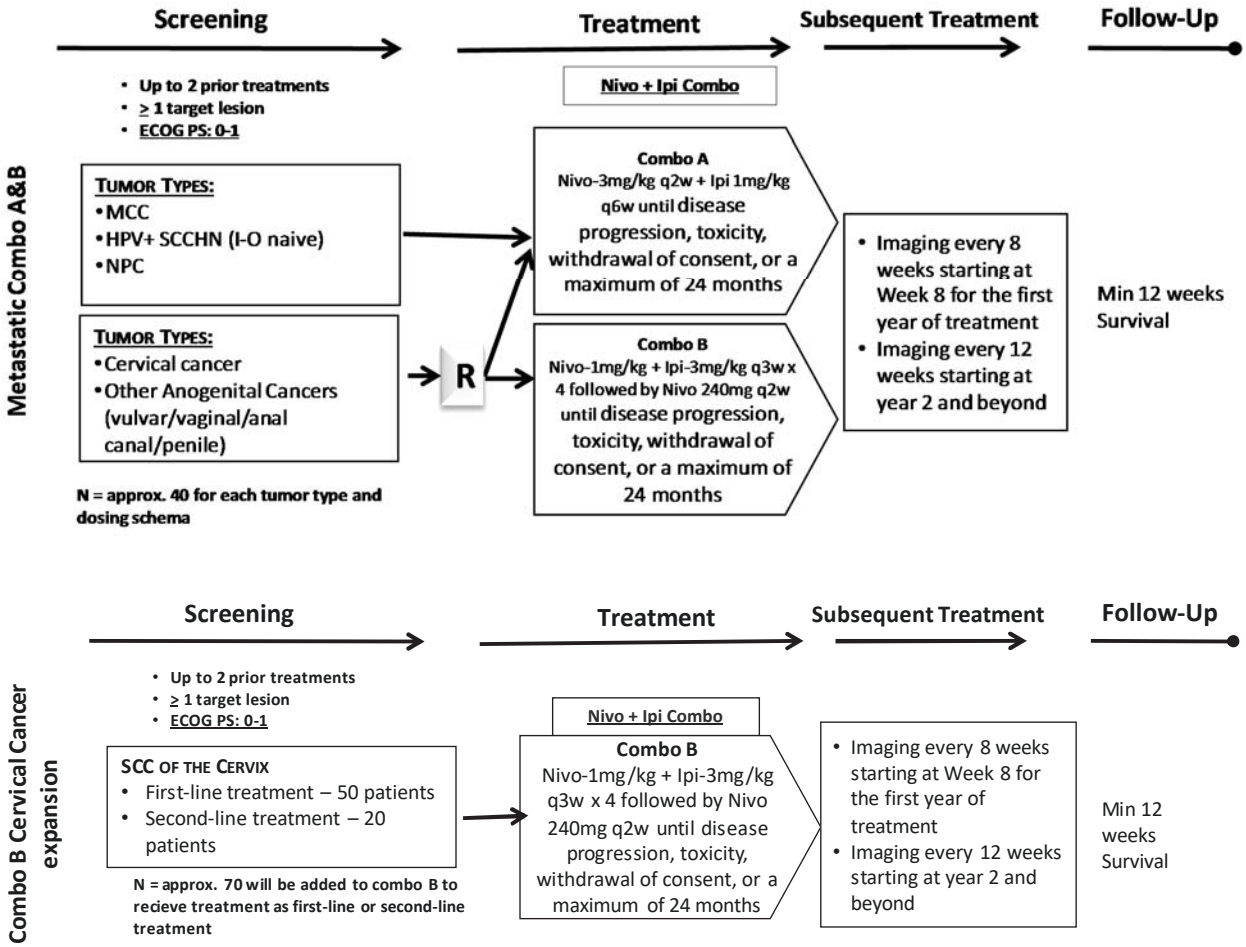
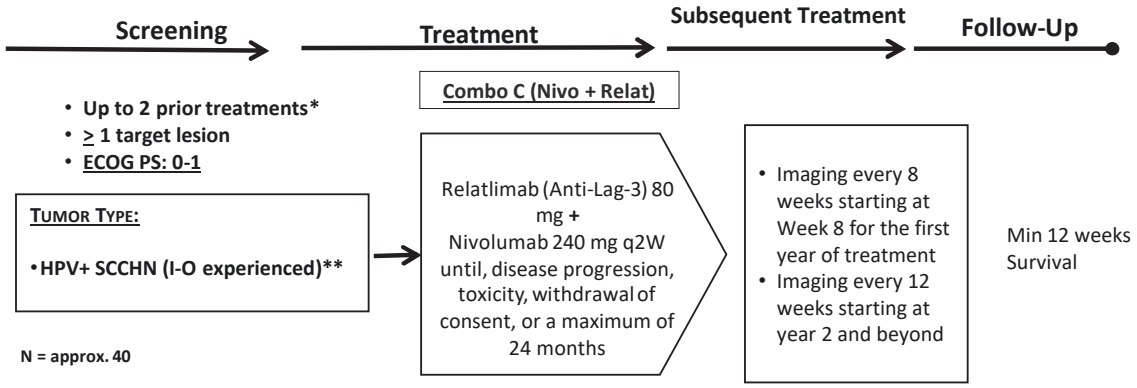


Figure 2.1-4: Study Design Schematic for the Metastatic Cohort Combination Arm C

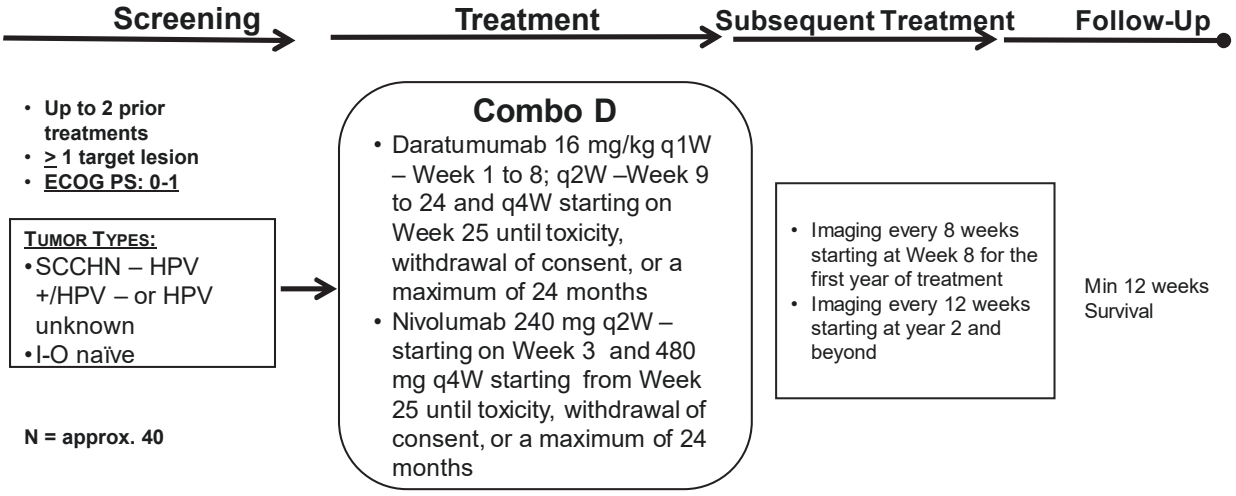


*Prior I-O therapy is permitted and is not counted toward the number of prior systemic treatment
**Include subjects that have had prior exposure to anti-PD-1, anti-PD-L1 or anti-CTLA-4 antibodies monotherapy or combination therapy

The disease or tumor type for the recurrent/metastatic combination D therapy cohort are listed below and the study design schematic for the recurrent/metastatic combination cohort for combination therapy D is presented in Figure 2.1-5.

- HPV positive or HPV negative or unknown SCCHN
- Immuno-Oncology therapy naive (anti-tumor vaccine and any T cell co-stimulation or checkpoint pathways therapy)

Figure 2.1-5: Study Design Schematic for the Metastatic Cohort Combination Therapy D: Tumor Type SCCHN HPV positive, negative or unknown I-O naive.



Neoadjuvant Cohort: Confirmation of viral status is required prior to study drug assignment for SCCHN subjects enrolled. Viral testing determined more than 35 days prior to first dose may be used. For SCCHN tumor types in the neoadjuvant cohort, 21 evaluable subjects with virus positive disease and 21 evaluable subjects with virus negative disease will be enrolled. No prior screening for GYN (cervical, vaginal, vulvar) or MCC cohorts is necessary due to the high prevalence of viral positivity and the technical aspects of the MCPyV assay. MCC and GYN (cervical, vaginal, or vulvar) cancers tumor types will contain 21 evaluable subjects each. Viral positivity will be tested retrospectively for MCC and GYN tumor types.

Metastatic Monotherapy Cohort: Gastric and SCCHN subjects will be tested for viral status prior to study drug assignment. MCC, NPC, and GYN (cervical, vaginal, vulvar) subjects will not require viral screening prior to study entry. With the exception of gastric cancer (n=12), each specific tumor type in the metastatic monotherapy cohort will contain 23 subjects and will be treated with nivolumab 240 mg IV every 2 weeks until disease progression or unacceptable toxicity. Viral positivity will be tested retrospectively for MCC, NPC, and GYN tumor types.

The study will enroll prospective subjects diagnosed with gastric cancer. Gastric subjects will provide pre-screening informed consent for determination of EBV+ viral status during the screening period and be registered in IRT. Viral testing will be performed locally or by a central laboratory and test results will be collected. After positive test result confirmation, consent for demographic and further eligibility will be collected. Subjects with EBV negative gastric cancer will be considered screen failures and will not be eligible for the study.

Metastatic Combination Therapy Cohort - Combo A, Combo B, and Combo C: SCCHN subjects will be tested for viral status prior to study drug assignment. Subjects with MCC, NPC, cervical cancer and other HPV associated tumors (vaginal, vulvar, anal canal, and penile) will not require viral screening prior to study entry. Viral positivity will be tested retrospectively for MCC, NPC, cervical cancer and anogenital HPV associated tumors (vulvar/vaginal/anal canal/penile) tumor types.

The HPV+ SCCHN, MCC, and NPC tumor types in the recurrent/metastatic cohort will each contain approximately 40 subjects that will be enrolled to the **Combo A** treatment arm. Patients with cervical cancer and anogenital HPV associated tumors (vulvar/vaginal/anal canal/penile) tumor types will be randomized in a 1:1 ratio to one of two dosing schema (**Combo A or Combo B**). Each dosing schema will contain approximately 40 subjects.

Subjects with HPV+ SCCHN with prior PD-1/PD-L1 treatment will be enrolled in Metastatic Combination Cohort (**Combo C**). Combo C will contain approximately 40 subjects. As of Revised Protocol 05, enrollment will close.

Approximately 40 I-O naive HPV positive, negative, or indeterminate SCCHN subjects will be enrolled to the **Combo D** treatment arm.

The study will enroll prospective subjects diagnosed with SCCHN. SCCHN subjects will provide consent, via pre-screening informed consent, for determination of HPV viral status, if prior results are not available during the screening period and be registered in IRT (Combo A and C). Viral

testing will be performed locally or by a central laboratory and test results will be collected. After viral test result is confirmed positive, consent for demographic and further eligibility will be collected. If subjects decline pre-screening informed consent or are unwilling to undergo viral testing, they are eligible to enroll in Combo D. However, viral status should be determined retrospectively.

