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): May 7, 2019

Protocol Number: CA209358
IND Number: 129,947
EUDRACT Number 2015-000230-29
Date: 22-Apr-2015
Revised Date: 07-May-2019

Clinical Protocol CA209358

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

Revised Protocol Number: 07

Incorporates Administrative Letter 02

[redacted]

24-hr Emergency Telephone Number

[redacted]

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to partners to which BMS has transferred obligations, eg, a Contract Research Organization (CRO).

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

DOCUMENT HISTORY

Document	Date of Issue	Summary of Changes
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.
Administrative Letter 01	05-Mar-2019	[redacted]
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 associated tumor types.
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). • 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.” In addition to the above changes, other minor changes have been made, including correction of typographical errors, and administrative updates.
Revised Protocol 04	28-Oct-2016	Incorporates Amendment 13
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 an anti-LAG3 agent (BMS-986016) 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

Document	Date of Issue	Summary of Changes
		• 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 03	16-Mar-2016	Incorporates Amendment 09 and Administrative Letter 01
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 • 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
Administrative Letter 01	18-Dec-2015	[redacted]
Revised Protocol 02	16-Oct-2015	Incorporates Amendment 07
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

Document	Date of Issue	Summary of Changes
		• 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 01	23-Jul-2015	Incorporates Amendment 03
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
Original Protocol	22-Apr-2015	Not applicable

OVERALL RATIONALE FOR REVISED PROTOCOL 07:

Based on discussion with medical team and key investigators, the newly proposed endpoint of recurrence-free survival (RFS) is more clinical meaningful and suitable than the previous endpoint of progression-free survival (PFS) in terms of reflecting the efficacy of nivolumab as neoadjuvant therapy.

During Protocol Revision 06, the inclusion/exclusion criteria sequencing was inadvertently changed from a lettering scheme to bullets. Per Protocol Revision 07, this has been corrected and the inclusion/exclusion criteria are again sequenced with letters.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Synopsis, Exploratory Objectives	Revised progression-free survival after 1 year objective to recurrence-free survival after surgery.	More clinically meaningful.
Synopsis, Exploratory Objectives	Clarified the EQ-5D to EQ-5D-3L; added "questionnaire" to each.	Clarification.
Synopsis, Exploratory Endpoints	Revised progression-free survival to recurrence-free survival.	More clinically meaningful.
Synopsis, Outcomes Research Assessments	Revised language describing the EQ-5D-3L and EORTC-QLQ-C30.	Clarification.
Synopsis, Sample Size	Deleted Table 6.	Not referenced in synopsis text.
1.3.3, Exploratory Objective(s)	Revised progression-free survival after 1 year objective to recurrence-free survival after surgery.	More clinically meaningful.
1.3.3, Exploratory Objective(s)	Clarified the EQ-5D to EQ-5D-3L; added "questionnaire" to each.	Clarification.
3.3.1, Inclusion Criteria 3.3.2, Exclusion Criteria	Reformatted lists from bullets to letters.	Reverted to original letter sequencing to align with CRFs.
5, Study Assessments and Procedures Table 5.1-3: On-Treatment Assessments Metastatic Combination Therapy Cohorts (CA209358)	Added missing footnote identifier to study drug administration for Cohorts A and B.	Footnote identifier was inadvertently missing from previous version (though footnote was in place).
5.7, Outcomes Research Assessments	Revised language describing the EQ-5D-3L and EORTC-QLQ-C30.	To bring in line with current standards.
8.3.3, Exploratory Endpoint(s)	Revised progression-free survival description to recurrence-free survival.	More clinically meaningful.
8.4.6.1, EQ-5D	Revised language.	Clarification.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
8.4.6.2, EORTC QLQ-C30	Revised language.	Clarification.
11, List of Abbreviations	Added definitions for EQ-5D-3L and EORTC-QLQ-C30.	Clarification.

SYNOPSIS

Clinical Protocol CA209358

Protocol Title: 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

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

On the basis of eligibility and tumor type (Epstein Barr Virus [EBV] positive gastric cancer, EBV positive nasopharyngeal cancer [NPC], cervical cancer, HPV positive and negative squamous cell cancer of the head and neck [SCCHN], anogenital HPV associated cancers [vaginal, vulvar, anal canal, penile], and Polyomavirus positive Merkel cell cancer [pMCC]), the study will enroll or randomize subjects into neoadjuvant treatment or recurrent/metastatic monotherapy, or assign or randomize into the recurrent/metastatic combination therapies cohorts (A, B, C or D).

Treatments for each cohort are as follows:

Neoadjuvant cohort:

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

Metastatic Monotherapy Cohorts:

- 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 240 mg IV over 30 minutes plus BMS-986016 (relatlimab) 80 mg IV over 60 minutes administered every 2 weeks for a maximum of 24 month, or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first. As of Revised Protocol 05, enrollment will be closed in Combination C.
- 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. As of Revised Protocol 05, enrollment will be closed in Combination C.

Study Phase: 1/2

Research Hypothesis (A): Nivolumab, in the neoadjuvant 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 either ipilimumab, BMS-986016 (relatlimab), 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.

Primary Objectives

- 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
  - Merkel Cell Carcinoma
  - Cervical, vaginal, or vulvar cancers
- In the metastatic cohort (nivolumab monotherapy), to evaluate the investigator-assessed objective response rate (ORR) in subjects with the following diseases:
  - Metastatic or recurrent nasopharyngeal carcinoma (NPC)
  - Metastatic or Recurrent EBV related gastric cancer
  - Metastatic or Recurrent Merkel Cell Carcinoma
  - Metastatic or Recurrent cervical, vaginal, or vulvar cancers
  - Metastatic or recurrent HPV positive cell cancer of the head and neck (SCCHN)
- In the metastatic cohort combination therapies (nivolumab combined with either ipilimumab or BMS-986016), to evaluate the investigator-assessed ORR in subjects with the following diseases:
  - Metastatic or recurrent NPC
  - Metastatic or recurrent Merkel Cell Carcinoma
  - Metastatic or recurrent cervical cancer
  - Metastatic or recurrent HPV positive SCCHN (with prior exposure to anti-PD-1; anti-PD-L1 antibody or anti-CTLA-4 therapy [Combination C])
  - Other metastatic or recurrent anogenital HPV associated tumors (vulvar, vaginal, anal canal, penile)
- In the metastatic cohort combination therapy (nivolumab combined with daratumumab), to evaluate the investigator-assessed ORR in subjects with the following diseases:
  - Metastatic or recurrent HPV positive or negative or unknown SCCHN (without prior I-O therapy exposure)

Secondary Objectives

- Metastatic cohort (monotherapy and combination therapies): To evaluate the duration of response, progression-free survival and overall survival.

Exploratory Objectives

Neoadjuvant Cohort

- To determine the percent change from baseline of select 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-3L questionnaire.
- To evaluate cancer specific health related quality of life as assessed by EORTC QLQ-C30 questionnaire.
- To characterize pharmacokinetics of nivolumab and explore exposure-response relationships.
- To characterize the immunogenicity of nivolumab.

Metastatic Cohort (Monotherapy and Combination Therapies)

- 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).

Study Design: This is an open label, multi-center, phase 1/2 trial to investigate the safety and efficacy of nivolumab as a single agent or in combination with either ipilimumab, BMS-986016 (relatlimab, anti-LAG3 antibody), or daratumumab in viral positive and viral negative tumor types of the following tumor types: EBV positive gastric cancer, EBV positive NPC, cervical cancer, HPV positive and negative SCCHN, anogenital HPV associated cancers (vaginal, vulvar, anal canal, penile), and pMCC.

On the basis of eligibility and tumor type, patients will be enrolled into the neoadjuvant or recurrent/metastatic monotherapy, or assigned or randomized into the recurrent/metastatic combination therapies cohorts (A, B, C or D).

Upon approval of Revised Protocol 05, all Metastatic Combination Cohorts A, B, and D will enroll patients concurrently and enrollment will be closed for Combination Cohort C.

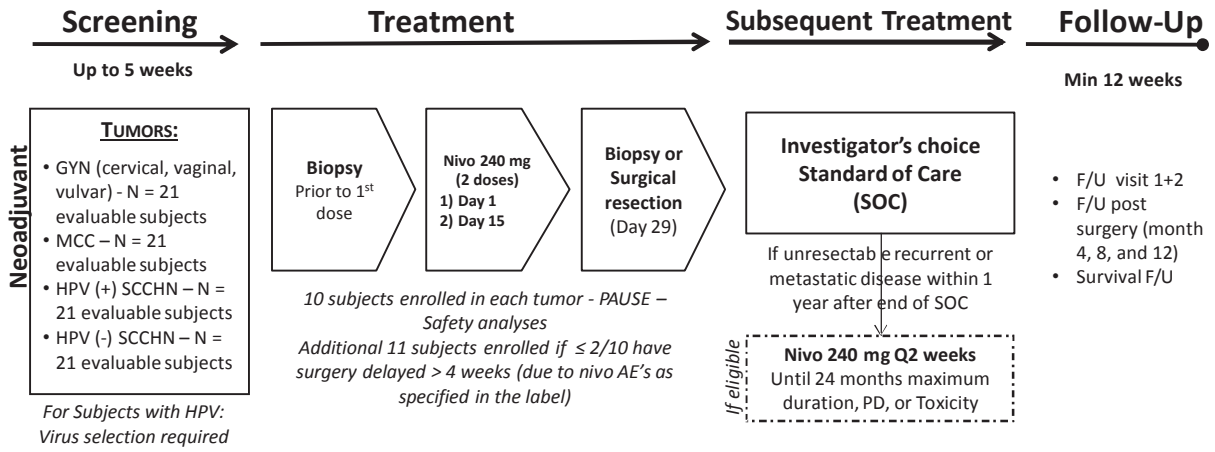
Combination B squamous cell cancer (SCC) of the cervix cohort is being expanded to add approximately 70 patients to further confirm the efficacy signal. Approximately 50 patients will be added to receive Combination B study drug as first-line treatment of their recurrent/metastatic disease if unfit or unsuitable to receive platinum-based therapy; and approximately 20 patients will be added to receive study drug as second-line treatment of their recurrent/metastatic SCC of the cervix.

Treatments for each cohort are as presented above.

Study Design Schematic for the Neoadjuvant Cohort

The tumor types for the neoadjuvant cohort and the study design schematic for the neoadjuvant cohort are presented below:

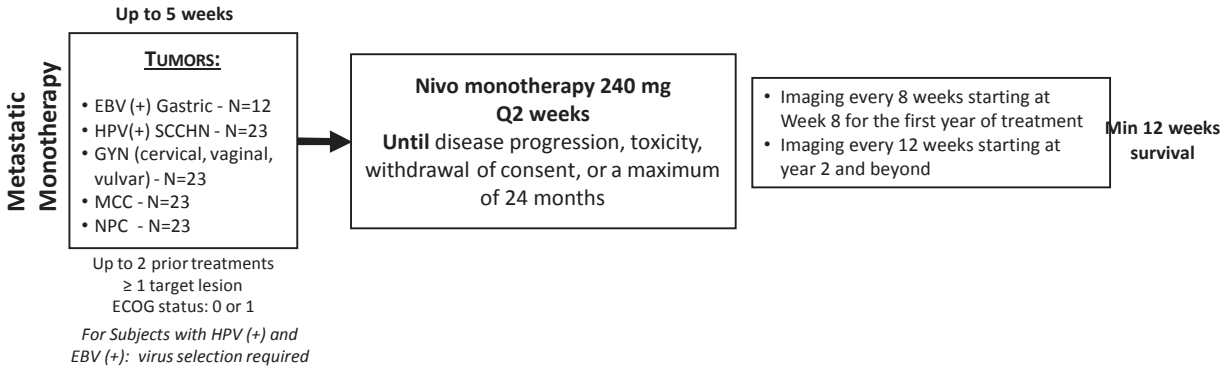
- HPV positive SCCHN and HPV negative SCCHN
- Cervical, Vaginal, Vulvar carcinoma
- Merkel Cell Carcinoma



The diseases or tumor types for the recurrent/metastatic monotherapy cohort and the study design schematic for the recurrent/metastatic monotherapy cohort are presented below:

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

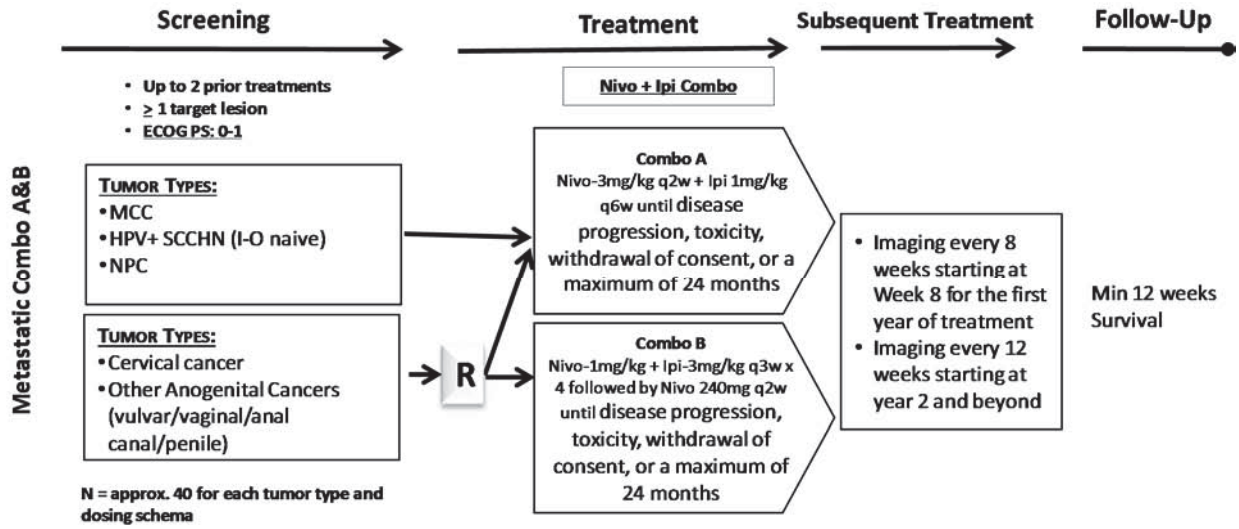
Study Design Schematic for the Metastatic Monotherapy Cohort

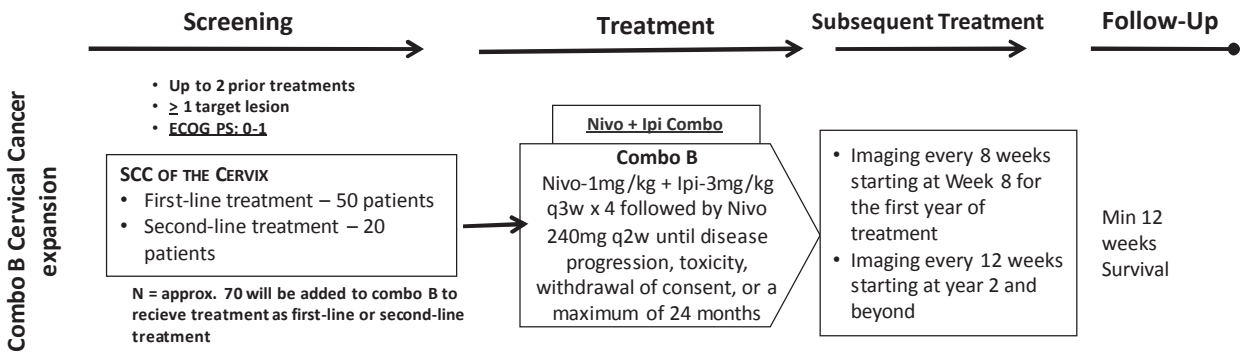


The diseases or tumor types for the recurrent/metastatic combination therapy cohorts (Combo A, B and C) and the study design schematics for the recurrent/metastatic combination therapies A, B, and C are presented below.

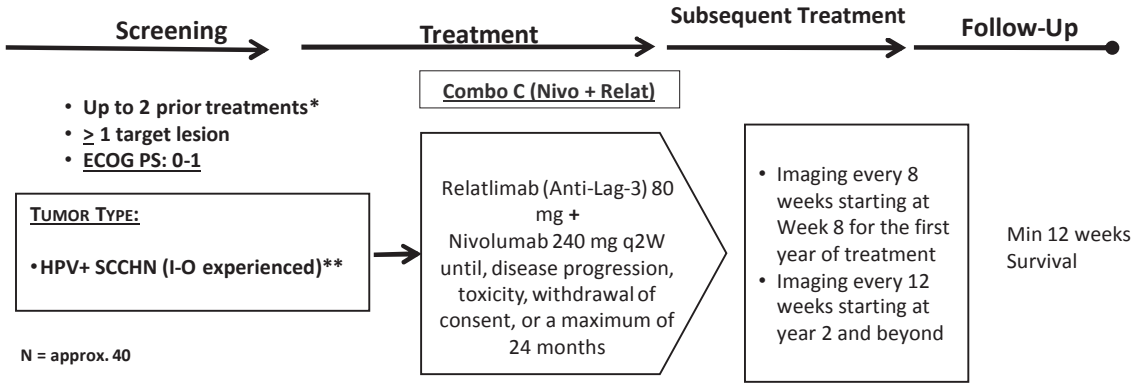
- HPV positive SCCHN
  - Immuno-Oncology naive (anti-tumor vaccine and any T cell co-stimulation or checkpoint pathways therapy) (Combo A)
  - Prior PD-1/PD-L1 experienced (Combo C)
- Cervical cancer
- Anogenital HPV associated tumors (vaginal, vulvar, anal canal, penile)
- Merkel Cell Carcinoma
- Nasopharyngeal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

Study Design Schematic for the Metastatic Cohort Combination Therapies A and B and Combo B SCC of the Cervix Expansion





Study Design Schematic for the Metastatic Cohort Combination Therapy C

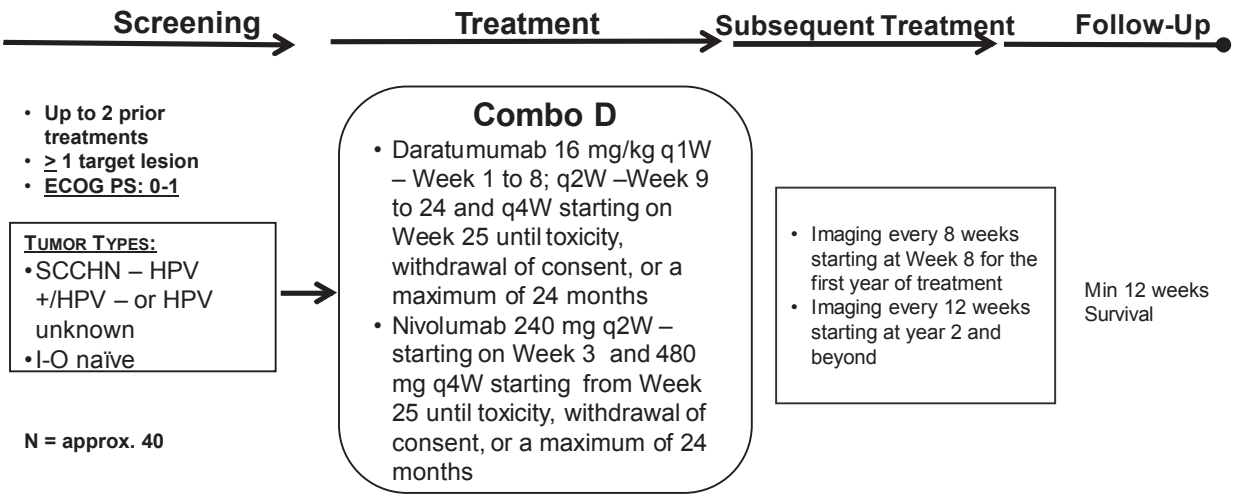


*Prior I-O therapy is permitted and is not counted toward the number of prior systemic treatment
**Include subjects that have had prior exposure to anti-PD-1, anti-PD-L1 or anti-CTLA-4 antibodies monotherapy or combination therapy

The disease or tumor type for the recurrent/metastatic combination D therapy cohort and the study design schematic for the recurrent/metastatic combination cohort for combination therapy D are presented below:

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

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



All subjects will complete 3 periods of the study: **Screening**, **Treatment**, **Follow-up**, including survival follow-up.

Duration of Study: The last visit will be defined as the latest survival visit included in the final analysis of OS (ie, the latest subject death, loss to follow up, or withdrawal of consent) for a tumor type within each cohort. Additional survival follow-up may continue for up to 5 years from the time of this analysis. The study will end once survival follow-up collection has concluded.

Study Population:

Inclusion Criteria:

a) Histopathologic confirmation of the following tumor types
   i) Merkel Cell Carcinoma
      (1). MCPyV status will be determined after enrollment
   ii) EBV-Positive Gastric or Gastro-Esophageal junction carcinoma (including adenocarcinoma arising from the lower esophagus)
      (1). For subjects in the metastatic cohorts (monotherapy only) with gastric tumor types, EBV positivity is defined by EBER in situ hybridization. Testing for EBV positivity will be performed prior to study drug assignment using the EBER1 DNP probe from Ventana in a properly certified lab. Samples interpreted as (+) if nuclear staining of any intensity above the background in tumor cells, provided the negative internal controls (adjacent normal tissue) are negative.
   iii) Nasopharyngeal Carcinoma
      (1). For subjects in the metastatic cohorts (monotherapy and combination) with nasopharyngeal carcinoma tumor types, EBV positivity is as defined by EBER in situ hybridization as specified above. Virus testing will be performed retrospectively only if results from prior accepted testing are not available.
   iv) Squamous cell carcinoma of the cervix, vagina, vulva, anal canal, and penile **(Note: anal canal and penile for metastatic combination cohorts only)**
      (1). For subjects in the neoadjuvant and metastatic (monotherapy and combination) cohorts with gynecological tumors, HPV positivity is defined by FDA approved tests (Cobas HPV Test; Digene Hybrid Capture 2 High-Risk HPV DNA Test; Cervista™ HPV HR and Genfind™ DNA Extraction Kit; Cervista™ HPV 16/18; APTIMA® HPV Assay) or other well validated commercially available tests (such as Ventana Inform HPV ISH test) comprising in situ hybridization, real-time PCR, or immunohistochemistry (IHC). High-risk HPV positivity includes the following subtypes: 16, 18,

31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. Virus testing will be performed retrospectively only if results from prior accepted testing are not available.

v) Squamous cell carcinoma of the Head and Neck

(1). For subjects in the neoadjuvant and metastatic (monotherapy and combination) cohorts HPV positivity is defined by p16INK4a (p16) IHC employing clone E6H4 form MTM (Roche). HPV p16 IHC should be interpreted as positive if > 70% strong and diffuse nuclear and cytoplasmic staining is specific to tumor cells. Testing for HPV 16 will be performed prior to study drug assignment using an appropriately validated test.

(2). HPV positive status can be obtained from either the primary tumor or metastatic lymph node.

(3). For subjects in the virus negative neoadjuvant cohort, HPV status should be documented as defined above. The p16 IHC should be interpreted as negative if < 70% strong and diffuse nuclear and cytoplasmic staining is specific to tumor cells.

b) For subjects in the neoadjuvant cohort

i) Squamous cell carcinoma of the Head and Neck for whom surgical resection is planned.

(1). Subjects must have newly diagnosed, histologically or cytologically confirmed squamous cell carcinoma or undifferentiated carcinoma of the oral cavity, pharynx and larynx. Subjects must have been determined to have resectable disease.

(2). Subjects must have tumor amenable to pre-treatment biopsy. Post-treatment biopsy will consist of the operative specimen. Excisional, incisional or core needle samples are acceptable. Fine needle aspirates are prohibited. See Section 5.6.9 for further details. The biopsy may have been obtained from the primary tumor or metastatic lymph node.