2.2 Treatment Assignment

After the subject's informed consent has been obtained and eligibility is established, the subject will be enrolled and a number will be assigned through an interactive voice response system (IVRS). If the tumor group for which the subjects would be assigned to has not yet met the expected number of subjects for the study, the subject will be assigned a treatment vial number and will receive study treatment.

Neoadjuvant Cohort:

- Nivolumab administered intravenously (IV) over 30 minutes at 240 mg for 2 doses, on Day 1 and Day 15 (before surgery).

Metastatic Monotherapy Cohort:

- Nivolumab administered IV over 30 minutes at 240 mg every 2 weeks for a maximum of 24 months or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first.

Metastatic Combination Cohorts (Combinations A, B, C, and D):

- Combo Arm A: Nivolumab 3 mg/kg IV over 30 minutes every 2 weeks plus Ipilimumab 1 mg/kg IV over 30 minutes every 6 weeks for a maximum of 24 months or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first.
- Combo Arm B: Nivolumab 1 mg/kg IV over 30 minutes plus Ipilimumab 3 mg/kg IV over 30 minutes every 3 weeks for 4 doses followed by Nivolumab 240 mg IV over 30 minutes every 2 weeks for a maximum of 24 months or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first.
- Combo Arm C: Nivolumab 480 mg IV over 30 minutes plus BMS-986016 160 mg IV over 60 minutes administered every 4 weeks for a maximum of 24 month, or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first. Subjects enrolled in Combo C prior to Revised Protocol 05 and on treatment with BMS-986016 80 mg + Nivolumab 240 mg q2W will remain on this dose regimen for the duration of their time on treatment.
- Combo Arm D: Daratumumab 16 mg/kg IV administered weekly for the first 8 weeks. Starting at Week 3, nivolumab 240 mg IV over 30 minutes will be administered every 2 weeks. Nivolumab will be administered before the daratumumab infusion on study days when both study drugs are administered on the same day. Daratumumab 16 mg/kg will be administered every 2 weeks from Weeks 9-24. Starting at Week 25, nivolumab 480 mg IV

flat dose over 30 minutes every 4 weeks; daratumumab 16 mg/kg every 4 weeks for a maximum of 24 months or until progression, unacceptable toxicity, or withdrawal of consent, whichever comes first. The infusion rates for the first, second, and subsequent daratumumab infusions should closely follow the specifications of the currently approved (USPI)/pharmacy reference manual.

2.3 Blinding and Unblinding

Not applicable. This is an open-label study.

2.4 Protocol Amendments

This SAP incorporates the following protocol amendments.

Table 2.4-1: Protocol Amendments

Amendments	Date of Issue	Summary of Major Changes
Original Protocol	20-Oct-2015	Not applicable
Revised Protocol 01 (Incorporates Amendment 03)	23-Jul-2015	This global amendment was written primarily to address the following: • Addressed feedback [redacted] regarding contraceptive language In addition to the above changes, other minor changes have been made, including the following: • Corrected discrepancy in the protocol schema regarding the screening period duration • Clarified, updated, and corrected discrepancies pertaining to, information regarding virus testing throughout the protocol • Provided clarification regarding entry criteria related to specific tumor types • Provided specificity for entry criteria related to prior therapies • Provided specificity and updates related to biomarker sample requirements and biomarker testing methodologies • Corrected discrepancies regarding oxygen saturation testing • Updated safety laboratory testing requirements pertaining to bicarbonate or total CO2 testing • Provided information regarding clinical interest related to objective response rate. • Corrected typographical and spelling errors throughout the document

Table 2.4-1: Protocol Amendments

Amendments	Date of Issue	Summary of Major Changes
Revised Protocol 02 (Incorporates Amendment 07)	16-Oct-2015	This global amendment was written primarily to address the following: • Removed an exclusion criterion regarding prior surgeries that require general anesthesia and surgeries requiring local/epidural anesthesia. This change was made based on feedback provided by disease experts working on this trial In addition to the above changes, other minor changes have been made, including the following • Provided viral status determination clarifications • Removed a smoking history requirement for neoadjuvant cohort HPV positive SCCHN subjects • Edited the allowable window for safety lab testing prior to dosing • Omitted protocol content to reduce redundancy between sections explaining protocol discontinuation • Provided updates regarding dose delays in the neoadjuvant cohort • Added four month post-surgery follow-up assessments for neoadjuvant cohort subjects • Made updates regarding tumor scan assessment timing during follow-up period for neoadjuvant cohort • Corrected discrepant information regarding windows for protocol-specified cycles • Removed the requirement to discontinue tumor assessments one year after a complete response is determined • Added a description regarding research related to ex vivo functional assays • Corrected typographical errors, and made administrative updates
Revised Protocol 03 (Incorporates Amendment 09)	16-Mar-2016	This global amendment was written primarily to address the following: • Addition of a metastatic combination cohort that will investigate the safety and efficacy of nivolumab in combination with ipilimumab in virus-positive and virus-negative solid tumors. o Updated the dose delay, resume and discontinuation criteria to include ipilimumab o Updated the sample size, interim analysis, and analysis populations to include the metastatic combination cohort • Clarified collection of tumor tissue samples

Table 2.4-1: Protocol Amendments

Amendments	Date of Issue	Summary of Major Changes
		• Provided specificity and updates related to biomarker sample requirements and biomarker testing methodologies In addition to the above changes, other minor changes have been made, including the following: • Clarified dose delay, resume and discontinuation criteria • Clarified that the analysis will be performed by tumor type in each cohort • Omitted protocol content to reduce redundancy between sections explaining protocol discontinuation • Corrected typographical errors, and made administrative updates
Revised Protocol 04 (Incorporates Amendment 13)	28-Oct-2016	This global amendment was written primarily to address the following: • Addition of two treatment arms, consisting of nivolumab combined with BMS-986016 agent and nivolumab combined with daratumumab to the metastatic combination cohort. • Updates to the sample sizes for various tumor types in the metastatic monotherapy and metastatic combination therapy cohorts for combinations A and B • Addition of HPV positive anal canal and penile cancers to the metastatic combination cohort • □Clarification that results of Day 29 tumor biopsy for neoadjuvant cohort must be reviewed by pathologist and a copy of the pathology report must be sent to BMS • Nivolumab program level revisions, including algorithm update and contraception requirements. • Updates to references in Section 12 in accordance with information added to the protocol In addition to the above changes, other minor changes have been made, including correction of typographical errors, and administrative updates.
Revised Protocol 05	18-Apr-2018	• Added 24-month maximum treatment duration for nivolumab. • Clarified sample sizes for neoadjuvant tumor types. • Allow concurrent enrollment for Combination Cohorts A, B, and D. • Removed gastric cancer from Combination Cohorts. • Enrollment to Combination C is closed (including to crossovers).

Table 2.4-1: Protocol Amendments

Amendments	Date of Issue	Summary of Major Changes
		• Added new safety data from BMS-986016 and daratumumab. • Changed order of nivolumab and daratumumab administration so that nivolumab is now administered before daratumumab. • Removed oxygen saturation testing from vital signs collection in all on-treatment groups. • Clarified imaging duration to be consistently starting at week 8. • Added 400-mg vials for daratumumab. • Updated naming of tumor types from "HPV associated tumors" to "Anogenital Cancers."
Revised Protocol 06	18-Jul-2018	• Terminated enrollment and treatment of daratumumab combination cohorts. • Added a Combination B cohort expansion for SCC of the cervix. • Changed the neoadjuvant secondary endpoint to an exploratory endpoint. • Closed enrollment in the combination cohorts for anogenital HPV associate tumor types.
Revised Protocol 07	07-May-2019	• Incorporates Administrative Letter 02. • Changed exploratory objective and endpoint of progression-free survival to recurrence-free survival. • Updated inclusion/exclusion criteria from bulleted lists back to letters. • Updated language for EQ-5D-3L and EORTC-QLQ-C30. • Added missing footnote identifier to Table 5.1-3.

2.5 Data Monitoring and Other External Committees

Not applicable.

3 OBJECTIVES

3.1 Primary

- In the neoadjuvant cohort, to investigate the safety and tolerability of neoadjuvant nivolumab administration in the following tumor types:
  - HPV positive SCCHN
  - HPV negative SCCHN
  - GYN (Cervical, Vaginal, Vulvar) Carcinoma
  - Merkel Cell Carcinoma

- In the metastatic/recurrent nivolumab monotherapy cohort, to evaluate the investigator-assessed objective response rate (ORR) of nivolumab monotherapy in subjects with the following diseases:
  - Metastatic or recurrent EBV positive related Gastric cancer,
  - Metastatic or recurrent HPV positive SCCHN
  - Metastatic or recurrent GYN (Cervical, Vaginal, Vulvar) Carcinoma
  - Metastatic or recurrent Merkel Cell carcinoma
  - Metastatic or recurrent Nasopharyngeal Carcinoma (NPC)

- In the metastatic/recurrent combination therapy (nivolumab combined with either ipilimumab [Combo A or B], or BMS-986016 [Combo C]) cohort, to evaluate the investigator-assessed objective response rate (ORR) of nivolumab combination in subjects with the following diseases:
  - Metastatic or recurrent NPC
  - Metastatic or recurrent MCC
  - Metastatic or recurrent cervical cancers
  - Metastatic or recurrent HPV positive SCCHN (with primary exposure to anti-PD-1, anti-PD-L1 or anti-CTLA-4 antibody therapy [Combination C])
  - Other metastatic or recurrent anogenital HPV associated tumors (vulvar, vaginal, anal, canal, penile)

- In the metastatic cohort nivolumab combined with daratumumab (Combo D) to evaluate the investigator-assessed objective response rate (ORR) in subjects with:
  - Metastatic or recurrent HPV positive, negative, or unknown SCCHN (without prior I-O therapy exposure)

3.2 Secondary

3.2.1 Metastatic Cohorts (Monotherapy and Combination Therapy)

- To evaluate the duration of response, progression-free survival and overall survival.

3.3 Exploratory

3.3.1 Neoadjuvant Cohort

- To determine the percent change from baseline of immune cells and the percent change from baseline of select immune activation/inhibitory molecules of viral-specific T cells in tumor specific subsets of nivolumab treated subjects.
- To evaluate the recurrence-free survival after neoadjuvant administration of nivolumab and surgery
- To determine the percent change from baseline in tumor volume after two doses of neoadjuvant nivolumab.

- To determine pathologic complete response of tumors in subjects who receive surgical resection after two doses of neoadjuvant nivolumab in SCCHN, resectable Merkel Cell Carcinoma, and cervical, vaginal, or vulvar cancer.
- To evaluate changes in anti-viral and anti-tumor immune responses at the tumor site, using proliferative and/or functional assays.
- To investigate the potential association between selected biomarker measures in peripheral blood and tumor tissue, including PD-L1, with safety and clinical efficacy measures.
- To investigate the pharmacodynamic activity of nivolumab in the peripheral blood and tumor tissue as measured by gene expression, flow cytometry, immunohistochemistry and soluble factor assays.
- To study the effect of nivolumab on the viral antigen specific T cell responsiveness in the peripheral blood.
- To evaluate the potential association between the number of tumor mutations and neoantigens with clinical efficacy measures and determine if tumor antigen-specific T cells are present in the periphery.
- To assess the subject's overall health status as assessed by the EQ-5D.
- To evaluate cancer specific health related quality of life as assessed by EORTC QLQ-C30.
- To characterize pharmacokinetics of nivolumab and explore exposure-response relationships.
- To characterize the immunogenicity of nivolumab.