(3). Subjects must have both of the following:

a. T1 or greater primary lesions,

b. N1 or greater nodal disease,

ii) Squamous cell cervical, vulvar, or vaginal cancer

(1). Stage II to IVA cervical cancer who have planned surgical staging or chemotherapy/radiation treatment

(2). Stage II to IVA vulvar or vaginal cancer who have planned curative intent surgery or chemotherapy/radiation treatment

(3). Subjects must have tumor amenable to pre-treatment biopsy. Post-treatment biopsy will consist of the operative specimen. Excisional, incisional or core needle samples are acceptable. Fine needle aspirates are prohibited. See Section 5.6.9 for further details.

iii) Merkel Cell Carcinoma:

(1). Subjects must have tumor amenable to pre-treatment biopsy (core needle); post-treatment biopsy will consist of the operative specimen. Excisional, incisional or core needle samples are acceptable. Fine needle aspirates are prohibited. See section 5.6.9 for further details.

(2). Resectable disease of the following tumor types. Subjects must have one of the following Stages of disease

a. Stage II A-IIIB:

i. Primary tumor ≥ 2 cm, or

ii. Primary tumor of any size with palpable regional lymph node metastases or resectable in-transit metastases.

b. Stage IV disease with resectable limited metastasis

c. Local/Regional recurrent disease as defined as total burden ≥ 1 cm diameter with resectable disease defined by local or institutional surgical practices

c) For subjects in the metastatic (monotherapy and combination) cohorts

i) Progressive metastatic or recurrent disease treated with no more than 2 prior systemic therapies or regimens in the metastatic setting. (In combo C, prior I-O therapy is not included in the number of prior systemic therapies)

ii) Measurable disease by CT or MRI per RECIST 1.1 criteria (radiographic tumor assessment must be performed within 35 days prior to first dose).

iii) Subjects who actively refuse chemotherapy or other standard therapies for the treatment of unresectable or metastatic disease (advanced Stage III or Stage IV), despite being informed by the investigator about the treatment options may enroll. The subject's refusal must be thoroughly documented. The investigator will discuss each individual subject refusing chemotherapy with the sponsor's medical monitor or study director to confirm eligibility. Written approval from the sponsor's medical monitor is required for eligibility.

iv) The following tumor types

(1). Histologically confirmed Gastric or Gastro-Esophageal Junction Carcinoma (including adenocarcinoma arising from the lower esophagus) who are EBV positive, as defined above (monotherapy only).

(2). Histologically confirmed HPV positive (monotherapy and Cohorts A and C or HPV negative or unknown (Combo D only) as defined above, Squamous Cell Carcinoma of the Head and Neck (oral cavity, pharynx, larynx) not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy).

a. Histologically confirmed HPV-positive or HPV-negative or unknown subjects naive to I-O

i. Subjects cannot have had prior exposure to I-O therapies such as, but not limited to, anti-CTLA-4, anti-PD-1, combination of PD-1/CTLA-4 antibody, anti-PD-L1, anti-PD-L2, anti-KIR, anti-CD137, or anti-OX40 antibodies.

b. Histologically confirmed HPV positive subjects progressing while on or after therapy with anti-PD-1 or anti-PD-L1 as most recent therapy, defined as Squamous Cell Carcinoma of the Head and Neck (oral cavity, pharynx, larynx) not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy).**(Combo C only)**

i. Cannot have had therapy discontinued due to serious and/or life-threatening anti-PD-1 or anti-PD-L1 antibody-related toxicity (e.g., dose-limiting toxicity in prior study) per Investigator's assessment in consultation with the BMS Medical Monitor.

ii. Last dose of antibody therapy must have been received ≥ 30 days of first dose of study medication

iii. Cannot have had prior exposure to other I-Os, such as, but not limited to, anti-CTLA-4, anti-PD-L2, anti-KIR, anti-CD137, or anti OX40 antibodies.

iv. anti-PD-1/PD-L1/CTLA-4 does not need to be considered a one of the previous lines of therapy.

(3). Histologically confirmed cervical, vulvar, or vaginal cancer, as defined above. If the viral results are known prior to enrollment, and they are viral negative, the patient would be ineligible.

(4). Histologically confirmed Merkel Cell Carcinoma

a. Subjects with no prior systemic treatment will be allowed to enroll

(5). Histologically confirmed Nasopharyngeal Carcinoma, as defined above. If the viral results are known prior to enrollment, and they are viral negative, the patient would be ineligible.

a. HPV associated NPC is excluded in this cohort

b. Keratinizing squamous cell carcinoma (WHO Type I) is excluded in this cohort due to the low prevalence of EBV infection in this population.

(6). Histologically confirmed anal canal or penile carcinoma. If the viral results are known prior to enrollment, and they are viral negative, the patient would be ineligible (**Metastatic Combination Cohorts only**).

(7). Recurrent/metastatic SCC of the cervix patients not amenable to curative treatment with surgery and/or radiation therapy who are unsuitable for platinum-based therapy (ie, creatinine clearance of less than 60 mL/min or have experienced toxicity from prior platinum-based therapy) may enroll in the cervical cancer Combination B expansion cohort.

d) For both neoadjuvant and metastatic (monotherapy and combination) cohorts

i) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

ii) Men and women of age 18 or older.

iii) Subject willing to comply to provide tumor tissue for PD-L1 expression analysis and other biomarker correlative studies. Biopsy should be excisional, incisional or core needle. Fine needle aspirates are prohibited.

Exclusion Criteria:

1. Target Disease Exceptions

a) Active brain metastases or leptomeningeal metastases. **Exception:** Subjects with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for at least 4 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.

2. Medical History and Concurrent Diseases

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

b) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured or successfully resected, such as basal or squamous cell skin cancer, superficial bladder cancer, or gastric cancer, or carcinoma in situ of the prostate, cervix, or breast.

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

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

e) Subjects with primary tumor or nodal metastasis fixed to the carotid artery, skull base or cervical spine.

f) Prior therapy with experimental anti-tumor vaccines; any T cell co-stimulation or checkpoint pathways, such as anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, including ipilimumab; or other medicines specifically targeting T cell co-stimulation or checkpoint pathways is also prohibited. Exception: Combo C SCCHN prior exposure to anti PD-1/PD-L1/CTLA-4 therapy

g) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of study drug. Subjects with toxicities attributed to prior anti-cancer therapy which are not expected to resolve and result in long lasting sequelae, such as neuropathy after platinum based therapy, are permitted to enroll.

h) Treatment with any chemotherapy, radiation therapy, biologics for cancer, or investigational therapy within 28 days of first administration of study treatment (subjects with prior cytotoxic or investigational products < 4 weeks prior to treatment might be eligible after discussion between investigator and sponsor, if toxicities from the prior treatment have been resolved to Grade 1 (NCI CTCAE version 4).

i) Active neurological disease or confirmed history of encephalitis, meningitis, or uncontrolled seizures in the year prior to informed consent **for Combo C only**

j) Uncontrolled or significant cardiovascular disease including, but not limited to, any of the following (**Combo C only**):

  i) Myocardial infarction (MI) or stroke/transient ischemic attack (TIA) within the 6 months prior to consent

  ii) Uncontrolled angina within the 3 months prior to consent

  iii) Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes)

  iv) QTc prolongation > 480 msec

  v) History of other clinically significant cardiovascular disease (i.e., cardiomyopathy, congestive heart failure with New York Heart Association [NYHA] functional classification III-IV, pericarditis, significant pericardial effusion, significant coronary stent occlusion, deep venous thrombosis, etc.)

  vi) Cardiovascular disease-related requirement for daily supplemental oxygen

  vii) History of two or more MIs OR two or more coronary revascularization procedures

  viii) Subjects with history of myocarditis, regardless of etiology

k) For **Combo D** only

  i) Known history of stage 3-or 4 chronic obstructive pulmonary disease (COPD).

  ii) Known moderate or severe persistent asthma within the past 2 years, or uncontrolled asthma of any classification. Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed to participate in the study.

  iii) Screening 12-lead ECG showing a baseline QT interval as corrected (QTc) >480 msec

l) Treatment with botanical preparations (eg herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to randomization/treatment.

m) For the expansion cohort for subjects with SCC of the cervix and for patients eligible to receive study drug (Combo B) as first-line treatment for their recurrent/metastatic disease, must not have been treated previously with chemotherapy except when used concurrently with radiation therapy.

3. Physical and Laboratory Test Findings

a) Any positive test result for hepatitis B virus or hepatitis C virus indicating acute or chronic infection, and/or detectable presence of virus, e.g. Hepatitis B surface antigen (HBsAg, Australia antigen) positive, or Hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative).

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

4. Allergies and Adverse Drug Reaction

a) History of allergy to study drug components.

b) History of severe hypersensitivity reaction to any monoclonal antibody.

5. Sex and Reproductive Status

a) WOCBP who are pregnant or breastfeeding

b) Women with a positive pregnancy test at enrollment or prior to administration of study medication

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

Study Drug Dosing					
Cohort	**Drug**	**Dose**	**Frequency of administration**	**Route of administration**	**Duration**
Neoadjuvant	Nivolumab	240 mg flat dose	Day 1, Day 15[a]	30 minute Intravenous (IV) infusion	Two doses
Metastatic Monotherapy	Nivolumab	240 mg flat dose	every 2 weeks	30 minute Intravenous (IV) infusion	Maximum of 24 months or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first
Neoadjuvant Subjects Treated with Study Drug Post-Standard of Care	Nivolumab	240 mg flat dose	every 2 weeks	30 minute Intravenous (IV) infusion	Maximum of 24 months or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first
Metastatic Combination Cohort Combo A	Nivolumab	3 mg/kg	every 2weeks	30 minute Intravenous (IV) infusion	Maximum of 24 months or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first
	Ipilimumab	1 mg/kg	every 6week	30 minute Intravenous (IV) infusion	
Metastatic Combination Cohort Combo B (Cervical cancer and anogenital HPV associated tumors only)	Nivolumab	1 mg/kg 240 mg flat dose	every 3 weeks for 4 doses then every 2 weeks	30 minute Intravenous (IV) infusion	Maximum of 24 months or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first
	Ipilimumab	3 mg/kg	every 3weeks for 4 doses	30 minute Intravenous (IV) infusion	

<table>
<tr><th colspan="6">Study Drug Dosing</th></tr>
<tr><th>Cohort</th><th>Drug</th><th>Dose</th><th>Frequency of administration</th><th>Route of administration</th><th>Duration</th></tr>
<tr><td rowspan="3">Metastatic Combination Cohort
Combo C</td><td>Nivolumab</td><td>240 mg</td><td>every 2 weeks</td><td>30 minute Intravenous (IV) infusion</td><td rowspan="3">Maximum of 24 months or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first discontinuation from study</td></tr>
<tr><td rowspan="2">BMS-986016 (relatlimab)</td><td>80 mg</td><td>every 2 weeks</td><td>60 minute Intravenous (IV) infusion</td></tr>
<tr><td colspan="3"></td></tr>
<tr><td rowspan="4">Metastatic Combination Cohort
Combo D</td><td rowspan="3">Nivolumab</td><td>240 mg flat dose</td><td>Every 2 weeks starting at Week 3</td><td rowspan="3">30 minute Intravenous (IV) infusion</td><td rowspan="4">Maximum of 24 months or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first</td></tr>
<tr><td>480 mg flat dose</td><td>then every 4 weeks starting at Week 25</td></tr>
<tr><td colspan="2">Nivolumab will be administered before daratumumab when both study drugs are administered on the same day.</td></tr>
<tr><td>Daratumumab</td><td>16 mg/kg</td><td>Every week (Wks 1-8) then every 2 weeks (Wks 9-24), then every 4 weeks starting at Week 25</td><td>Intravenous (IV) infusion
See Section 4.3</td></tr>
</table>

[a] A delay of the 2nd dose of nivolumab is acceptable for up to 1 week (up to Day 22); however, the 2nd dose of nivolumab should not be administered after Day 22 in order to avoid postponing surgery/biopsy beyond Day 29 and subsequent standard of care.

Study Assessments:

Safety:

Safety assessments at baseline will include a medical history to be obtained to capture relevant underlying conditions. Baseline examinations should include signs and symptoms, weight, height, ECOG Performance Status, BP, HR, temperature, and respiratory rate should be performed within 14 days prior to first dose. Concomitant medications will also be collected from within 14 days prior to first dose and through the study treatment. Baseline safety laboratory assessments should be done within 14 days prior to the first dose.

Subjects will be evaluated for safety if they have received any study drug. Toxicity assessments will be performed continuously during the treatment phase. On-study assessments including weight, height, ECOG Performance Status, BP, HR, temperature, respiratory rate, and oxygen saturation by pulse oximetry at rest and after exertion will be performed. On-study safety laboratory assessments will also be performed.

Efficacy:

Tumor imaging assessments for ongoing study treatment decisions will be completed by the investigator using RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 criteria.

Statistical Considerations:

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 cervical, vaginal, or vulvar cancers tumor types will contain 21 evaluable subjects each. A sample size of 21 subjects 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.

2) Recurrent/metastatic monotherapy cohort:

HPV+ SCCHN, GYN, MCC and NPC tumor types in the recurrent/metastatic cohort will contain 23 subjects. Table 1 shows the probabilities of observing 0, 1 or 2 responders and ≥ 3 responders assuming 5%, 20% and 30% true response rate of ORR. Table 2 shows 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 12 subjects, due to the low prevalence. Table 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.

Table 1 Probability of Observing Responses Given True ORR for Sample Size of 23 Subjects

True response rate of 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 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 3 **Two-sided 95% Exact CI Using Clopper-Pearson Method Based on the Number of Observed Responses out of 12 Subjects**

The 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%)

3) 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 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 anti PD-1/PD-L1/CTLA-4 treatment will be enrolled in Metastatic Combination Cohort (Combo C). Combo C will contain approximately 40 subjects.

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).

Approximately 40 I-O naive HPV-negative, -indeterminate, and -positive SCCHN subjects will be enrolled to the Combo D treatment arm. 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 2-sided alpha of 5%. In addition Table 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%.

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

Table 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 Nivo 240mg q2w	Combo C Nivo+ Anti-Lag-3	Combo D Nivo+Dara
Cervical	40	110[a]		
Anogenital HPV associated tumors (vaginal/vulvar/ anal canal/penile)	40	40		

Table 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 Nivo 240mg q2w**	**Combo C Nivo+ Anti-Lag-3**	**Combo D Nivo+Dara**
MCC	40			
NPC	40			
HPV+ SCCHN (I/O naive)	40			
HPV+ SCCHN (Prior PD-1/PD-L1)			40	
I-O Naive SCCHN (HPV positive/negative/ unknown)				40

[a] Includes 40 from Combination B and 75 from Combination B expansion.

Table 5 **Two-sided 95% Exact CI Using Clopper-Pearson Method Based on the Number of Observed Responses out of 40 Subjects**

The 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)

Endpoints:

Primary Endpoints:

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.

Metastatic cohort (monotherapy and combination therapies): The 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. BOR is defined as the best response designation recorded between the date of first dose and the date of the initial objectively documented tumor progression per investigator assessment using RECIST 1.1 criteria or the date of the last tumor assessment date prior to subsequent therapy. In this study, an ORR in excess of 10% will be considered of clinical interest, and an ORR of 25% or greater will be considered of strong clinical interest.

Secondary Endpoints:

Metastatic cohort **(monotherapy and combination therapies)**:

- Duration of response (DOR) is defined as the time from first confirmed response (CR or PR) to the date of the initial objectively documented tumor progression as determined per investigator assessment using RECIST 1.1 criteria or death due to any cause, whichever occurs first. 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 prior to death and 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. DOR will only be evaluated in subjects with objective response of CR or PR
- 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 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 prior to death and 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.

Exploratory Endpoints:

Neoadjuvant cohort:

- 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.
- Recurrence-free survival (RFS), which is defined in Section 8.3.3.
- 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 cervical, vaginal, or vulvar cancer. Pathological complete response (pCR) is defined as the absence of residual viable 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.

Metastatic cohort **(monotherapy and combination therapies)**:

- 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 and nasopharyngeal carcinoma. The change in EBV DNA levels will be used to determine the effect of BMS-936558 (nivolumab).

Neoadjuvant and Metastatic cohort **(monotherapy and combination therapies)**:

- The PK samples collected will be used to determine summary measures of nivolumab, ipilimumab, BMS-986016 (relatlimab) and daratumumab exposure (see Section 8.4.4 in protocol).
- Exploratory endpoints for pharmacodynamics, outcomes research and immunogenicity are discussed in detail in Sections 5.6, 5.7, and 5.8.

Other exploratory endpoints will be discussed in details in the statistical analysis plan.

Analyses:

Analyses for primary endpoints:

Neoadjuvant cohort:

- Analyses of drug-related select AEs and drug-related SAEs are discussed in Section of safety analyses.
- Rate of surgery delay will be summarized by binomial response rates and their corresponding two-sided 95% exact CIs using Clopper-Pearson method.

Metastatic cohort (monotherapy and combination therapies):

- The investigator assessed ORR in the metastatic cohort will be summarized by binomial response rates and their corresponding two-sided 95% exact CIs using Clopper-Pearson method.

Analyses for secondary endpoints:

Metastatic cohort (monotherapy and combination therapies):

- Time to event distribution will be estimated using Kaplan Meier techniques. This will be done for PFS (based on investigator assessments) and OS. Median PFS or OS along with 95% CI will be constructed based on a log-log transformed CI for the survivor function. Rates at some fixed time points will be derived from the Kaplan Meier estimate and corresponding confidence interval will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function.
- The DOR will be summarized for all treated subjects who achieve confirmed PR or CR using the Kaplan-Meier (KM) product-limit method. Median values of DOR, along with two-sided 95% CI using Brookmeyer and Crowley method, will also be calculated.

Analyses for exploratory endpoints:

Methods for exploratory endpoints will be discussed in details in the statistical analysis plan.

Safety Analyses

Safety analyses will be performed in all treated subjects. Descriptive statistics of safety will be presented using NCI CTCAE version 4. All on-study AEs, drug-related, AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE version 4 criteria by system organ class and MedDRA preferred term. On-study lab parameters including hematology, chemistry, liver function, thyroid function, and renal function will be summarized using worst grade per NCI CTCAE version 4 criteria.

The proportion of subjects in the neoadjuvant cohort with surgery delayed > 4 weeks due to a drug-related AE will be reported for each tumor type and the Clopper-Pearson method will be used to estimate the two-sided 95% confidence interval.

Pharmacokinetic Analyses

The nivolumab, ipilimumab, BMS-986016 (relatlimab), and daratumumab concentration data obtained in this study may be combined with data from other studies in any of the clinical development programs (nivolumab, ipilimumab, BMS-986016, and daratumumab) to develop or refine a population PK model. The models may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of nivolumab or other compounds and to determine measures of individual exposure (such as steady-state peak, trough, and time-averaged concentration). In addition, model

determined exposures may be used for exposure-response analyses. If performed, results of population PK and exposure response-analyses will be reported separately.

Biomarker Analyses

The pharmacodynamic effects of nivolumab as monotherapy or in combination with ipilimumab, BMS-986016 (relatlimab) or daratumumab on selected biomarkers will be assessed by summary statistics and corresponding changes (or percent changes) from baseline tabulated by time and cohort. In addition, the time course of biomarker outcomes will be investigated graphically, by summary plots or individual subject plots. If there is an indication of a meaningful pharmacodynamic trend, methods such as linear mixed models may be used to characterize the pattern of change over time. The potential association between PD-L1 expression level (IHC) and clinical efficacy measures will be assessed using Fisher's exact test or other methodology as appropriate.

Potential associations of various biomarker measures with pharmacokinetic exposure, safety and clinical efficacy measures will be investigated based on data availability. Methods such as, but not limited to, logistic regression and graphical summaries may be used to assess these associations.

The methodology for additional exploratory biomarker analyses will be described in the statistical analysis plan.

Outcomes Research Analyses

EQ-5D

Outcomes Research Subject's overall health on the EQ-5D VAS at each assessment time point will be summarized using descriptive statistics (N, mean, standard deviation, median, first and third quartiles, 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 the number subjects with EQ-5D data at each assessment time point.

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) and EQ-5D VAS will be provided.

EORTC QLQ-C30

The analysis of EORTC QLQ-C30 data will be performed in all Outcomes Research Subjects.

For each cohort, baseline scores and post-baseline score changes for all EORTC QLQ-C30 scales will be summarized using descriptive statistics (N, mean, standard deviation, median, first and third quartiles, minimum, maximum). Baseline and change from baseline in EORTC QLQ-C30 global health status/QoL composite scale data and the remaining EORTC QLQ-C30 scale data will be summarized by time point using descriptive statistics for each cohort (N, mean, standard deviation, median, first and third quartiles, minimum, maximum). 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 time point. Percentages will be based on the number of subjects with EORTC QLQ-C30 data at each assessment time point.

Immunogenicity Analyses

Immunogenicity may 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. Effect of immunogenicity on safety, efficacy, biomarkers and PK may be explored. Additional details will be described in the statistical analysis plan.

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1 INTRODUCTION AND STUDY RATIONALE

1.1 Study Rationale

Programmed Cell Death-1 (PD-1; CD279) is a cell surface signaling molecule that delivers inhibitory signals that regulate the balance between T cell activation and tolerance by interacting with its ligands, PD-L1 (CD274; B7-H1) and PD-L2 (B7-DC/CD273). PD-1 is a 55 kD type I transmembrane protein that is a member of the CD28 family of T-cell regulatory receptors, which also includes CTLA-4, ICOS, and BTLA.[1] PD-1 is primarily expressed on activated T cells, B cells, and myeloid cells.[2] Its ligands, PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273), have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems.[3,4] PD-1 contains an intracellular membrane proximal immunoreceptor tyrosine inhibitory motif (ITIM) and a membrane distal immunoreceptor tyrosine-based switch motif (ITSM), that when phosphorylated, delivers a negative signal to the lymphocyte by the recruitment of SHP-2 to the phosphorylated tyrosine residue in the ITSM in its cytoplasmic region.[5,6]

Evidence for a negative regulatory role of PD-1 comes from studies of PD-1-deficient mice. PD-1-deficient mice develop various autoimmune phenotypes, including dilated cardiomyopathy and a lupus-like syndrome with arthritis and nephritis.[7,8,9] The emergence of these autoimmune phenotypes is dependent upon the genetic background of the mouse strain; many of these phenotypes emerge at different times and show variable penetrance. In addition to the phenotypes of null mutations, PD-1 inhibition by antibody-mediated blockade in several murine models has been found to play a role in the development of autoimmune diseases such as encephalomyelitis, graft-versus-host disease, and type I diabetes.[10,11,12] Taken together, these results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

Preclinical animal models of tumors have shown that blockade of PD-1 by monoclonal antibodies (mAbs) can enhance the anti-tumor immune response and result in tumor rejection. This suggests that host mechanisms limit the antitumor response.[13,14,15,16,17,18]

In humans, PD-L1 is constitutively expressed on macrophage-lineage cells, activated T cells, lung, vascular endothelial cells, and placental syncytiotrophoblasts.[19] Aberrant expression of PD-L1 by tumor cells has been reported in a number of human malignancies.[20,21,22,23,24,25,26] PD-L1 expressed by tumor cells has been shown to enhance apoptosis of activated tumor-specific T cells in vitro.[27] Moreover, the expression of PD-L1 may protect the tumor cells from the induction of apoptosis by effector T cells.[28] Retrospective analyses of several human tumor types suggest that tumor over-expression (as measured by immunohistochemistry) of PD-L1 may permit immune evasion by tumors. In renal cell carcinoma, high surface expression levels of PD-L1 on tumor cells are related to tumor aggressiveness. Patients with high tumor and/or lymphocyte PD-L1 levels are 4.5 times more likely to die from their cancer than patients exhibiting low levels of PD-L1 expression.[29]

Nivolumab is a fully human, IgG4 (kappa) isotype, mAb that binds to PD-1. Blockade of the PD-1 pathway by nivolumab was studied using the mixed lymphocyte reaction (MLR). PD-1 blockade resulted in a reproducible enhancement of both proliferation and IFN-γ release in the MLR.[30] The effect of nivolumab on antigen-specific recall response was investigated using a CMV-restimulation assay with human peripheral blood mononuclear cells (PBMCs) and was evaluated by ELISA. These data indicated that nivolumab, versus an isotype-matched control antibody, augmented IFN-g secretion from CMV-specific memory T cells in a dose-dependent manner.