3.3.2 Metastatic Cohorts (Monotherapy and Combination Therapy)

- To determine the safety and tolerability [defined as toxicity rates (worst CTC grade per subject) of adverse events and specific laboratory tests] of nivolumab monotherapy and combination therapy (ipilimumab, BMS-986016, or daratumumab) in subjects with metastatic or recurrent viral-mediated tumors.
- To evaluate the pre and post treatment EBV DNA levels in subjects with EBV positive gastric cancer (monotherapy only) and nasopharyngeal carcinoma.
- To investigate the potential association between selected biomarker measures in peripheral blood and tumor tissue, including PD-L1, with safety and clinical efficacy measures.
- To investigate the pharmacodynamic activity of nivolumab monotherapy and combination therapy (ipilimumab, BMS-986016, or daratumumab) in the peripheral blood and tumor tissue as measured by gene expression, flow cytometry, immunohistochemistry and soluble factor assays.
- To study the effect of nivolumab monotherapy and combination therapy (ipilimumab, BMS-986016, or daratumumab) on the viral antigen specific T cell responsiveness in the peripheral blood.
- To evaluate the potential association between the number of tumor mutations and neoantigens with clinical efficacy measures and determine if tumor antigen-specific T cells are present in the periphery.
- To assess the subject's overall health status as assessed by the EQ-5D.
- To evaluate cancer specific health related quality of life as assessed by EORTC QLQ-C30.

- To characterize pharmacokinetics of nivolumab monotherapy and combination therapy (ipilimumab, BMS-986016, or daratumumab) and explore exposure-response relationships.
- To characterize the immunogenicity of nivolumab monotherapy and combination therapy (ipilimumab, BMS-986016, or daratumumab).

4 ENDPOINTS

4.1 Primary Endpoint

4.1.1 Neoadjuvant Cohort

- The safety and tolerability objective will be measured by the incidence of drug-related select AEs and drug-related SAEs
- Rate of surgery delay, which is defined as the proportion of subjects in the neoadjuvant cohort with surgery delayed > 4 weeks from the planned surgery date or planned start date for chemoradiation due to a drug-related AE will be reported for each tumor type.

4.1.2 Metastatic Cohorts (Monotherapy and Combination Therapies)

- The investigator-assessed objective response rate (ORR)

  ORR is defined as the number of subjects with a best overall response (BOR) of confirmed complete response (CR) or partial response (PR) divided by the number of treated subjects. The BOR is defined as the best response designation, as determined by the investigator, recorded between the date of treatment assignment and the date of objectively documented progression per RECIST 1.1 or the start date of subsequent anticancer therapy, whichever occurs first. CR or PR determinations included in the BOR assessment must be confirmed by a second scan no less than 4 weeks after the criteria for response are first met. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment. For subjects who continue treatment beyond progression, the BOR should be determined based on response designations recorded up to the time of the initial RECIST 1.1-defined progression.

4.2 Secondary Endpoints

4.2.1 Metastatic Cohorts (Monotherapy and Combination Therapies)

- Duration of response (DOR) is computed for subjects with a BOR of PR or CR and is defined as the time from first confirmed response (CR or PR) to the date of the first documented tumor progression as determined using RECIST 1.1 criteria or death due to any cause, whichever occurs first. For subjects who neither progress nor die, the DOR will be censored on the date of their last evaluable tumor assessment. The magnitude of reduction in tumor volume is defined as the percent decrease in tumor volume from baseline to nadir, observed up until the time of the first documented tumor progression or death.
- Clinical Benefit Rate (CBR) is defined as the number of participants with a best overall response (BOR) of confirmed complete response (CR) or partial response (PR) or stable disease (SD) divided by the number of treated subjects.

- Overall survival (OS) is defined as the time from first dosing date to the date of death. A subject who has not died will be censored at last known date alive.
- Investigator-assessed progression free survival (PFS) is defined as the time from first dosing date to the date of the first documented tumor progression, as determined by investigators (per RECIST 1.1), or death due to any cause. Subjects who had no baseline tumor assessment will be censored on the first dose date. Subjects who did not start subsequent anti-cancer therapy and die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on the date they were treated. Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy.

Table 4.2-1: Censoring scheme used in primary definition of PFS

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments and no death	First Dosing date	Censored
No on study tumor assessments and no death	First Dosing date	Censored
Progression per RECIST 1.1 documented at scheduled visit or unscheduled visit and no new anticancer treatment started before	Date of the first documented tumor progression	Progressed
Subject progression free per RECIST 1.1 and no new anticancer treatment started	Date of last tumor assessment	Censored
New anticancer treatment started without a prior reported progression per RECIST 1.1 or death	Date of last tumor assessment prior or on the date of initiation of the subsequent anti-cancer therapy	Censored
Death without progression per RECIST 1.1 and no new anticancer treatment started	Date of death	Progressed

4.3 Exploratory Endpoints

4.3.1 Neoadjuvant Cohort only

- The percent change from baseline of immune cells and the percent change from baseline of select immune activation/inhibitory molecules of viral-specific T cells in tumor specific subsets of nivolumab treated subjects will be evaluated. The percent change is the ratio of change from the baseline and baseline measurement.
- Recurrence-free survival (RFS), which is defined as the time from surgery to the date or recurrence (local, regional, metastasis, locally advanced unresectable recurrence, clinical or radiographic progression occurs after surgery) as determined by investigators, or death due to any cause, whichever occurs first. (Note: a subject who dies without reported recurrence will be considered to have recurred on the date of death.)

Table 4.3-1: Censoring scheme used in primary definition of RFS

Situation	Date of Recurrence or Censoring	Outcome
Recurrence (local, regional, metastasis, locally advanced unresectable recurrence, clinical/radiographic progression occurs after surgery)	Date of the earliest documented recurrence/progression after surgery	Event
Death without documented recurrence after surgery/biopsy	Date of death	Event
No post-surgery disease assessment and no death	Date of surgery	Censored
No recurrence and no death	Date of last evaluable disease assessment	Censored
New anticancer therapy[a] started without recurrence or death	Date of last evaluable disease assessment prior to or on the same date of initiation of subsequent therapy	Censored

[a] Protocol allowed adjuvant therapy in SOC follow up phase is not counted as subsequent therapy.

Table 4.3.1-2: Censoring scheme used in sensitivity analysis of RFS

Recurrence (local, regional, metastasis, locally advanced unresectable recurrence, clinical/radiographic progression occurs after surgery)	Date of the earliest documented recurrence/progression after surgery	Event
Death without documented recurrence after surgery/biopsy	Date of death	Event
No post-surgery disease assessment and no death	Date of surgery	Censored
No recurrence and no death	Last known alive date	Censored
New anticancer therapy[a] started without recurrence or death	Date of last evaluable disease assessment prior to or on the same date of initiation of subsequent therapy	Censored

[a] Protocol allowed adjuvant therapy in SOC follow up phase is not counted as subsequent therapy.

- Safety endpoints (Section 7.6)
- The percent change in tumor volume from baseline after two doses of neoadjuvant nivolumab is defined as the ratio of the change in tumor volume and the baseline tumor volume.
- The proportion of treated subjects who experiences pathologic complete response will be used to determine pathologic response rate of tumors after two doses of neoadjuvant nivolumab in HPV positive and negative SCCHN, resectable Merkel Cell Carcinoma, and HPV positive

cervical, vaginal, or vulvar cancer. Pathological complete response (pCR) is defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected tumor specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy.

4.3.2 Metastatic Cohorts only

- The safety and tolerability objective will be measured by the incidence of adverse events, serious adverse events, deaths and laboratory abnormalities.
- Pre and post treatment EBV DNA levels will be collected in the subjects with EBV positive gastric cancer (monotherapy only) and nasopharyngeal carcinoma. The change in EBV DNA levels will be used to determine the effect of BMS-936558 (nivolumab).
- Efficacy endpoints in GYN tumor type (monotherapy only) will also be reported in two subgroups, Cervical and Vaginal/Vulvar, when data allows.

4.3.3 Neoadjuvant and Metastatic Cohorts

- **PD-L1 Expression:**

  PD-L1 expression missing: Subjects without an available tumor biopsy specimen for PD-L1 evaluation will be considered as PD-L1 expression missing.

  For subjects with an available tumor biopsy specimen(s), the following will be considered:

  PD-L1 expression is quantified and reported by two methods: tumor proportion score (TPS) and combined positive score (CPS). TPS is defined as the percent of tumor cells membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 IHC assay. CPS is evaluated based on the number of viable tumor cells that exhibit PD-L1 membrane staining and associated immune cell (lymphocytes and macrophages) that exhibit PD-L1 membrane and/or cytoplasmic staining. This is referred as quantifiable PD-L1 expression. If the PD-L1 staining could not be quantified, it is further classifies as:
  - Indeterminate: PD-L1 staining hampered for reasons attributed to the biology of the tumor tissue sample and not because of improper sample preparation or handling
  - Not evaluable: Tumor tissue sample was not optimally collected or prepared (e.g. PD-L1 expression is neither quantifiable nor indeterminate). Not evaluable can be determined from H&E process before the tumor biopsy specimen is sent for PD-L1 evaluation or from the H&E process during PD-L1 evaluation.

  If more than one tumor biopsy specimen is available, PD-L1 expression is determined from the most recently collected specimen before first dose date with a quantifiable result. If all specimens for a given subject are either indeterminate or not evaluable, then the PD-L1 expression will be considered indeterminate as long as at least one specimen is indeterminate. Otherwise, PD-L1 expression will be considered not evaluable.

- **Pharmacokinetics:**

  The PK objective will be measured from serum concentration. Samples will be collected to characterize pharmacokinetics of nivolumab and to explore exposure-safety and exposure-efficacy relationships.

- **Biomarkers:**

  Biomarkers potentially associated with clinical endpoints will be measured by analyzing tumor and blood samples. Biomarker endpoints include, but are not limited to, single-nucleotide polymorphisms (SNPs), proteins in tumor specimens and serum, and immune cell populations.

- **Immunogenicity:**

  Serum samples collected will be analyzed by a validated immunogenicity assay. Selected serum samples may be analyzed by an exploratory orthogonal method that measures anti-nivolumab. Potential results generated from any orthogonal method are intended as informational for technology exploration purposes and will not be reported.

  In addition, ad hoc serum samples designated for pharmacokinetic or biomarker assessments may also be used for immunogenicity analysis if required (e.g., insufficient volume for complete immunogenicity assessment or to follow up on suspected immunogenicity related AE).

- **EQ-5D:**

  Subjects' overall health status will be assessed using the EuroQoL Group's self-reported health status measure (EQ-5D-3L). EQ-5D essentially has 2 components: the EQ-5D descriptive system and the EQ visual analogue scale (EQ-VAS).