1.1.1 Disease Background

Study CA209358 is an open label, multicenter, Phase 1/2 trial to investigate the safety and efficacy of nivolumab as a single agent or in combination with either ipilimumab, relatlimab (anti-LAG3 antibody), or daratumumab in viral positive and viral negative tumor types - Epstein Barr Virus (EBV) positive gastric cancer, EBV positive nasopharyngeal cancer (NPC), cervical cancer, HPV positive and negative squamous cell cancer (SCC) of the head and neck (SCCHN), anogenital HPV associated cancers (vaginal, vulvar, anal canal, penile), and Polyomavirus positive Merkel cell cancer (pMCC).

1.1.1.1 EBV Positive Tumors

Gastric Cancer

As of 2012, gastric cancer is the fifth most common malignancy in the world with 952,000 cases globally and is the third leading cause of cancer death with 723,000 deaths.[31] Gastric cancer often presents with advanced disease upon diagnosis (except in countries like Japan and Korea where early detection is common). In about 20-30% of cases, patients will present with resectable disease but in many of these, intraoperative discovery of lymph node metastasis is common and where curative surgery is possible, the recurrence rate after resection is high. For resectable disease, treatment options include neo and adjuvant chemotherapy with fluoropyrimidine, a platinum agent, and an anthracycline or a fluoropyrimidine in combination with radiation for adjuvant chemoradiotherapy. Despite these treatment options, the 5-year survival for Stage II-III gastric cancer remains 9-46%.[32] For patients developing advanced and metastatic disease, the reported 1-year survival is approximately 30% with a median survival of patients receiving treatment of 8 to 14 months and those receiving best supportive care alone only 3 months.[33]

Recent analyses from The Cancer Genome Atlas (TCGA) project have proposed dividing gastric cancer into four subtypes, tumors positive for Epstein–Barr virus, which display recurrent PIK3CA mutations, extreme DNA hypermethylation, and amplification of JAK2, CD274 (also known as PD-L1) and PDCD1LG2 (also known as PD-L2); microsatellite unstable tumors, which show elevated mutation rates, including mutations of genes encoding targetable oncogenic signaling proteins; genomically stable tumors, which are enriched for the diffuse histological variant and mutations of RHOA or fusions involving RHO-family GTPase-activating proteins; and tumors with chromosomal instability, which show marked aneuploidy and focal amplification of receptor tyrosine kinases.[34] TCGA classified 26 (8.8%) of the 295 gastric cancers samples evaluated as EBV positive, matching a larger meta-analysis which estimated the prevalence of EBV positive

gastric cancers, as assessed by *in situ* hybridization for EBV-encoded small RNA, at 8.7% (95% CI: 7.5, 10.0) out of 70 trials and 15,952 cases.[35] The EBV positive subtype demonstrated enriched amplifications at 9p24.1, a locus that contains JAK2, PD-L1, and PD-L2, which both bind PD-1, the target of nivolumab. Classification by molecular subtype would allow for selection of gastric subtypes that may be more likely to respond to targeted therapies compared to the WHO gastric cancer subsets of papillary, tubular, mucinous (colloid) and poorly cohesive carcinomas.[36] Clinical observations of EBV positive gastric cancer include distinct clinicopathologic characteristics, including male predominance, preferential location in the gastric cardia or postsurgical gastric stump, lymphocytic infiltration, a lower frequency of lymph node metastases, and a diffuse type of histology, as well as a more favorable prognosis.[37,38]

EBV Positive NPC

As of 2012, there were 86,691 cases of NPC with 50828 deaths.[31] Several etiologic factors have been proposed including diet, genetic factors, chromosome loss, and HPV, but EBV appears to be the primary etiologic agent.[39,40,41] The current WHO classification for NPC reflects the importance of EBV as it classifies NPC into the following histopathologic types:[42]

1) Keratinizing squamous cell carcinoma (WHO Type I): The sporadic form of nasopharyngeal carcinoma most commonly is the keratinizing subtype (WHO Type I);
2) Nonkeratinizing carcinoma which is subdivided into the differentiated (Type II) and undifferentiated (Type III) forms. The endemic form of nasopharyngeal carcinoma, found in Southeast Asia, is commonly the undifferentiated, nonkeratinizing subtype (Type III). This is strongly associated with EBV and has a more favorable prognosis than other types.
3) Basaloid squamous cell carcinoma: Basaloid squamous cell carcinoma was added to the WHO classification of head and neck tumors in 2005.

Along with T and N stage, quantification of EBV DNA levels is a prognostic factor, with higher levels having a worse prognosis. Stage I-II with low DNA (< 4000 copies/mL) have a 5 year survival rate of 91 % whereas patients with the same stage but high DNA (> 4000 copies/mL) have a 5 year survival rate of 64%; for patients with Stage III-IV the rates are 66% and 54% respectively.[43] The presence of detectable post-treatment EBV DNA, which may reflect microscopic residual tumor, appears to provide an even greater estimate of the risk of disease recurrence and death than pretreatment EBV DNA.[44,45]

Current treatment options include radiation for Stage I disease, combined chemotherapy, usually cisplatin, and radiation therapy for Stages II-IVB. The 5-year overall survival (OS) for nasopharyngeal carcinoma according to disease stage in a contemporary case series was 90%, 84%, 75%, and 58% for stage I through IV, respectively.[46] For recurrent disease, surgical resection can be an option. For non-surgical disease, chemotherapy doublets have produced response rates (between 60% and 74%) with no statistically significant differences in progression-free survival (PFS) (median 5.0 to 6.6 months) or overall survival (median 19 to 21 months and 3-year survival

rates 19 to 21.5 months).[47] For patients with recurrent or metastatic disease after one line of chemotherapy, there is no standard of care with several Phase 2 trials with single agents such as capecitabine[48], irinotecan[49], docetaxel[50], gemcitabine[51], and pemetrexed.[52]

1.1.1.2 HPV Positive Tumors

HPV Positive SCCHN

Head and neck carcinomas (HNC) are the fifth most common cancer in the world, with increasing incidence.[53,54] In 2014 in the United States, the American Cancer Society estimates 55,000 new cases are diagnosed and approximately 12,000 deaths due to this cause occur yearly.[55] HNCs describe malignancies of the upper aerodigestive tract which include squamous cell carcinomas (SCCHN) of the oral cavity, nasopharynx, pharynx and larynx. While tobacco and alcohol use are the most common risk factors for HNCs, Epstein-Barr virus and human papilloma virus (HPV) may also play a role in the development of carcinomas of the nasopharynx and squamous cell carcinomas of the oropharynx, respectively.[53,54,56,57,58,59]

A TNM-based classification is used to stage all SCCHN for treatment and outcome measures (American Joint Committee on Cancer [AJCC] Cancer Staging Manual 7th edition, 2010). At initial diagnosis, SCCHN can be of early stage (ES - 33%; Stage I/II), locally advanced (LA - 52 - 60%; stage III/IV-A/IV-B) or metastatic (met - ~ 10%; Stage IV-C). With standard of care treatment, the 5-year survival for ES is 80%, for LA it is 50% and for metastatic disease, it is 25%.[60] Approximately 50% of the treated population returns with recurrent or refractory disease. For recurrent or refractory disease, the 1-year survival rate is 5% - 33% by various estimates with a median OS of 6 to 9 months.[61,62] Metastatic and recurrent HNC that is no longer amenable to local surgical/radiation therapy causes substantial morbidity and high mortality, with a median PFS of ≤ 6 months due to the lack of effective therapeutic options.[63,64,65]

Treatment of recurrent or metastatic disease consists of cytotoxic chemotherapies such as methotrexate, organoplatinum compounds, fluorouracil (5-FU), or taxanes - either alone or in combination - and the biologic agent cetuximab. Patients whose disease progresses after platinum based therapy have a poor prognosis. In a retrospective analysis of 151 subjects with platinum-refractory recurrent metastatic SCCHN, 68 patients (45%) receiving best supportive care had a median OS of 56 days (95% CI, 46 - 67 days) whereas in 43 subjects (28%), second line chemotherapy (platinum based or methotrexate) had no ORR and median OS was 107 days (95% CI, 83 - 135 days).[66] In 2006, the US Food and Drug Administration (FDA) approved cetuximab (Erbitux®), for use as monotherapy in patients with recurrent or metastatic HNC who have progressed after platinum-based therapy based on a single-arm, multicenter clinical trial in 103 patients with recurrent or metastatic SCCHN who had documented disease progression within 30 days of a platinum-based chemotherapy regimen. The objective response rate (ORR) was 13% (95% confidence interval 7% - 21%) and the median duration of response was 5.8 months (range 1.2 - 5.8 months).[67] According to national guidelines, other single agents appropriate for this population include paclitaxel, docetaxel, and methotrexate, whose response rates range from

15 - 40%.[68,69] In a Phase 2 trial in subjects who progressed within 3 months since last platinum administration for the treatment of recurrent or metastatic HNC, the addition of docetaxel to cetuximab resulted in a partial response rate of 11% indicating that combination therapies with cetuximab in the platinum refractory setting have limited efficacy.[70] In 2011, the FDA approved cetuximab in combination with platinum-based therapy with 5-FU in patients with recurrent or metastatic HNC based on an improvement of median OS from of 10.1 months compared to 7.4 months for patients treated with platinum/5-FU alone.[67]

Despite the numerous treatment options, metastatic or recurrent HNC remains an area of high unmet medical need as patients who progress after treatment (refractory or platinum-resistant disease) have the worst prognosis with median OS of 3 - 4 months and 1 year survival rate of < 5%.[71] In conclusion, there is no effective standard of care that provides survival benefits beyond 4 - 6 months in second line platinum refractory recurrent or metastatic SCCHN.

HPV-associated head and neck cancer, largely presenting in the oropharynx has been increasing in incidence.[61,63] In the US, some two-thirds of patients with oropharynx cancer have HPV-associated tumors. In 2010 approximately 4,200 squamous cancers of the oropharynx (OPC) caused by tobacco and alcohol and 8,400 new HPV-associated oropharynx cancer will present for treatment. HPV status is an independent prognostic factor for OS and PFS among patients with squamous-cell OPC.[72] In this study, 64% of OPC patients had HPV-positive tumors, as measured in-situ hybridization for the HPV subtype 16. The presence of HPV DNA correlated well with p16 expression (kappa = 0.80; 95% CI, 0.73 to 0.87). Patients with HPV-positive tumors had significantly increased OS as well as PFS compared to patients with HPV-negative tumors. Furthermore, after adjusting for demographics, T stage, N stage, and smoking, patients with HPV-positive OPC had a 58% reduction in the risk of death and a 51% reduction in risk of progression or death. Patients with HPV-negative tumors had a 25.1% reduction in OS at 3 years (57.1% vs 82.4%) when compared to patients with HPV-positive tumors.[63] Local-regional relapse at 3 years was 21% higher in patients with HPV-negative tumors: 35.1% (95% CI: 26.4 - 43.8) versus 13.6% (95% CI: 8.9 - 18.3) for HPV-positive tumors ($p < 0.001$). These poor outcomes for HPV-negative patients occur despite the gradual trend toward increasing intensification of treatment with altered fractionation schema,[64] concurrent chemoradiation,[57,65] multi-drug induction chemotherapy,[73] and targeted molecular therapies.[58] For patients with HPV-negative tumors, altering the method of radiation delivery and the dosing and/or types of concurrent chemotherapy is not sufficient to improve oncologic outcomes.

Because HPV-associated head and neck cancers more frequently present in a younger population and seem particularly responsive to treatment with a better overall survival,[74] attention has focused on the subpopulation of > 10 pack-year smoking and N2-N3, whose prognosis is worse (60% - 70% 2 year PFS) as well as HPV-negative HNC patients, whose clinical outcome has not improved despite intensification of standard chemotherapeutic agents and combinations. Thus novel therapeutic approaches, such as immune modulation and blockade of suppressive immune cells and signals, are needed in clinical evaluation.

Cervical, Vaginal, Vulvar, Anal Canal, and Penile Cancers

In the United States, almost 4900 cases of vulvar cancer are diagnosed each year, with over 1000 of those women expected to die from the disease; for cervical cancer in the US there are 12,000 new cases of invasive cervical cancer and approximately 4000 cancer-related deaths occur each year.[56] HPV infection is associated with the development of cervical, vulvar, anal canal, and penile cancers.[75] HPV 16 and 18 are the most common subtypes for vulvar, anal canal, and penile cancers; HPV 16, 18, 33, 6 and 31 are the 5 most frequently observed HPV types for cervical cancer. Whereas cervical cancer HPV infection occurs in nearly 100% of patients[76], HPV associated squamous vulvar cancer affects younger women[77] and is a warty squamous cell compared to keratinizing or differentiated. Only 70% of cases are associated with HPV infection.[78]

Treatment for vulvar or vaginal cancer is typically surgical resection, though chemoradiotherapy is another option.[79] The 5-year survival for vulvar cancer depends on spread of disease, Local 86%, Regional 54%, and Distant 16%.[80] Treatment of recurrent disease includes surgical reexcision or resection and platinum based chemotherapy for metastatic disease. Recurrences are more likely local compared to distant (5.7%) and the 5-year survival rate was 60% for perineal recurrences, 27% for inguinal and pelvic recurrences, 15% for distant recurrences, and 14% for multiple recurrences.[81]

Treatment for cervical cancer is typically surgery for Stages IA - IIA1 and concurrent chemoradiation for Stages IB2 to IVA. The 5-year survival rate for cervical cancer depends on stage: IA 93%, IB 80%, IIA 63%, IIB58%, IIIA 35%, IIIB 32%, IVA 16%, and IVB 15%.[82] Treatment of recurrent disease is typically with surgery for resectable disease or chemotherapy plus bevacizumab, which improved ORR (48% vs 36%) and mOS (17 vs 13.3 months) compared to chemotherapy alone.[83] After first line chemotherapy, there is no standard of care that has demonstrated improved benefit over best supportive care.

Anal cancer comprises 2.5% of all digestive system malignancies in the United States; 8080 new cases are diagnosed annually, with 1080 deaths.[84] The incidence of anal cancer in the general population has increased over the last 30 years. A higher incidence has been associated with female gender, infection with human papillomavirus (HPV), lifetime number of sexual partners, genital warts, cigarette smoking, receptive anal intercourse, and infection with human immunodeficiency virus (HIV).[85]

Anal squamous cell cancer is believed to be directly linked to the presence of a complex inflammatory process most commonly caused by HPV infection (particularly with serotypes 16 and 18) in the histologically unique area of the anal squamocolumnar epithelium.[86]

United States Surveillance, Epidemiology and End Results (SEER) data reveal approximately 7000 to 8000 new anal cancer cases (64% female) and 1000 deaths recorded annually.[87] About 91% are believed to be caused by HPV. With anal cancer presentations at all stages, 5-year survival is 66.4%. Approximately 48% of patients have localized disease at presentation, and 5-year

survival in this group is 80.7%, whereas in those who present with metastatic disease, 5-year survival is 30.4%.[87]

Consensus-based guidelines from NCCN and ESMO[88] recommend cisplatin plus FU as a first-line regimen. If this regimen fails, no other regimens have been shown to be effective for metastatic disease.

Penile cancer is rare in Western countries. The American Cancer Society estimated that in 2016, 2,030 penile cancers would be diagnosed in the United States, with 340 deaths.[84] This death rate of 17% underscores the seriousness of this cancer; for comparison, only 3% of men with prostate cancer die from this disease. About 63% of cases of penile cancer are believed to be caused by HPV.

The prognosis of penile cancer is primarily related to the presence or absence of inguinal node metastasis. Untreated patients with inguinal metastases rarely survive 2 years. Of those with clinically palpable adenopathy and histologically proven metastases, 20 to 50% are alive at 5 years following inguinal lymphadenectomy. The results are even better when the extent of the nodal involvement is considered. An 82 to 88% 5-year survival rate has been reported when only 1 to 3 lymph nodes are involved.[89]

Men with a history of penile cancer are at risk for both localized recurrence and distant metastases, and up to 30% of all patients will subsequently recur.[90] Partial or total penile amputation is preferred for men with a local recurrence, whereas individualized chemotherapy treatment based on the patient's performance status and symptoms[91] is preferred for patients presenting with or who develop metastatic disease. Platinum based chemotherapies results in overall response rates of up to 30 to 38% in patients with distant metastatic penile carcinoma.[92,93,94,95] For patients who progress after their initial chemotherapy, the prognosis is poor with a median survival of less than six months.[96]

1.1.1.3 Polyomavirus Positive Merkel Cell Cancer (pMCC)

According to a review of the SEER database, there were 3,870 cases of Merkel cell carcinoma (MCC) between 1973 and 2006.[97] The review concluded that stage of disease was the best predictor of survival and the 10-year relative survival rate was higher in women than men (64.8% vs 50.5%, $p < 0.001$). For advanced disease, however, the 2-year survival rate for patients with American Joint Committee on Cancer (AJCC) stage IV disease is estimated to be 26%.[98]

Clinical observations have linked UV exposure and immune status to merkel cell carcinoma based on the observations that diagnosis occurs in the sun-exposed areas of skin in older individuals as well as in patients with immunocompromised states.[99,100,101] Another etiologic factor is Merkel Cell Polyomavirus (MCPyV) which can integrate into tumor genome prior to the clonal expansion of tumor cells.[102,103]

Treatment of resectable disease involves surgery, wide local excision, and assessment of lymph nodes by sentinel node biopsy. A retrospective analysis of 1187 cases in the SEER database

demonstrated a longer overall survival for patients who received adjuvant radiation compared to those who did not with a median survival of 63 months vs 45 months with pronounced improvement for patients with tumors lager than 2 cm (median survival 50 months vs 21 months)[104] which led to the recommendation by the NCCN to offer adjuvant radiation to all patients with resected MCC.[105] For metastatic disease, the NCCN recommends cisplatin or carboplatin with or without etoposide, topotecan, or the combination of cyclophosphamide, doxorubicin/epirubicin, and vincristine. Metastatic disease is incurable with chemotherapy and overall survival estimates for patients with metastatic disease come from single institution publications with small sample sizes, often less than 10[106,107,108], highlighting an unmet medical need.

Overall, this trial will examine the activity of nivolumab, alone or in combination with either ipilimumab, relatlimab, or daratumumab in viral positive and viral negative tumor types including: EBV positive gastric cancer, EBV positive NPC, HPV positive and negative SCCHN, HPV associated cervical cancer, anogenital HPV associated cancers (vaginal, vulvar, anal, penile, rectal) and Polyomavirus positive Merkel cell carcinoma (pMCC). These tumor types may be more likely to respond to nivolumab which blocks the interaction of PDL-1/PD-L2 and PD-1, in two settings, a neoadjuvant or window of opportunity cohort in patients with resectable disease and a cohort of patients with metastatic disease who have progressed after one line of therapy or refused standard of care.

1.1.2 Infection and Tumorigenesis

The establishment of a virus as the inducer of cellular transformation[109] by Petyon Rous in the early 20th century paved the way for modern tumor biology. Since Rous' observation, many cancers of different origins have been linked to chronic viral infections that are partly responsible for driving tumorigenesis through several mechanisms, including the disruption of tumor suppressor proteins such as p53 and Rb, activation of cellular proliferation pathways, and inhibiting the apoptotic machinery.[110] Two major classes of virus, Human Papilloma virus (HPV) and Epstein-Barr virus (EBV), are associated with ~ 670,000 oncological cases per year, worldwide.[110]

1.1.2.1 HPV

Promotion of tumorigenesis by HPV is mediated by two key viral proteins, E6 and E7, both of which target cell cycle regulation, proliferation, and apoptosis pathways that drive cells toward transformation. The viral E6 protein binds to E6-AP, an ubiquitin ligase, resulting in degradation of p53 protein.[111] In addition, E6, binds to histone acetyltransferases p300, ADA3, and CREB binding protein (CBP) preventing acetylation of p53 and inhibiting the transcription of p53-responsive genes. E6 has also been shown to inhibit apoptotic signaling by binding tumor necrosis factor (TNF)-α receptor (TNFR1), FAS-associated protein with death domain (FADD) and caspase 8, and through the degradation of pro-apoptotic BAX and BAK. Direct killing of cells through IFN is inhibited by E6 through inhibition of IRF3.[112]

The HPV protein E7 also targets a tumor suppressor, retinoblastoma (Rb), leading to its inactivation and resulting in constitutive activation of E2F-responsive genes. Further disruption of cell cycle control by E7 is achieved by inhibition of cyclin-dependent kinase inhibitors. Similar to E6, E7 results in cellular immune escape by inhibiting IFN signaling.[112]

1.1.2.2 EBV

Similar to HPV, infection of host cells with EBV may lead to their immortalization through multiple mechanisms of dysregulated cellular proliferation and apoptosis. The EBV-encoded protein EBNA-3C binds to several cell-cycle regulatory proteins, including cyclin D1, cyclin D2, cyclin D3, cyclin A, and CtBP. In addition, EBNA-3C negatively regulates cyclinB1 activity through a p53-dependent mechanism. The cumulative effects of EBNA-3C drive the infected cell into an uncontrolled proliferative state.[113] In addition, the LMP1 viral protein has transformational properties through its activation of the NF-kB pathway.[114]

1.1.2.3 Polyomavirus

Three proteins encoded by the polyomavirus, large T, middle T, and small T, have roles in inducing transformation of virally infected cells. Large T antigen binds to the tumor suppressor Rb inducing a block in apoptosis.[115] Middle T antigen induces cellular transformation in conjunction with large and small T through activation of cellular kinases, such as PI3K and PLCg.[116] Small T antigen binds to the translational repressor 4E-BP1, resulting in dysregulated cap-dependent translation through activation of eIF4e.[117]

Many viral proteins, including HPV E6, E7 and EBV and polyoma virus proteins, EBNA-1, EBNA-3A, are immunogenic proteins and T cells that recognize viral protein epitopes can be found in the circulation of infected patients.[118,119] The existence of viral-reactive T cells in cancer patients with viral-positive tumors is important, as anti-tumor immunity may be driven by these T cells, in addition to T cells that are specific to tumor-associated antigens.

The mechanisms of tolerance found in tumor-specific T cells, including expression of PD-1, have been shown to be similar to viral-specific T cells.[120] However, the ability of viral antigen-specific T cells to mediate anti-tumor immunity leading to tumor burden reduction is unknown in human tumors. The rationale for targeting virally-infected tumors is described below.

1.1.3 Rationale for Nivolumab in the Neoadjuvant Setting

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. Additional objectives are to evaluate the biological responses of the tumor microenvironment and periphery after nivolumab therapy. The surgically resected tumor will provide adequate sample to perform an in-depth analysis of the tumor and immune system. CA209-358 will provide preliminary safety and biomarker data utilizing nivolumab in the neoadjuvant setting prior to surgery.

Previous data indicate that short term doses of immune checkpoint inhibitors can be safely administered in the preoperative setting. In a 12 patient bladder cancer Phase 1 trial 6 subjects

received two doses of 3 mg/kg and 6 patients received 10 mg/kg ipilimumab monotherapy with a 3-week interval between doses prior to surgery of the urothelial tumor.[121] Surgical delay was noted in 3 patients. Of note, at the approve dose of ipilimumab (3 mg/kg), none of the subjects had a delay in surgery due to a drug-related adverse event, and preoperative ipilimumab was safe and well tolerated. Two patients at the 10 mg/kg dose had delay due to irAE (Grade 2 and 3 diarrhea). An additional patient developed Grade 3 diarrhea and delayed surgical planning, but surgery was cancelled due to disease progression.