  The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, severe problems. Once the data have been collected and a database created, a scoring function can be used to assign a value (i.e., EQ-5D index score) to self-reported health states from a set of population-based preference weights.

  The EQ VAS records the subject's self-rated health state on a 100-point vertical, visual analogue scale (0 = worst imaginable health state; 100 = best imaginable health state).

- **EORTC-QLQ-C30:**

  Health-related quality of life (HRQoL) will be assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire Version 3. It is a 30-item instrument that has gained wide acceptance in oncology clinical studies. The EORTC QLQ-C30 is composed of multi-item and single scales. These include five functional scales (physical, role, emotional, social, and cognitive), three symptom (fatigue, nausea and vomiting and pain) and a global health status/QOL scale and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties). All scales and single items meet the standards for reliability. The reliability and validity of the questionnaire is highly consistent across different language-cultural groups[2]. Except for the overall health status and global quality of life items, responses for all items are 4-point categorical scales ranging from 1 (Not at all) to 4 (Very much). The overall health status/quality of life responses are 7-point Likert scales.

Data will be scored according to the algorithm described in the EORTC QLQ-C30 scoring manual, as follows:

Functional scales:

- Physical functioning: (1 - ((Q1+Q2+Q3+Q4+Q5)/5-1)/3) * 100
- Role functioning: (1 - ((Q6+Q7)/2-1)/3) * 100
- Emotional functioning: (1 - ((Q21+Q22+Q23+Q24)/4-1)/3) * 100
- Cognitive functioning: (1 - ((Q20+Q25)/2-1)/3) * 100
- Social functioning: (1 - ((Q26+Q27)/2-1)/3) * 100

Global health status:

- Global health status/QoL: ((Q29+Q30)/2-1)/6 * 100

Symptom scales/items:

- Fatigue: ((Q10+Q12+Q18)/3-1)/3 * 100
- Nausea and vomiting: ((Q14+Q15)/2-1)/3 * 100
- Pain: ((Q9+Q19)/2-1)/3 * 100
- Dyspnea: (Q8-1)/3 * 100
- Insomnia: (Q11-1)/3 * 100
- Appetite loss: (Q13-1)/3 * 100
- Constipation: (Q16-1)/3 * 100
- Diarrhea: (Q17-1)/3 * 100
- Financial difficulties: (Q28-1)/3 * 100

Missing values will be imputed for missing items by "assuming that the missing items have values equal to the average of those items which are present" for any scale in which at least half the items are completed. A scale in which less than half of the items are completed will be treated as missing. This is the method proposed in the scoring manual. A questionnaire will be considered as received if at least one of the 15 scales is non-missing (after imputation).

All questionnaires completed at baseline and on-study will be assigned to a time-point according to the windowing criteria in Table 4.3-3 and included in the analysis. In case a subject has two on-study assessments within the same window, the assessment closest to the time-point will be used. And, in the case of two assessments at a similar distance to the time-point, the latest one will be chosen. In the event where the subject has no assessment at all in a specific window, the observation will be treated as missing for that time-point.

Table 4.3-3: Time Windows for EORTC-QLQ-C30 and EQ-5D Assessments

Nominal Time-Point	Time Window
Nivolumab Monotherapy Metastatic Cohorts	

Table 4.3-3: Time Windows for EORTC-QLQ-C30 and EQ-5D Assessments

Nominal Time-Point	Time Window
Baseline	Prior to first dose on Day 1
Week 9	Day 2 thru Day 85, inclusive
Every 8 Weeks up to week 25	Nominal Day (+28 days/-27 days, inclusive)
Week 33	Nominal Day 225 (+42 days/-27 days, inclusive)
Every 12 weeks thereafter	Nominal Day (+42 days/-41 days, inclusive)
Follow-up 1	Any data associated with Follow-up X01 visit
Follow-up 2	Any data associated with Follow-up X02 visit
Survival Follow-up Visits (applies to EQ-5D only)	
Survival Follow-up Visit 1	Any data associated with Survival Follow-up Visit 1
Survival Follow-up Visit 2	Any data associated with Survival Follow-up Visit 2
...	...
Nivolumab Monotherapy Neoadjuvant Cohorts	
Baseline	Prior to first dose on Day 1
Week 3	Day 2 thru Day 28 or the day before surgery/biopsy date, whichever is earlier, inclusive.
SOC Follow-up 1	Any data associated with Follow-up E01 visit
SOC Follow-up 2	Any data associated with Follow-up E02 visit
Post SOC Week 1	Post SOC Day 1 (prior to first dose of post SOC Nivo)
Post SOC Week 9	Post SOC Day 2 thru Post SOC Day 85, inclusive
Post SOC Week 17	Post SOC Day 86 thru Post SOC Day 141, inclusive
Post SOC Week 25	Post SOC Day 142 thru Post SOC Day 197, inclusive
Post SOC Week 33	Post SOC Day 198 thru Post SOC Day 267, inclusive
Every 12 weeks thereafter	Nominal Post SOC Day (+42 days/-41 days, inclusive)
Follow-up 1	Any data associated with Follow-up X01 visit
Follow-up 2	Any data associated with Follow-up X02 visit
Survival Follow-up Visits (applies to EQ-5D only)	
Survival Follow-up Visit 1	Any data associated with Survival Follow-up Visit 1
Survival Follow-up Visit 2	Any data associated with Survival Follow-up Visit 2
...	...
Nivolumab combination therapy A, C, D treatment group	
Same as **Nivolumab Monotherapy Metastatic Cohorts**	

Table 4.3-3: Time Windows for EORTC-QLQ-C30 and EQ-5D Assessments

Nominal Time-Point	Time Window
Nivolumab combination therapy B treatment group	
Baseline	Prior to first dose on Day 1
Week 10	Day 2 thru Day 99, inclusive
Week 19	
Week 27	Day 100 thru Day 155, inclusive
Week 35	Day 156 thru Day 211, inclusive
Week 47	Day 212 thru Day 267, inclusive
Every 12 weeks thereafter	Nominal Day 323 (+42 days/-55 days, inclusive) Nominal Day (+42 days/-41 days, inclusive)
Follow-up 1	Any data associated with Follow-up X01 visit
Follow-up 2	Any data associated with Follow-up X02 visit
Survival Follow-up Visits (applies to EQ-5D only)	
Survival Follow-up Visit 1	Any data associated with Survival Follow-up Visit 1
Survival Follow-up Visit 2	Any data associated with Survival Follow-up Visit 2
...	...

5 SAMPLE SIZE

Sample size determination is not based on statistical power calculation.

1) Neoadjuvant Cohort:

The SCCHN tumor types will contain 21 HPV-positive and 21 HPV-negative evaluable subjects. MCC and HPV positive cervical, vaginal, or vulvar cancers tumor types will contain 21 evaluable subjects each. A sample size of 21 can detect, with more than 66% and 89% probability, a safety event that occurs at an incident rate of 5% and 10%, respectively. Assuming 10%, 15%, and 20% for pathologic complete response rate, a sample size of 21 can detect, more than 89%, 97% and 99% probability, at least one pathologic complete response respectively.

1) Recurrent/Metastatic Monotherapy Cohort:

HPV+ SCCHN, GYN, MCC and NPC tumor type in the recurrent/metastatic cohort will contain 23 subjects. Table 5-1 shows the probabilities of observing 0, 1 or 2 responders and □ 3 responders assuming 5%, 20% and 30% true response rate of ORR. shows the two sided 95% exact CI using Clopper-Pearson methods based on observed 3, 4 and 5 responders out of 23 subjects.

EBV+ Gastric tumor type will contain approximately 12 subjects, due to the low prevalence. Table 5-3 shows the precision of the estimation of ORR based on the two-sided 95% exact CI using Clopper Pearson methods based on 1, 2, 3, 4 and 5 responders out of 12 subjects. Assuming the

true ORR is 25%, 12 subjects can provide approximately 84% probability to observe at least 2 responders.

Table 5-1: Probability of observing responses given true ORR for sample size of 23 subjects

True ORR	Probability of observing 0,1 or 2 responses	Probability of observing ≥ 3 responses
5%	89.5%	10.5%
20%	13.3%	86.7%
30%	1.6%	98.4%

Table 5-2: Two-sided 95% exact CI using Clopper-Pearson method based on number of observed responses out of 23 subjects

The number of observed responses	3	4	5
Observed Response Rate	3/23 (13.0%)	4/23 (17.4%)	5/23 (21.7%)
95% exact CI	(2.8%, 33.6%)	(5.0%, 38.8%)	(7.5%, 43.7%)

Table 5-3: Two-sided 95% exact CI using Clopper-Pearson method based on the number of observed responses out of 12 subjects

Number of observed responses	1	2	3	4	5
Observed Response Rate	1/12 (8.3%)	2/12 (16.7%)	3/12 (25.0%)	4/12 (33.3%)	5/12 (41.7%)
95% exact CI (%)	(0.2, 38.5)	(2.1, 48.4)	(5.5, 57.2)	(9.9, 65.1)	(15.2, 72.3)

2) Recurrent/Metastatic Combination Cohort:

The HPV+SCCHN, MCC, and NPC tumor types in the recurrent/metastatic cohort will each contain approximately 40 subjects that will be enrolled to the Combo A treatment arm. Patients with cervical cancer and other HPV associated tumors (vulvar/vaginal/anal canal/penile) tumor type will be randomized in a 1:1 ratio to one of two dosing schema (Combo A or Combo B). Approximately 40 subjects will be randomized into each dosing schema. With Revised Protocol 06, no new subjects will be randomized in the anogenital HPV associated tumors cohorts.

Additionally, the metastatic cervical Combination B cohort will be expanded to treat approximately 50 subjects as first-line treatment for their recurrent/metastatic disease if unfit or unsuitable to receive platinum-based therapy and approximately 20 subjects as second-line treatment for their recurrent/metastatic SCC of the cervix to confirm the efficacy signal. With

Combo B and the Combo B expansion, there should be a total of approximately 75 subjects with first-line treatment and approximately 35 subjects with second-line treatment of cervical cancer (approximately 110 cervical subjects total).

The HPV+ SCCHN with prior PD-1/PD-L1 treatment tumor type will be enrolled in Metastatic Combination Cohort (Combo C). Combo C will contain approximately 40 subjects. However, at Revised Protocol 05, no new subjects will be enrolled in this cohort.

Approximately 40 HPV negative and HPV indeterminate I-O naive SCCHN subjects will be enrolled to the Combo D treatment arm. With Revised Protocol 06, no new subjects will be enrolled in this cohort.

Sample sizes of each treatment arm in each tumor type are summarized in Table 5-4.

Table 5-4: Sample size in recurrent/metastatic combination cohort

	Combo A **Nivo-3mg/kg q2w + Ipi-1mg/kg q6w**	**Combo B** **Nivo-1mg/kg + Ipi-3mg/kg q3w x 4 followed by Niov 240mg q2w**	**Combo C** **Nivo+ BMS-986016**	**Combo D** **Nivo+Dara**
Cervical	40	110[a]		
Anogenital HPV associated tumors (vaginal/vulvar/anal canal/penile)	40	40		
MCC	40			
NPC	40			
HPV+ SCCHN (I/O naive)	40			
HPV+ SCCHN (Prior PD-1/PD-L1)			40	
I-O Naive SCCHN				40

[a] Includes 40 from Combination B and 70 from Combination B expansion.

In this study, an ORR in excess of 10% will be considered of clinical interest. Assuming the true ORR is 25%, 40 subjects in each tumor type can provide approximately 79.8% power to reject the null hypothesis that the true ORR is□10%, considering a two-sided alpha of 5%. In addition, Table 5-5 shows the precision of the estimation of ORR based on the two-sided 95% exact CI using Clopper Pearson methods based on 8, 9, 12, 16 and 20 responders out of 40 subjects. At observed more than or equal to 9 responders, i.e., ORR ≥ 22.5%, the lower bound of the 95% CI excludes 10%.

Table 5-6 shows the precision of the estimation of ORR based on the two-sided 95% exact CI using Clopper-Pearson methods based on 20, 22, 26, 30, 33, and 35 responders out of 50 subjects.

At observed more than or equal to 22 responders, i.e., ORR ≥ 44%, the lower bound of the 95% CI excludes 30%; at observed more than or equal to 26 responders, i.e., ORR ≥ 52%, the lower bound of the 95% CI excludes 37%.

Table 5-7 shows the precision of the estimation of ORR based on the two-sided 95% exact CI using Clopper-Pearson methods based on 3, 5, 8, 10, 12 and 14 responders out of 35 subjects. At observed more than or equal to 8 responders, i.e., ORR ≥ 22.9%, the lower bound of the 95% CI excludes 10%.

Due to the low prevalence of EBV+ Gastric tumor types and the current investigation of this tumor type in other BMS-sponsored studies, combination cohorts in this study will no longer include EBV+ Gastric tumor type.

Table 5-5: Two-sided 95% exact CI using Clopper-Pearson method based on the number of observed responses out of 40 subjects

Number of observed responses	8	9	12	16	20
Observed Response Rate	8/40 (20.0%)	9/40 (22.5%)	12/40 (30.0%)	16/40 (40.0%)	20/40 (50.0%)
95% exact CI (%)	(9.1, 35.6)	(10.8, 38.5)	(16.6, 46.5)	(24.9, 56.7)	(33.8, 66.2)

Table 5-6: Two-sided 95% Exact CI Using Clopper-Pearson Method Based on the Number of Observed Responses out of 50 Subjects

Number of observed responses	20	22	26	30	33	35
Observed Response Rate	20/50 (40.0%)	22/50 (44%)	26/50 (52%)	30/50 (60%)	33/50 (66%)	35/50 (70%)
95% exact CI (%)	(26.4, 54.8)	(30.0, 58.8)	(37.4, 66.3)	(45.2, 73.6)	(51.2, 78.8)	(55.4, 82.1)

Table 5-7: Two-sided 95% Exact CI Using Clopper-Pearson Method Based on the Number of Observed Responses out of 35 Subjects

Number of observed responses	3	5	8	10	12	14
Observed Response Rate	3/35 (8.6%)	5/35 (14.3%)	8/35 (22.9%)	10/35 (28.6%)	12/35 (34.3%)	14/35 (40%)

Table 5-7: Two-sided 95% Exact CI Using Clopper-Pearson Method Based on the Number of Observed Responses out of 35 Subjects

Number of observed responses	3	5	8	10	12	14
95% exact CI (%)	(1.8,23.1)	(4.8, 30.3)	(10.4, 40.1)	(14.6, 46.3)	(19.1, 52.2)	(23.9,57.9)

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

6.1.1 Baseline Period

Baseline evaluations or events are defined as evaluations or events that occur before the date and time of the first dose of study treatment.

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 are defined as AEs with an onset date prior to but not including the day of the first dose of study treatment
- Baseline evaluations (laboratory tests, pulse oximetry and vital signs) are defined as evaluations with a date on or prior to the day of first dose of study treatment

If there are multiple valid assessments, the assessment that is closest to a day (and time if collected) of the first dose of study treatment will be used as the baseline in the analyses. If multiple assessments are collected at the same date (and time if collected), the assessment with the latest database entry date (and time if collected) will considered as baseline.

6.1.2 Post Baseline Period

On-treatment AEs are 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). An AE will be counted as on-treatment if the event occurred within 30 (or 100) days of the last dose of study treatment. Specifically, re-initiation study treatment is excluded for the purpose of determining the last dose of study treatment as part of the definition of on-treatment; separate safety analyses for re-initiation therapy may be performed.

On-treatment evaluations (laboratory tests, pulse oximetry, and vital signs) are defined as evaluations taken after the day (and time, if collected and not missing) of first dose of study treatment. An evaluation will be counted as on-treatment if it occurred within 30 (or 100) days of the last dose of study treatment.

Late emergent drug-related AEs are defined as drug-related AEs with an onset date greater than 100 days after the last dose of study treatment in subjects off study treatment.

Table 6.1-1: Primary On-Treatment Definition For Safety in Treated Subjects

Cohort	Option for Re-Initiation	On-Treatment Definition
Neoadjuvant	Yes	On or after first dose of nivolumab and within 30 (or 100) days after last dose of nivolumab prior to re-initiation dosing
Metastatic	No	On or after first dose of study treatment and within 30 (or 100) days after the last dose of study treatment

6.2 Treatment Regimens

Neoadjuvant Cohort:

- Nivolumab administered intravenously (IV) over 30 minutes at 240 mg for 2 doses, on Day 1 and Day 15 (before surgery).

Metastatic Monotherapy Cohort:

- Nivolumab administered IV over 30 minutes at 240 mg every 2 weeks for a maximum of 24 months or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first.

Metastatic Combination Cohort (Combinations A, B, C, and D):

- Combo Arm A: Nivolumab 3 mg/kg IV over 30 minutes every 2 weeks plus Ipilimumab 1 mg/kg IV over 30 minutes every 6 weeks for a maximum of 24 months or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first.
- Combo Arm B: Nivolumab 1 mg/kg IV over 30 minutes plus Ipilimumab 3 mg/kg IV over 30 minutes every 3 weeks for 4 doses followed by Nivolumab 240 mg IV over 30 minutes every 2 weeks for a maximum of 24 months or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first.
- Combo Arm C: Nivolumab 480 mg IV over 30 minutes plus BMS-986016 160 mg IV over 60 minutes administered every 4 weeks for a maximum of 24 month, or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first. Subjects enrolled in Combo C prior to Revised Protocol 05 and on treatment with BMS-986016 80 mg + Nivolumab 240 mg q2W will remain on this dose regimen for the duration of their time on treatment.
- Combo Arm D: Daratumumab 16 mg/kg IV administered weekly for the first 8 weeks. Starting at Week 3, nivolumab 240 mg IV over 30 minutes will be administered every 2 weeks. Nivolumab will be administered before the daratumumab infusion on study days when both study drugs are administered on the same day. Daratumumab 16mg/kg will be administered every 2 weeks from Weeks 9-24. Starting at Week 25, nivolumab 480 mg IV flat dose over 30 minutes every 4 weeks; daratumumab 16 mg/kg every 4 weeks for a

maximum of 24 months or until progression, unacceptable toxicity, or withdrawal of consent, whichever comes first. The infusion rates for the first, second, and subsequent daratumumab infusions should closely follow the specifications of the currently approved (USPI)/pharmacy reference manual.[183]

6.3 Populations for Analyses

6.3.1 Study Cohorts

The tumor types for the neoadjuvant cohort are:

(N-1): HPV positive SCCHN

(N-2): HPV negative SCCHN

(N-3): GYN (Cervical, Vaginal, Vulvar) Carcinoma

(N-4): Merkel Cell Carcinoma

The diseases or tumor types for the recurrent/metastatic monotherapy cohort are

(M-1): EBV positive related Gastric cancer,

(M-2): HPV positive SCCHN

(M-3): GYN (Cervical, Vaginal, Vulvar) Carcinoma

(M-4): Merkel Cell carcinoma

(M-5): Nasopharyngeal Carcinoma (NPC)

The diseases or tumor types for the recurrent/metastatic combination therapy cohort are

(MC-1a): HPV positive Squamous Cell cancer of the Head and Neck (SCCHN) PD-1/PD-L1 naive: combo A

(MC-2a): Cervical Carcinoma: combo A

(MC-2b): Cervical Carcinoma: combo B

(MC-exp): Squamous Cell Cancer of the Cervix: combo B expansion

(MC-3a): Anogenital HPV associated tumors (vaginal/vulvar/anal canal/penile) Carcinoma: combo A

(MC-3b): Anogenital HPV associated tumors (vaginal/vulvar/anal canal/penile) Carcinoma: combo B

(MC-4a): Merkel Cell Carcinoma: combo A

(MC-5a): Nasopharyngeal carcinoma (NPC): combo A

(MC-6c): HPV positive Squamous Cell cancer of the Head and Neck (SCCHN) Prior PD-1/PD-L1: combo C

(MC-7d): Squamous Cell cancer of the Head and Neck (SCCHN) I-O naive: combo D

6.3.2 Analysis Populations

Within each tumor type in each cohort the following populations will be defined.

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

- **Treated subjects**: All subjects who received at least one dose of nivolumab. This is the primary population for efficacy and safety analyses.
- **Response evaluable subjects**: All treated subjects who have a BOR of CR, PR, SD, Non-CR/Non-PD or PD, and target lesion(s) assessed at baseline, and one of the following: i) at least one on-study timepoint (before sub-sequent therapy) with all baseline target lesion(s) assessed; ii) clinical progression or death before any on-study tumor assesment.
- **Evaluable neoadjuvant subjects**: All treated subjects in neoadjuvant cohorts (N-1, N-2, N-3, N-4) who have available paired tissue samples at screening and Day 29.
- **Pathologic response evaluable subjects**: All treated subject in neoadjuvant cohorts who received study treatment surgery and have known pathological response based on Day 29 TN classification.
- **Outcomes research subjects**: All treated subjects who have an assessment at baseline and at least one post baseline assessment.
- **Pharmacokinetic subjects:** All treated subjects have available serum concentration data.
- **Immunogenicity subjects:** All treated subjects with baseline and at least 1 post baseline immunogenicity assessment.
- **PD-L1 tested subjects:** All subjects who had a tumor tissue sample available for assessment of PD-L1 expression at baseline.
- **Treated PD-L1 tested subjects:** All PD-L1 tested subjects who received at least one dose of study treatment.
- **PD-L1 evaluable subjects:** All treated PD-L1 tested subjects with quantifiable PD-L1 expression.

7 STATISTICAL ANALYSES

7.1 General Methods

Unless otherwise noted, the following subsections describe tabulations of discrete variables, by the frequency and proportion of subjects falling into each category. Percentages given in these tables will be rounded and, therefore, may not always sum to 100%. Continuous variables will be summarized using the mean, standard deviation, median, minimum and maximum values. If a missing category is not being presented in the data display, only those subjects with non-missing values for the parameter being assessed are included in the percentage calculation.