Based on the safety/tolerability profile as described in Section 1.4.1.2, it is unlikely that subjects in the neoadjuvant cohort receiving 2 doses of nivolumab will experience a significant delay in surgery. In addition, as of 10-Mar-2015, there have been approximately 3289 subjects treated with nivolumab monotherapy in BMS sponsored clinical trials. Overall, there has been an approximate 3% frequency of any grade, drug-related serious adverse events within the first 4 weeks of treatment, with the most frequent being pneumonitis (0.33%), pyrexia (0.3%), infusion-related reaction (0.24%), and hypersensitivity reaction (0.12%). All other drug-related serious adverse events have occurred at a frequency of < 0.1%. Given the low frequency of SAEs and a manageable toxicity profile of nivolumab, BMS anticipates a favorable benefit-risk profile with short term administration of nivolumab in the neoadjuvant setting.

1.1.4 Rationale for Immunotherapy in Virus-Associated Tumors

As described above, the adaptive T cell response largely depends upon presentation of antigens by MHC in the context of an immune-stimulatory environment. Viral proteins, mutated proteins (neoantigens), and spatio-temporally dysregulated self-proteins represent targets of the T cell response that have potential to result in tumor-cell clearance. As evidence, T cell responses to viral antigens in patients with EBV+ or polyomavirus+ tumors can be identified and T cells against tumor neoantigens and self-antigens have been widely reported in the literature.[122] Further, overall survival of both gastric and Merkel cell carcinoma patients is prognostically associated with the presence of tumor infiltrating T cells, suggesting immunosurveillance of tumor growth is taking place.[123,124]

Nonetheless, endogenous immune responses do not cause all tumors to regress. One plausible explanation, which has direct therapeutic consequences, is that virus associated tumors express PD-1 ligands as an adaptive response to virus antigen-specific cytokine-secreting T cells in the tumor microenvironment. Recently published results on HPV+ SCCHN and MCC support this notion. A recent review of MCC specimens for PD-L1 expression by tumor cells and tumor infiltrating lymphocytes (TILs) found that PD-L1 expression was present in 49% and 55% of samples, respectively, and specimens with PD-L1+ tumor cells, 97% (28/29) showed a geographic association with immune infiltrates.[125] Among specimens with moderate-severe TIL intensities, 100% (29/29) showed PD-L1 expression by tumor cells, but MCPyV(-) tumor cells were uniformly PD-L1(-).

These results demonstrated that virtually all HPV+ SCCHN and a majority of MCV+ MCC are PD-L1+ and, when positive, demonstrate focal PD-L1 expression associated with areas of lymphocyte infiltration. Conversely, among 8 MCV- MCCs, none expressed PD-L1.

Taken together, these data suggest that virus associated cancers have distinct patterns of immune responses and a distinct tumor immune microenvironment.

1.1.5 Rationale and Aims for Biomarker Assessments

The biological basis of nivolumab, ipilimumab, relatlimab, and daratumumab in the treatment of oncological disease is to modulate the immune system to both generate and restore a durable anti-tumor response leading to clearance of tumor. Clinical data supports the hypothesis that inhibition of the PD-1 pathway results in rejection of tumor by the host immune system.

The precise mechanisms by which nivolumab, ipilimumab, relatlimab, and daratumumab exert their immune-modulatory and anti-tumor activities is unclear; however, particular cell types, such as effector T cells and regulatory T cells, are critical for the anti-tumor response.

Therefore, the major questions that will be addressed through the conduct of this study are:

- Are tumor and/or viral-specific T cells present at the tumor site prior to nivolumab monotherapy and in combination with ipilimumab, relatlimab, or daratumumab therapy?
- Do nivolumab monotherapy and in combination with ipilimumab, relatlimab, or daratumumab alter the frequency and activation state of tumor and/or viral-specific tumor infiltrating T cells?
- Does expression of PD-L1 or PD-L2 on tumor cells prior to therapy correlate with clinical efficacy to monotherapy and combination therapies?
- Does the mutational status of tumor cells correlate with clinical efficacy to monotherapy and combination therapies?
- Can we define distinct pharmacodynamic markers of monotherapy and combination therapies in the peripheral compartment?
- How do nivolumab monotherapy and combination with ipilimumab, relatlimab, or daratumumab alter the activating and negative costimulatory molecules on immune cells in the periphery and at the tumor site?
- Do non-responding subjects have distinct mechanisms of resistance to study drugs (such as an increase in additional negative regulatory proteins, an increase in MDSC or Treg, or loss of tumor-associated antigens in the tumor)?
- Is the intratumoral or peripheral T cell repertoire predictive of response to study drugs?
- Does the composition and phenotype of the tumor microenvironment, at baseline, or on treatment, correlate with clinical efficacy?

1.1.6 Rationale for Dose Selection for Nivolumab

Nivolumab is currently approved for the treatment of various tumors, including melanoma, adjuvant treatment of melanoma, NSCLC, RCC, classical Hodgkin Lymphoma, SCCHN, hepatocellular carcinoma, and urothelial carcinoma, using a regimen of either nivolumab 240 mg Q2W or nivolumab 3 mg/kg Q2W.

The nivolumab dose of 240 mg Q2W or 480 mg Q4W was selected for this study based on clinical data and modeling and simulation approaches using PPK and exposure-response analyses examining relationships between nivolumab exposures and efficacy and safety responses, using data from studies in multiple tumor types with body weight-normalized dosing (mg/kg). Flat dosing is expected to reduce prescription dosing errors, shorten pharmacy preparation time, and improve ease of administration. Additionally, in case of 480 mg Q4W, extending the dosing interval to 4 weeks provided numerous benefits to participants as they would have increased flexibility between clinical visits.

Using the PPK and exposure-response models, nivolumab exposures and probabilities of efficacy responses and risks of AEs were predicted following nivolumab 480 mg Q4W administration and compared to those following nivolumab 3 mg/kg Q2W administration. The overall distributions of average nivolumab steady-state exposures ($C_{av,ss}$) are comparable following administration with either nivolumab 3 mg/kg Q2W or nivolumab 480 mg Q4W over a wide range of body weights. Nivolumab 480 mg Q4W administration is predicted to result in approximately 43% greater steady-state peak concentrations ($C_{max,ss}$) compared to nivolumab 3 mg/kg Q2W. Although the $C_{max,ss}$ of nivolumab is expected to be greater following nivolumab 480 mg Q4W compared to nivolumab 3 mg/kg Q2W, the predicted $C_{max,ss}$ following nivolumab 480 mg Q4W is well below the median $C_{max,ss}$ achieved following administration of nivolumab 10 mg/kg Q2W, a safe and tolerable dose level across a wide body range (35 to 160 kg).

Exposure-safety analysis demonstrated that the exposure margins for safety are maintained following nivolumab 480 mg Q4W, and the predicted risks of AEs due to discontinuation or death, ≥ Grade 3 AEs, and ≥ Grade 2 immunotherapy-mediated AEs (IMAEs) are predicted to be similar following administration of nivolumab 480 mg Q4W relative to nivolumab 3 mg/kg Q2W across tumor types. Safety analyses using available data following nivolumab 3 mg/kg Q2W and 10 mg/kg Q2W administration indicated there were no differences in AE profiles across body-weight groups. Finally, initial clinical evidence demonstrates that, following administration of nivolumab 480 mg Q4W, nivolumab is well tolerated.

Nivolumab 480 mg Q4W is predicted to have approximately 16% lower steady-state trough concentrations ($C_{min,ss}$) compared to nivolumab 3 mg/kg Q2W. While these exposures are predicted to be lower, they are on the flat part of the exposure-response curves and are not predicted to affect efficacy. Exposure-efficacy analyses of multiple PK measures and efficacy endpoints indicated that following administration of nivolumab 480 mg Q4W, efficacy is predicted to be similar to that following administration of nivolumab 3 mg/kg Q2W across multiple tumor types. Based on these data, nivolumab 480 mg Q4W is expected to have similar efficacy and safety profiles to nivolumab 240 mgQ2W or nivolumab 3 mg/kg Q2W.

1.1.7 Rationale for Shorter Infusion Times for Nivolumab and Ipilimumab

Long infusion times place a burden on patients and treatment centers. Establishing that nivolumab and ipilimumab can be safely administered using shorter infusion times of 30 minutes duration in subjects will diminish the burden provided no change in safety profile. Previous clinical studies of nivolumab monotherapy and ipilimumab monotherapy and the combination of nivolumab and

ipilimumab have used a 60 minute infusion duration for nivolumab and 90-minute infusion duration for ipilimumab (1 - 3 mg/kg dosing for both). However, both nivolumab and ipilimumab have been administered at up to 10 mg/kg with the same infusion duration.

- Nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg safely over long treatment duration. In Study CA209010, (a Phase 2, randomized, double blinded, dose-ranging study of nivolumab in subjects with advanced/metastatic clear cell RCC) a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg and 18.5% at 10 mg/kg). All the events were Grade 1 - 2 and were manageable. An infusion duration of 30 minutes for 3 mg/kg nivolumab (30% of the dose provided at 10 mg/kg) is not expected to present any safety concerns compared to the prior experience at 10 mg/kg nivolumab dose infused over a 60-minute duration
- Similarly, ipilimumab at 10 mg/kg has been safely administered over 90 minutes. In the CA184022 study, where ipilimumab was administered up to a dose of 10 mg/kg, on-study drug related hypersensitivity events (Grade 1 - 2) were reported in 1 (1.4%) subject in the 0.3 mg/kg and in 2 (2.8%) subjects in the 10 mg/kg group. There were no drug-related hypersensitivity events reported in the 3 mg/kg group. Across the 3 treatment groups, no Grade 3 - 4 drug-related hypersensitivity events were reported and there were no reports of infusion reactions. Ipilimumab 10 mg/kg monotherapy has also been safely administered as 90 minute infusion in large phase 3 studies in prostate cancer (CA184043) and as adjuvant therapy for stage 3 melanoma (CA184029), with infusion reactions occurring in subjects. Administering 1 mg/kg of ipilimumab represents one-tenth of the 10 mg/kg dose.

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

1.1.8 Rationale for Nivolumab plus Ipilimumab Combination Therapy

Ipilimumab is a monoclonal IgG1κ that binds to the CTLA-4 antigen expressed on a subset of T cells from human and nonhuman primates. The proposed mechanism of action for ipilimumab is interference of the interaction of CTLA-4 with B7 molecules on APCs, with subsequent blockade of the inhibitory modulation of T-cell activation promoted by the CTLA 4/B7 interaction. Ipilimumab has been approved for use in over 40 countries including the United States in March 2011 and the European Union in July 2011. The safety profile is detailed in the Investigator Brochure.[126]

Immune checkpoint blockade is a rapidly advancing therapeutic approach in the field of immuno-oncology and treatment with investigational agents targeting this mechanism has induced regressions in several types of cancer. Programmed death 1 (PD-1) receptor and cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) are two important cellular targets that play

complementary roles in regulating adaptive immunity. Whereas PD-1 contributes to T-cell exhaustion in peripheral tissues, CTLA-4 inhibits at earlier points in T-cell activation.