Time to event distribution (e.g. progression free survival, overall survival, time to response, and duration of response) will be estimated using Kaplan Meier techniques. When appropriate, the median along with the corresponding log-log transformed 95% CI will be estimated. Rates at fixed time points will be derived from the Kaplan Meier estimate and corresponding confidence intervals will be derived based on Greenwood formula[3] for variance derivation and on log-log transformation applied on the survivor function S(t) [4].

Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method[5].

All analyses will be performed separately for each tumor type upon completion of follow-up for the primary endpoint in each tumor type. Safety analyses will also be performed for each tumor type.

7.2 Study Conduct

7.2.1 Accrual

The following will be presented on the enrolled population:

- Number of subjects accrued by country and investigational site
- Number of subjects accrued by month

7.2.2 Relevant Protocol Deviations

The following programmable deviations will be considered as relevant protocol deviations. Non-programmable relevant eligibility and on-treatment protocol deviations, as well as significant (both programmable and non-programmable) eligibility and on-treatment protocol deviations will be reported through [redacted] listings.

At entrance:

- Subjects with baseline ECOG performance status > 1
- Subjects without measurable disease at baseline (only for metastatic cohort)
- Subjects with baseline tumor diagnosis of a tumor type that is not planned in the cohort that the subject was enrolled in.

On-study:

- Subjects receiving anti-cancer therapy (chemotherapy, hormonal therapy, immunotherapy, standard or investigational agents for treatment of cancer) while on study therapy.

A summary table will be produced separately for each tumor type in all treated subjects. A by subject listing will be produced.

7.3 Study Population

7.3.1 Subject Disposition

The total number of subjects enrolled (treated or not) will be presented along with the reason for not being treated. This analysis will be performed on all enrolled population only.

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

A subject list for all treated subjects will be provided showing the subject's enrollment date, first and last dosing date, off study date and reason for going off-study.

7.3.2 Demographics and Baseline Characteristics

Descriptive statistics will be summarized the following baseline characteristics for all treated subjects. All baseline presentations will identify subjects with missing measurements. In

tabulations of categorical variables, percentages are based on subjects with measurements. Listings will also be provided.

- Age group 1 (descriptive statistics); Age categories (< 65, ≥ 65 and < 75, ≥ 75)
- Age group 2 (descriptive statistics): Age categories (18-64, 65-84, >= 85)
- Weight (descriptive statistics)
- Gender (Male, Female)
- Race (White, Black, Asian, and Other)
- Region (US/Canada, Europe, Rest of the World)
- ECOG PS (0/1)
- Time from initial disease diagnosis to treatment (< 1 year, 1 - < 2 year, 2 - < 3 year, 3 - < 4 year, 4 - < 5 year, ≥ 5 year)
- Time from initial disease diagnosis to study entry (<=1 year, >1 year)
- All lesions (Investigator Tumor Assessments at Baseline): sites of diseases, number of disease sites per subject
- Target Lesions (Investigator Tumor Assessments at Baseline): Presence of target lesions, site of target lesion, sum of diameters of target lesions.
- Virus status (Positive / Negative) in tumor types **(M-3)** GYN (Cervical, vaginal, and vulva) Carcinoma, **(MC-2a, MC-2b, MC-exp)** Cervical Carcinoma, **(MC-3a, MC-3b)** anogenital HPV associated tumors (vaginal/vulvar/anal canal/penile), **(M-4, MC-4a)** Merkel Cell Carcinoma and **(M-5, MC-5a)** Nasopharyngeal Carcinoma (NPC), SCCHN **(MC-7d),** for which the virus status are tested retrospectively.
- Smoking status (never, current, former, unknown) for SCCHN cohorts **N-1, N-2, M-2, M5, MC-1a, MC-5a, MC-6c, MC-7d**
- Disease location for SCCHN subjects (oral cavity, hypopharynx, oropharynx, larynx, other)
- Disease location for MCC subjects (primary only, lymph nodes only, primary and lymph nodes, visceral)

7.3.3 Medical History

General medical history will be listed by subject.

7.3.4 Prior Therapy

The following will be summarized by tumor type for all treated population:

- Prior therapy (1, 2, 3, ≥ 4)
- Best response to most recent prior regimen (CR/PR vs. SD vs. PD)
- Prior metastatic therapy (yes/no)
- Prior neo-adjuvant therapy (yes/no)
- Prior adjuvant therapy (yes/no)
- Number of prior systemic cancer therapy in metastatic settings (0, 1, 2)
- Time from completion of most recent prior regimen to progression (<= 3, <3 - <=6, <6 - <=12, >12 months)

- Time from completion of most recent prior regimen to study entry (<= 3, <3 - <=6, <6 - <=9, <9 - <=12, >12 months)
- Prior surgery related to cancer (yes or no)
- Prior radiotherapy (yes or no)
- Prior/current non-study medication classified by anatomic and therapeutic classes.

Medication will be reported using the generic name. A listing by subject will also be provided.

7.3.5 Baseline Examinations

Percentage of subjects with abnormal baseline physical examination will be tabulated by examination criteria and tumor type for all treated subjects.

7.4 Extent of Exposure

The extent of exposure will be characterized according to the number of subjects exposed, and the duration of exposure. Analyses in this section will be performed on all Treated Subjects for each tumor type in different cohorts.

7.4.1 Administration of Study Therapy

The following parameters will be summarized (descriptive statistics) by tumor type:

- Number (%) of treated subjects exposed for specified periods of time such as less than 1 week, 1 week to 1 month, 1 month to 6 months by treatment.
- Number of doses received (summary statistics)
- Cumulative dose
- Relative dose intensity (%) using the following categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%.
- Duration of treatment: duration of treatment will be presented using a Kaplan-Meier curve whereby the last dose date will be the event date for subjects who discontinued study therapy. Subjects who are still on study therapy will be censored on their last dose date. Median duration of treatment and associated 95% CI will be provided.
- A by-subject listing of dosing of study medication (record of study medication, infusion details and dose change) and a listing of batch number will be also provided.
- A by-subject listing of extent of exposure (weight, number of doses, date of first and last dose, cumulative dose, duration of treatment, and reason for discontinuation) will be provided.

Table 7.4.1-1: Administration of study therapy: definition of parameters

Nivolumab monotherapy

	Nivolumab
Dosing schedule per protocol	240 mg every 2 weeks
Cumulative Dose	Cum dose (mg) is sum of the doses (mg) administered to a subject during the treatment period.
Duration of treatment	Last dose date - Start dose date +1
Relative Dose Intensity (%)	Cum dose /[(Last dose date - Start dose date + 14) x 240/14] x 100

Nivolumab combined with Ipilimumab: Combo A

	Nivolumab	**Ipilimumab**
Dosing Schedule per Protocol	3 mg/kg every 2 weeks	1 mg/kg every 6 weeks
Dose	*Dose (mg/kg)* is defined as Total Dose administered (mg)/Most recent weight (kg). Dose administered in mg at each dosing date and weight are collected on the CRF	*Dose (mg/kg)* is defined as Total Dose administered (mg)/Most recent weight (kg). Dose administered in mg at each dosing date and weight are collected on the CRF
Cumulative Dose	Cum Dose (mg/kg) is the sum of the doses administered to a subject.	Cum Dose (mg/kg) is the sum of the doses administered to a subject.
Relative Dose Intensity (%)	Cum dose /[(Last dose date - Start dose date + 14) x 3/14] x 100	Cum dose /[(Last dose date - Start dose date + 42) x 1/42] x 100
Duration of Treatment	*Last dose date - Start dose date +1*	*Last dose date - Start dose date +1*

Nivolumab combined with Ipilimumab: Combo B

	Nivolumab	**Ipilimumab**
Dosing Schedule per Protocol	1 mg/kg every 3 weeks for 4 doses followed by 240 mg every 2 weeks	3 mg/kg every 3 weeks for 4 doses
Dose	*Dose (mg)* is defined as Total Dose administered (mg). Dose administered in mg at each dosing date is collected on the CRF	*Dose (mg/kg)* is defined as Total Dose administered (mg)/Most recent weight (kg). Dose administered in mg at each dosing date and weight are collected on the CRF
Cumulative Dose	Cum Dose (mg) is the sum of the doses administered to a subject.	Cum Dose (mg/kg) is the sum of the doses administered to a subject.
Cycle Duration$_{(i)}$ (wk)	(Dose date$_{(i+1)}$ - Dose date$_{(i)}$)/7	N/A

Nivolumab combined with Ipilimumab: Combo B		
	Nivolumab	**Ipilimumab**
	For the last dose N, if N<=4, cycle duration (N) (wk)=3; if N >4, cycle duration (N) (wk)=2.	
Cycle Intensity$_{(i)}$ (mg/kg/wk)	Dose$_{(i)}$/Cycle Duration$_{(i)}$	N/A
Relative Cycle Intensity $_{(i)}$ (%)	(Cycle Intensity$_{(i)}$/intended dose per week) * 100	N/A
Relative Dose Intensity (%)	Sum of all Relative Cycle Intensities divided by N	Cum dose /[(Last dose date - Start dose date + 21) x 3/21] x 100
Duration of Treatment	*Last dose date - Start dose date +1*	*Last dose date - Start dose date +1*

Volume infused, volume prepared, and weight are collected on the CRF. Nominal nivolumab dose collected in IVRS.

i = 1, 2,...,N, where N = number of infusions. Cycle Duration $_{(N)}$ = 3 weeks for nominal 1 mg/kg nivolumab doses for first 4 doses and 2 weeks for nominal 240 mg after 4th dose. Intended dose per week is xx mg (0.33 mg/kg times subject's weight in kg) for nominal 1 mg/kg nivolumab doses in the first 4 doses and 120 mg for nominal 240 mg nivolumab doses after 4th dose.

Nivolumab combined with BMS-986016: Combo C		
	Nivolumab	**BMS-986016**
Dosing Schedule per Protocol	240 mg every 2 weeks	80 mg every 2 weeks
Dose	*Dose (mg)* is defined as Total Dose administered (mg). Dose administered in mg at each dosing date is collected on the CRF	*Dose (mg)* is defined as Total Dose administered (mg). Dose administered in mg at each dosing date is collected on the CRF
Cumulative Dose	Cum Dose (mg) is the sum of the doses administered to a subject.	Cum Dose (mg) is the sum of the doses administered to a subject.
Relative Dose Intensity (%)	Cum dose /[(Last dose date - Start dose date + 14) x 240/14] x 100	Cum dose /[(Last dose date - Start dose date + 14) x 80/14] x 100
Duration of Treatment	*Last dose date - Start dose date +1*	*Last dose date - Start dose date +1*

Nivolumab combined with Daratumumab: Combo D		
	Nivolumab	**Daratumumab**
Dosing Schedule per Protocol	240 mg q2 weeks (starting at Week 3); 480 mg q4 weeks starting at Week 25	16 mg/kg q1 week (Weeks 1-8), q2 weeks (Weeks 9-24); q4 weeks starting at Week 25
Dose	*Dose (mg)* is defined as Total Dose administered (mg). Dose administered in mg at each dosing date is collected on the CRF	*Dose (mg/kg)* is defined as Total Dose administered (mg)/Most recent weight (kg). Dose administered in mg at each dosing date and weight are collected on the CRF

Nivolumab combined with Daratumumab: Combo D		
	Nivolumab	**Daratumumab**
Cumulative Dose	Cum Dose (mg) is the sum of the doses administered to a subject.	Cum Dose (mg/kg) is the sum of the doses administered to a subject.
Cycle Duration$_{(i)}$ (wk)	(Dose date$_{(i+1)}$ - Dose date$_{(i)}$)/7 For the last dose N, if N<=11, cycle duration (N) (wk)=2; if IN>11, cycle duration (N) (wk)=4.	(Dose date$_{(i+1)}$ - Dose date$_{(i)}$)/7 For the last dose N, if N<=8, cycle duration (N) (wk)=1; if 16>=N>8, cycle duration (N) (wk)=2; if N>16, cycle duration (N) (wk)=4.
Cycle Intensity$_{(i)}$ (mg/kg/wk)	Dose$_{(i)}$/Cycle Duration$_{(i)}$	Dose$_{(i)}$/Cycle Duration$_{(i)}$
Relative Cycle Intensity $_{(i)}$ (%)	(Cycle Intensity$_{(i)}$/intended dose per week) * 100	(Cycle Intensity$_{(i)}$/intended dose per week) * 100
Relative Dose Intensity (%)	Sum of all Relative Cycle Intensities divided by N	Sum of all Relative Cycle Intensities divided by N
Duration of Treatment	*Last dose date - Start dose date +1*	*Last dose date - Start dose date +1*

Volume infused, volume prepared, and weight are collected on the CRF. Nominal nivolumab dose collected in IVRS.

For nivolumab, i = 1, 2,...,N, where N = number of infusions. Cycle Duration $_{(N)}$ = 2 weeks for nominal 240 mg nivolumab doses for first 11 doses and 4 weeks for nominal 480 mg after 12th dose. Intended dose per week is 120 mg for nominal 240 mg or nominal 480 mg.

For Daratumumab, i = 1, 2, ..., N, where N = number of infusions. Cycle Duration (N) = 1 week for first 8 doses, 2 weeks for 9th~16th doses and 4 weeks after 17th dose for nominal 16 mg/kg daratumumab doses. Intended dose per week is 16mg/kg for the first 8 doses, 8mg/kg for 9th~16th doses and 4 mg/kg after 17th dose.

7.4.2 Modifications of Study Therapy

7.4.2.1 Dose Delays

Treatment may be delayed for up to a maximum of 6 weeks from the last dose. 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) for nivolumab and ipilimumab. All studies drugs must be delayed until treatment can resume. Length of delay for study treatment is summarized in Table 7.4.2.1-1. Dose delays will be divided into following categories: 4 - < 8 days, 8 - < 15 days, 15 - < 43, ≥ 43 days. Reason for dose delay will be retrieved from CRF dosing pages.
The following parameters will be summarized by tumor type:

- Number of subjects with at least one dose delayed, number of dose delayed per subject, length of delay and reasons for dose delay

Table 7.4.2.1-1: Length of Dose Delay

Nivolumab monotherapy	
Nivolumab Dose Delay	duration of previous cycle in days - 14

Table 7.4.2.1-1: Length of Dose Delay

Nivolumab monotherapy	
Nivolumab combined with Ipilimumab: Combo A	
Nivolumab Dose Delay	duration of previous cycle in days - 14
Ipilimumab Dose Delay	duration of previous cycle in days - 42
Nivolumab combined with Ipilimumab: Combo B	
Nivolumab Dose Delay	(duration of previous cycle in days - 21) for the first 4 doses (duration of previous cycle in days - 14) starting from the 5th dose
Ipilimumab Dose Delay	(duration of previous cycle in days - 21) for the first 4 doses
Nivolumab combined with BMS-986016: Combo C	
Nivolumab Dose Delay	duration of previous cycle in days - 14
BMS-986016 Dose Delay	duration of previous cycle in days - 14
Nivolumab combined with Daratumumab: Combo D	
Nivolumab Dose Delay	(duration of previous cycle in days - 14) for the first 11 doses (duration of previous cycle in days - 28) starting from the 12th dose
Daratumumab Dose Delay	(duration of previous cycle in days - 7) for first 8 doses, (duration of previous cycle in days - 14) for 9th~16th doses, (duration of previous cycle in days - 28) after 17th doses.

7.4.2.2 Infusion Interruptions and Rate Changes

Each nivolumab, or ipilimumab infusion can be interrupted and/or the IV infusion rate can be reduced. This information will be retrieved from CRF dosing pages.

The following parameters will be summarized by cohort, tumor type and treatment:

- Number of subjects with at least one dose infusion interruption, number of infusion interruptions per subject and the reason for interruption.
- Number of subjects with at least one IV infusion rate reduction, number of IV infusion rate reduction per subject and the reason for reduction

7.4.2.3 Dose Reductions /Escalations

There will be no dose escalations or reductions of nivolumab allowed.

7.4.3 Concomitant Medications

Concomitant medications, defined as medications other than study medications which are taken at any time on-treatment (i.e., on or after the first day of study therapy and within 100 days following the last dose of study therapy), will be coded using the WHO Drug Dictionary.

The following summary tables will be provided by tumor type:

- Concomitant medications (subjects with any concomitant medication, subjects by medication class and generic term).

A by-subject listing will accompany the table.

7.5 Efficacy

Analyses from this section will be produced separately for each tumor type in different cohorts, except where otherwise indicated. In (M-3, N-3) GYN (Cervical, vaginal, and vulvar) Carcinoma, all analyses will also be conducted in two subgroups, Cervical and Vaginal/Vulvar.

7.5.1 Primary Analyses

7.5.1.1 Neoadjuvant Cohort: Rate of Surgery Delay

Rate of surgery/biopsy delay will be summarized using all treated subjects. The Clopper-Pearson method will be used to estimate the two-sided 95% confidence intervals.

Surgical summary (e.g., type of surgery, median time from last dose to surgery, reasons for surgical delay/cancellation, and any other details) will be also provided if the data are collected and available.

7.5.1.2 Metastatic Cohorts: Objective Response Rate

The ORR based on investigator assessment (Per RECIST 1.1) will be summarized. The Clopper-Pearson method will be used to estimate the two-sided 95% confidence intervals.

BOR will be summarized by response category.

To assess consistency of ORR, investigator-assessed ORR (primary analysis) will be summarized for the following subgroups by tumor type:

- Age (descriptive statistics); Age categories (< 65, ≥ 65 and < 75, ≥ 75)
- Gender (Male, Female)
- Race (White, Black, Asian, and Other)
- Region (US/Canada, Europe, Rest of the World)
- ECOG PS (0/1)
- Time from initial disease diagnosis to study entry (<= 1 year, > 1 year)
- Prior therapy (surgery, radiotherapy, and systemic cancer therapy)
- Prior lines of therapy (1, 2, 3, >=4)

- Number of prior therapy in metastatic settings (0, >=1)
- Prior platinum (yes, no) for SCCHN, GYN, cervical, anogenital HPV associated tumors
- Prior bevacizumab (yes, no) for SCCHN, GYN, cervical, anogenital HPV associated tumors
- Time from completion of most recent prior regimen to study entry (<= 3, <3 - <=6, <6 - <=9, <9 - <=12, >12 months)
- All lesions (Investigator tumor assessments at Baseline): sites of diseases, number of disease sites per subject
- Target Lesions (Investigator tumor assessments at Baseline): presence of target lesions, site of target lesion, sum of diameters of target lesions.
- Virus status (Positive / Negative) in tumor types **(M-3)** GYN (cervical, vaginal, and vulva) Carcinoma, **(MC-2a, MC-2b, MC-exp)** Cervical Carcinoma, **(MC-3a, MC-3b)** Anogenital HPV associated tumors (vaginal/vulvar/anal canal/penile), **(M-4, MC-4a)** Merkel Cell Carcinoma and **(M-5,MC-5a)** Nasopharyngeal Carcinoma (NPC), for which the virus status are tested retrospectively.

7.5.2 Secondary Analyses (Metastatic Cohorts Only)

7.5.2.1 Duration of Response Based on Investigator Assessment

DOR will be summarized for subjects who achieve confirmed PR or CR using the Kaplan-Meier product-limit method. Median values of DOR, along with two-sided 95% CI using the log-log transformation will also be calculated by cohort. In addition, the percentage of responders still in response at different time points (3, 6, and 12 months) will be presented based on the KM plot.

7.5.2.2 Clinical Benefit Rate Based on Investigator Assessment

CBR based on investigator assessment (Per RECIST 1.1) will be summarized by binomial response rates and their corresponding two-sided 95% exact CIs using Clopper-Pearson method.

7.5.2.3 Overall Survival

OS curves for each tumor type will be estimated using the Kaplan-Meier (KM) product limit method. Median OS and the corresponding two-sided 95% confidence intervals using the log-log transformation will be computed. Survival rates at 3, 6, 12, 18, 24, 36, 48, and 60 months will be estimated using KM estimates on the OS curve for each tumor type. Minimum follow-up must be longer than the time point to generate the rate. Associated two-sided 95% CIs will be calculated.

7.5.2.4 Progression Free Survival

PFS curves for each tumor type will be estimated using the Kaplan-Meier (KM) product limit method. Median PFS and the corresponding two-sided 95% confidence intervals using the log-log transformation will be computed. Survival rates at 3, 6, 9, 12 months will be estimated using KM estimates on the PFS curve for each tumor type. Minimum follow-up must be longer than the time point to generate the rate. Associated two-sided 95% CIs will be calculated.

The source of progression (death vs. progression) will be summarized.

The status of subjects who are censored in the PFS Kaplan-Meier analysis will be tabulated using following categories:

- Still on-treatment
- Received subsequent anti-cancer therapy (stem cell transplant, other)
- Progression-free in follow-up
- Off-study (lost to follow-up, withdrew consent, other).

7.5.3 Exploratory Analyses

7.5.3.1 Neoadjuvant Cohort only

- The percent change from baseline of immune cells and the percent change from baseline of select immune activation/inhibitory molecules of viral-specific T cells in tumor specific subsets of treated subjects will be evaluated. Change from baseline will be summarized using descriptive statistics (n, mean, standard deviation, median, first and third quartiles, minimum, maximum).
- The following analyses will be conducted for RFS in primary analysis and sensitivity analysis. RFS curves for each tumor type will be estimated using the Kaplan-Meier (KM) product limit method. Median RFS and the corresponding two-sided 95% confidence intervals using the log-log transformation will be computed. Survival rates at 3, 6, 9, 12 months will be estimated using KM estimates on the RFS curve for each tumor type. Minimum follow-up must be longer than the time point to generate the rate. Associated two-sided 95% CIs will be calculated. Primary RFS analysis should use censoring scheme listed in Table 4.3-1. Sensitivity RFS analysis should use censoring scheme listed in Table 4.3.1-2.
- The percent change in tumor volume from baseline after two doses of neoadjuvant nivolumab will be summarized using descriptive statistics (n, mean, standard deviation, median, first and third quartiles, minimum, maximum).
- Pathological complete response (pCR) rate will be summarized using all treated subjects who received surgery by a binomial response rate. The Clopper-Pearson method will be used to estimate the two-sided 95% confidence intervals. Summary of continuous % residual viable tumor (%RVT) results will be provided descriptively if the data is available.

7.5.3.2 Metastatic Cohorts only

- Change in EBV DNA levels in subjects with EBV positive gastric cancer (monotherapy only) and nasopharyngeal carcinoma will be summarized using descriptive statistics (n, mean, standard deviation, median, first and third quartiles, minimum, maximum).

7.5.4 Interim Analyses

Under the circumstance that data of some tumor types mature faster than others or a strong signal is observed in some tumor types, interim analyses may be performed prior to the completion of

the study in order to facilitate program decisions and to support presentations or publication. These interim analyses will not impact the study duration and the trial will continue as planned.

7.6 Safety

For all safety related analyses, refer to the Core Safety SAP[6]. Safety will be summarized for: all treated, by tumor type; all dose escalation subjects, by tumor type.

7.6.1 Deaths

See Core Safety SAP.

7.6.2 Serious Adverse Events

See Core Safety SAP.

7.6.3 Adverse Events Leading to Discontinuation of Study Therapy

See Core Safety SAP.

7.6.4 Adverse Events Leading to Dose Delay of Study Therapy

See Core Safety SAP.

7.6.5 Adverse Events

See Core Safety SAP.

7.6.6 Select Adverse Events

See Core Safety SAP.

7.6.7 Immune Modulating Medication

See Core Safety SAP.

7.6.8 Multiple Events

See Core Safety SAP.

7.6.9 Clinical Laboratory Evaluations

7.6.9.1 Hematology

See Core Safety SAP.

7.6.9.2 Serum Chemistry

See Core Safety SAP.

7.6.10 Immunogenicity

Immunogenicity data generated from this study may be combined with data from other studies to further explore the incidence of immunogenicity following administration of nivolumab as monotherapy or in combination with ipilimumab, relatlimab or daratumumab. Selected serum samples may be analyzed by an exploratory method that measures anti-nivolumab, anti-ipilimumab, anti-BMS-986016 (relatlimab), or anti-daratumumab antibodies. Please also see section 7.8. These analyses, if conducted, will be reported separately. Immunogenicity will be

reported for anti-drug antibody (ADA) positive status (such as persistent positive, neutralizing positive, only last sample positive, baseline positive and other positive) and ADA negative status, relative to baseline, by cohort and treatment, if applicable. Further details on immunogenicity background and rationale, definitions, population for analyses and endpoints are described in Core Safety SAP.

7.6.11 Vital Signs and Pulse Oximetry

See Core Safety SAP.

7.7 Pregnancy

See Core Safety SAP.

7.8 Pharmacokinetics

The nivolumab, ipilimumab, relatlimab, or daratumumab concentration data obtained in this study may be combined with data from other studies in the clinical development program to develop a population PK model. This model may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of respective drug. Immunogenicity data generated from this study may also be added as one of the covariates of the model. In addition, exposure-response analyses with selected efficacy and safety endpoints may be conducted. Results of population PK and exposure response-analyses, if conducted using the concentration data (for nivolumab, ipilimumab, relatlimab, or daratumumab) from this study, will be reported separately.

7.9 Biomarkers

Analyses for PD-L1 and virus status are described below. Methodology for biomarkers other than PD-L1 and virus status will be detailed in a separate biomarker SAP.

7.9.1 PD-L1 Expression at baseline subgroups

The following PD-L1 expression subgroups will be considered by tumor type.

For TPS:

- Each baseline quantifiable PD-L1 expression status subgroup:
  - PD-L1 ≥ X%
  - PD-L1 < X%
  - Where X% is predefined as 1% and 5% if not otherwise specified.
- Baseline PD-L1 expression not evaluable or indeterminate subgroup.
- Baseline PD-L1 expression not reported.

For CPS:

- Each baseline quantifiable CPS status subgroup:
  - CPS ≥ X
  - CPS < X
  - Where X is predefined as 1 and 10 if not otherwise specified.
- Baseline CPS not evaluable or indeterminate subgroup.

- Baseline CPS not reported.

7.9.1.1 Analysis Methods

Analyses of PD-L1 will include:

- Examine the distribution of TPS and CPS
- Assess potential associations between TPS or CPS and efficacy measures

7.9.1.2 Distribution of PD-L1 Expression

Descriptive statistics of PD-L1 expression and PD-L1 status (for both TPS and CPS) will include:

- Listing of all PD-L1 IHC data using all PD-L1 tested subjects.
- Summary of tumor specimen acquisition and characteristics using all treated and PD-L1 tested subjects.
- Summary statistics of PD-L1 expression by tumor type using all treated and PD-L1 tested subjects.
- Waterfall plot of PD-L1 expression at baseline by tumor type using all treated and PD-L1 tested subjects.
- Frequency of PD-L1 expression status by tumor type using all treated and PD-L1 tested subjects, including indeterminate and not evaluable if over 5% of subjects in the population fall in this category.

7.9.1.3 Association Between PD-L1 Expression and Efficacy Measures

Analyses will be performed using all treated and PD-L1 tested subjects, if not otherwise specified, for the followings:

- BOR, PFS, OS, DOR and pCR will be summarized using frequency and percentage for each tumor type, by baseline PD-L1 status (both TPS and CPS). Objective response rate and pathologic complete response rate, with exact 95% CIs will be computed using the Clopper-Pearson method.
- Box plots of PD-L1 expression versus response status will be generated for each tumor type using all PD-L1 evaluable subjects.
- Waterfall plot of best reduction from baseline target lesion will be generated for each tumor type by PD-L1 status (both TPS and CPS) at baseline using all PD-L1 evaluable subjects.

7.9.2 Virus Status

- The following virus status subgroups will be considered by tumor type for cohorts (N-3) GYN (Cervical, vaginal, and vulva) Carcinoma, (N-4) Merkel Cell Carcinoma, **(M-3)** GYN (Cervical, vaginal, and vulva) Carcinoma, **(MC-2a, MC-2b, MC-exp)** Cervical Carcinoma, **(MC-3a, MC-3b)** anogenital HPV associated tumors (vaginal/vulvar/anal canal/penile), **(M-4, MC-4a)** Merkel Cell Carcinoma and **(M-5,MC-5a)** Nasopharyngeal Carcinoma (NPC), for which the virus status are tested retrospectively. .
- Virus status tested
  - Virus positive

  - Virus negative
- Virus status not tested

7.9.2.1 Association Between Virus Status and Efficacy Measures

- BOR, PFS, OS, DOR and pCR will be summarized using frequency and percentage for each tumor type, by virus status. Objective response rate and pathologic complete response rate, with exact 95% CIs will be computed using the Clopper-Pearson method.
- Waterfall plot of best reduction from baseline target lesion will be generated for each tumor type by virus status.

7.10 Outcome Research Analyses

7.10.1 EORTC-QLQ-C30

Unless otherwise specified, the analysis of EORTC QLQ C-30 will be performed in all treated subjects who have an assessment at baseline and at least one subsequent assessment. Analyses will be performed by tumor type.

Baseline measures will be summarized using descriptive statistics (n, mean, standard deviation, 95% confidence intervals, median, first and third quartiles, minimum, maximum) for each scale, based on subjects with a baseline measurement.

Change from baseline will be summarized using descriptive statistics (n, mean, standard deviation, 95% confidence intervals, median, first and third quartiles, minimum, maximum) for each scale at each assessment time point. In addition, the percentage of subjects demonstrating a clinically meaningful deterioration (defined as a 10-point change from baseline) will be presented for each scale at each assessment timepoint. Percentages will be based on number subjects assessed at baseline and at assessment time point.

For all assessment timepoints, mean scores and mean score changes from baseline (n, mean, standard deviation, 95% confidence intervals, median, 25th and 75th percentiles, minimum, maximum) will be reported.

EORTC-QLQ-C30 questionnaire completion rate is defined as the proportion of subjects who answered the questionnaires out of number subjects assessed at assessment time point. Completion rate will be calculated and summarized for each assessment time point.

A by subject listing of QLQ-C30 with each QLQ-C30 item, functional scales, symptoms scales and global health status will be provided.

7.10.2 EuroQol EQ-5D

Unless otherwise specified, the analysis of EQ-5D[7] will be performed in all treated subjects who have an assessment at baseline and at least one subsequent assessment. Analyses will be performed by tumor type.

Subject's overall health state on a visual analog scale (EQ-VAS) and EQ-5D index using UK weighting algorithm at each assessment time point will be summarized using descriptive statistics

(n, mean, standard deviation, 95% confidence intervals, median, 25th and 75th percentiles, minimum, maximum).

Proportion of subjects reporting problems for the 5 EQ-5D dimensions at each assessment time point will be summarized by level of problem. Percentages will be based on number subjects assessed at assessment time point.

For all assessment timepoints, mean scores and mean score changes from baseline (n, mean, standard deviation, 95% confidence intervals, median, 25th and 75th percentiles, minimum, maximum) will be reported.

A by-subject listing of EQ-5D with the problem levels for each of the 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), health state (5 dimensions digits combined in a 5-digit number), EQ-5D index using UK weighting algorithm and EQ-VAS will be provided.

More results of EQ-5D-Index will be presented separately and will be described in the WWHEOR SAP.

7.11 End of Study Analyses at Study Closure

Subjects who remaining on study treatment following primary analysis will be followed for safety as defined in the protocol. The end of study analyses will be performed for the selected safety data and the duration of treatment using all enrolled subjects.

The following data will be reported:

- Subject disposition
- Duration of treatment
- Death
- Adverse events
- Serious adverse events

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[8]. Missing and partial Non-Study Medication Domain dates will be imputed using the derivation algorithm described in 4.3.3 of BMS Non-Study Medication Domain Requirements Specification[9].

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 date alive day 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 date alive day
- 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 day

For date of progression, 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.

*In cases where the date of death is present and complete, the imputed progression date will be compared to the date of death. The minimum of the imputed progression date and date of death will be considered as the date of progression.

For other partial/missing dates, the following conventions may be 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 from first diagnosis to first dosing date, duration of response, and time to response) will be calculated as follows:

Duration = (Last date - first date + 1)

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

All analyses described in this SAP will be included in the Clinical Study Report(s) except where otherwise noted. Refer to the Data Presentation Plan for mock-ups of all tables and listings.

10 REFERENCES

1 Core Safety Statistical Analysis Plan for CA209 v4, Bristol-Myers Squibb.

2 Aaronson N.K., Ahmedzai S., et al. The European Organisation for Research and Treatment of Cancer QLQ-30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst, 85: 365-376, 1993.

3 Greenwood, M. The errors of sampling of the survivorship tables, Reports on Public Health and Statistical Subjects, 33, Appendix 1, HMSO, London, 1926

4 Kalbfleisch, J. D. and Prentice, R. L. (1980), The Statistical Analysis of Failure Time Data, New York: John Wiley & Sons.

5 Clopper, CJ and Pearson, ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 26: 404-423, 1934.

6 Core Safety Statistical Analysis Plan for CA209, Bristol-Myers Squibb.

7 Dolan P. Modeling valuations for EuroQol health states. Medical Care 1997;35: 1095-1108

7 Adverse Event Domain Requirements Specification. Bristol-Myers Squibb Co. PRI. Version 2.1. April 23, 2012.

8 Non-Study Medication Domain Requirements Specification. Bristol-Myers Squibb Co. PRI. Version 2.2 April 24, 2012.