Preclinical data indicate that the combination of PD-1 and CTLA-4 receptor blockade may improve activity. In vitro combinations of nivolumab plus ipilimumab increase IFN-γ production 2- to 7-fold over either agent alone in a mixed lymphocyte reaction. Increased antitumor activity of the combination was also observed in 3 of 5 syngeneic murine cancer models. In a murine melanoma vaccine model, blockade with either CTLA-4 or PD-1 antibodies increased the proportion of CTLA-4 and PD-1-expressing CD4/CD8 tumor infiltrating T effector cells, and dual blockade increased tumor infiltration of T effector cells and decreased intratumoral T regulatory cells, as compared to either agent alone.[14,127]

Multiple studies suggest a higher response rate and antitumor activity with the combination of nivolumab plus ipilimumab. The combination of nivolumab and ipilimumab was evaluated in CA209004 (MDX1106-04), a Phase 1b multiple ascending dose study in subjects with treatment-naive and previously treated advanced melanoma. Results showed promising activity with higher, but tolerable toxicity than ipilimumab alone.[128] Based on these data, CA209069, a phase 2 study, compared the combination to ipilimumab alone in treatment-naïve patients with advanced melanoma: nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks x4 followed by nivolumab 3 mg/kg every 2 weeks versus ipilimumab 3 mg/kg every 3 weeks x 4.[129] In patients with BRAF wild type tumors, the ORR was 61% (44/72), including 22% (16/72) complete responses (CR) in the group treated with the combination, compared to 11% (4/37) with 0 CRs in those treated with ipilimumab alone. The median PFS was not reached in the combination versus 4.4 months for ipilimumab alone (HR=0.4). Recently, a phase 3 study (CA209067, n= 945) reported significantly improved PFS and ORR with the combination of nivolumab and ipilimumab versus ipilimumab alone in previously untreated melanoma. The median progression-free survival was 6.9 months (95% confidence interval [CI], 4.3 to 9.5) in the nivolumab group, 11.5 months (95% CI, 8.9 to 16.7) in the nivolumab-plus-ipilimumab group, and 2.9 months (95% CI, 2.8 to 3.4) in the ipilimumab group. Significantly longer progression-free survival was observed in the nivolumab-plus-ipilimumab group than in the ipilimumab group (hazard ratio for death or disease progression, 0.42; 99.5% CI, 0.31 to 0.57; P<0.001) and in the nivolumab group than in the ipilimumab group (hazard ratio, 0.57; 99.5% CI, 0.43 to 0.76; P<0.001). The hazard ratio for the comparison between the nivolumab-plus-ipilimumab group and the nivolumab group was 0.74 (95% CI, 0.60 to 0.92). Deep and durable responses were observed in previously treated, extensive stage SCLC, with a response rate of 31.1% with the combination of nivolumab and ipilimumab.[130]

Given the increased efficacy observed with combination approaches in other tumor types, nivolumab plus ipilimumab may offer subjects with metastatic or recurrent cancers, who have been previously treated with up to 2 prior therapies and have no other approved treatment options, the potential for benefit.

1.1.9 Rationale to Support Dose/Schedule of Nivolumab Combined with Ipilimumab

Rationale for Combo A: nivolumab 3 mg/kg q 2weeks + ipilimumab 1 mg/kg q 6weeks

The combination of nivolumab and ipilimumab was evaluated in CA209004 (MDX1106-04), a Phase 1b multiple ascending dose study in subjects with treatment-naive and previously treated advanced melanoma. Antitumor activity was observed in 5 different combination cohorts:

- nivolumab 0.3 mg/kg and ipilimumab 3 mg/kg (Cohort 1, n = 14)
- nivolumab 1 mg/kg and ipilimumab 3 mg/kg (Cohort 2, n = 17)
- nivolumab 3 mg/kg and ipilimumab 1 mg/kg (Cohort 2a, n = 16)
- nivolumab 3 mg/kg and ipilimumab 3 mg/kg (Cohort 3, n = 6)
- nivolumab 1 mg/kg and ipilimumab 3 mg/kg (Cohort 8, n = 41)

From this study, it has been found that the 3 mg/kg nivolumab and 3 mg/kg ipilimumab combination regimen exceeded the maximum tolerated dose. Even though the drug-related discontinuation rates in combination cohorts were approximately 26 - 27%, the ORR in these cohorts were still higher compared to nivolumab monotherapy (42% - 44% versus 36%).

Additional studies have demonstrated the potential for IO combinations to improve antitumor responses across the nivolumab program.[131] An ORR of 62 - 65% has been observed in advanced melanoma (CA209067 and CA209069, N = 407) with a combination regimen of nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for 4 doses. In RCC patients (CA209016), both nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (n = 21) and nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (n = 23) showed antitumor activity with an ORR of 38% - 40%.

Activity was observed in all cohorts, with response rates greater than 30% in the 2 cohorts in which nivolumab was dosed as 3 mg/kg. Follow-up time is limited, but PFS and OS was also encouraging in the nivolumab 3 mg/kg cohorts.

In summary, nivolumab and ipilimumab combinations have shown additive or synergistic activities across the tumor types investigated. To further improve the tolerability profile, other combination dosing regimens were also explored in the nivolumab development program. Less frequent dosing of ipilimumab at 1 mg/kg q6week when given with nivolumab 3 mg/kg q2week was found to have a similar discontinuation rate to that observed in nivolumab monotherapy (11% vs 10%) in preliminary data from CA209012.

Rationale for Combo B: nivolumab 1 mg/kg + ipilimumab 3 mg/kg, q3 weeks x4, followed by nivolumab 240 mg q2 weeks

In CA209004, the 3 mg/kg nivolumab and 3 mg/kg ipilimumab cohort exceeded the maximum tolerated dose per protocol. In CA209004, while both Cohort 2 (1 mg/kg nivolumab + 3 mg/kg ipilimumab) and Cohort 2a (3 mg/kg nivolumab + 1 mg/kg ipilimumab) had similar clinical activity, a dose of 3 mg/kg of ipilimumab every 3 weeks for a total of four doses and 1 mg/kg nivolumab every 3 weeks for four doses followed by nivolumab 3 mg/kg every 2 weeks until progression was chosen. Exposure-response analysis of nivolumab monotherapy across dose

ranges of 1 mg/kg to 10 mg/kg reveals similar clinical activity while exposure-response analysis of 0.3 mg/kg, 3 mg/kg, and 10 mg/kg of ipilimumab monotherapy have demonstrated increasing activity with increase in dose in the phase 2 study CA184022. Therefore, theoretically the selection of 3 mg/kg of ipilimumab (Cohort 2) may be more clinically impactful than selection of 3 mg/kg of nivolumab (Cohort 2a). The combination arm has a similar dose and schedule as that in CA209004 for the first 12 weeks, increasing the likelihood of replicating the clinical activity seen in the CA209004 study. Based on the clinical activity in CA209004, the majority of responses to the combination of nivolumab and ipilimumab occur in the first 12 weeks. Given the uncertainty of whether the ipilimumab administered past week 12 contributes to the clinical benefit and the fact that the approved schedule for ipilimumab is every 3 weeks for a total of four doses in the FDA and EMA approved label dosing section, ipilimumab will administered every 3 weeks for a total of 4 doses. Nivolumab monotherapy treatment every two weeks until progression was studied in CA209003 and has been studied across the nivolumab monotherapy Phase 3 registrational trials. Thus starting at week 12, which is after the completion of the four doses of combined nivolumab and ipilimumab, nivolumab would continue to be administered every two weeks until progression.

Based on these data, the following two dosing schema will be evaluated in the metastatic combination treatment arms for CA209358:

- Combo A: nivolumab 3 mg/kg q 2weeks + ipilimumab 1 mg/kg q 6weeks
- Combo B: nivolumab 1 mg/kg + ipilimumab 3 mg/kg, q3 weeks x4, followed by nivolumab 240 mg q2 weeks

In view of the safety and efficacy data seen with Combo A in patients with NSCLC, Combo A will be investigated in the EBV positive NPC, cervical, vaginal, vulvar, anal canal and penile cancer, HPV positive SCCHN and polyomavirus positive MCC tumor types.

In addition, Combo B will be investigated in patients with cervical, vaginal, vulvar, anal canal, and penile cancer tumor types in order to understand the effects of the higher dose of ipilimumab in viral positive tumor types. In addition, given the limited information on the optimal dose/regimen for these cancers, two doses are being proposed.

1.1.10 Rationale for Nivolumab plus Anti-LAG-3 Antibody (relatlimab, BMS-986016) Combination Therapy

Like PD-1, lymphocyte activation gene-3 (LAG-3; CD223) is also a type I transmembrane protein that is expressed on the cell surface of activated CD4+ and CD8+ T cells and subsets of NK and dendritic cells.[132,133] LAG-3 is closely related to CD4, which is a co-receptor for T helper cell activation. Both molecules have 4 extracellular Ig-like domains and require binding to their ligand, major histocompatibility complex (MHC) class II, for their functional activity. In contrast to CD4, LAG-3 is only expressed on the cell surface of activated T cells and its cleavage from the cell surface terminates LAG-3 signaling. LAG-3 can also be found as a soluble protein but it does not bind to MHC class II and its function is unknown.

It has been reported that LAG-3 plays an important role in promoting regulatory T cell (Treg) activity and in negatively regulating T cell activation and proliferation.[134] Both natural and induced Treg express increased LAG-3, which is required for their maximal suppressive function.[135,136] Furthermore, ectopic expression of LAG-3 on CD4+ effector T cells reduced their proliferative capacity and conferred on them regulatory potential against third party T cells.[136] Recent studies have also shown that high LAG-3 expression on exhausted lymphocytic choriomeningitis virus (LCMV)-specific CD8+ T cells contributes to their unresponsive state and limits CD8+ T cell antitumor responses.[120,137] In fact, LAG-3 maintained tolerance to self and tumor antigens via direct effects on CD8+ T cells in 2 murine models.

Immune tolerance observed in the setting of tumor development and tumor recurrence, however, seems to be mediated by the co-expression of various T cell negative regulatory receptors, not solely from LAG-3. Data from chronic viral infection models,[120,136,138] knock-out mice,[139,140,141] tumor recurrence models,[142] and, to a more limited extent, human cancer patients,[142,143,144] support a model wherein T cells that are continuously exposed to antigen become progressively inactivated through a process termed "exhaustion." Exhausted T cells are characterized by the expression of T cell negative regulatory receptors, predominantly CTLA-4, PD-1, and LAG-3, whose action is to limit the cell's ability to proliferate, produce cytokines, and kill target cells and/or to increase Treg activity. However, the timing and sequence of expression of these molecules in the development and recurrence of tumors have not been fully characterized.

It is hypothesized that CTLA-4 acts as the dominant off-switch for tolerance, but it is the strong synergy between the PD-1 and LAG-3 inhibitory pathways that seems to mediate tolerance to both self and tumor antigens.[139,140,142] Whereas CTLA-4 knockout (KO) mice die prematurely from multiorgan inflammation,[145] PD-1 and LAG-3 single knockout mice present minimal immunopathologic sequelae.[140] In contrast, dual knock-out mice (LAG3-/-PD1-/-) abrogates self-tolerance with resultant autoimmune infiltrates in multiple organs and even lethality.[139,140] These dual knock-out mice also show markedly increased survival from and clearance of multiple transplantable tumors.[139]

Conversely, extensive co-expression of PD-1 and LAG-3 on tumor-infiltrating CD4+ and CD8+ T cells has been shown in distinct transplantable tumors and samples from melanoma, RCC, head and neck, NSCLC and ovarian cancer patients.[142,146,147,148,149,150,151] Blockade of PD-1/PD-L1 interactions has been successfully used to restore antitumor immunity in preclinical and clinical studies. But the simultaneous blockade of PD-1 and LAG-3 pathways on T cells may exert an even more robust antitumoral immunity in naive as well as in recurrent tumors due to the possibility of reversing LAG-3–mediated T cell exhaustion. In 2 syngeneic mice models, for example, dual anti–LAG-3/anti–PD-1 antibody therapy is able to cure most mice of established tumors that are largely resistant to single antibody treatment.[139] Furthermore, recurrent tumors from a melanoma mouse model with increased Treg cell numbers and increased expression of checkpoint inhibitors PD-1, LAG-3, TIGIT, and TIM-3, can be controlled by depletion of Tregs (via FoxP3-DTR) plus the administration of anti–PD-L1 antibody. But more importantly, tumor regression of these recurrent

tumors can also be accomplished with the combination of anti-PD-L1 plus anti-LAG-3 antibodies (C9B7W mAb) which also increases T cell activity.[142]

Given the literature supporting synergistic activity of nivolumab and anti–LAG-3 antibody in viral models, it is hypothesized that this combination could have antitumor effects in virally-related cancers, including human papilloma virus (HPV)-related tumors such as HPV+ head and neck cancer (HNC). Recent evidence has shown a role of immune inhibitory receptors (e.g., PD-1/PD-L1) in the adaptive immune resistance seen in HNCs associated with HPV. In these cancers with high lymphocytic infiltration, there is PD-1 expression on the majority of CD8+ tumor infiltrating lymphocytes (TILs) and PD-L1 expression on both tumor cells and tumor-associated macrophages.[138] In a recent analysis, 33% to 47% of head and neck tumors showed a T cell-inflamed phenotype (TCIP) similar to melanoma, based on a gene expression signature. Interestingly, 75% of HPV (+) tumors showed a TCIP compared to 23% of HPV(-) tumors. Furthermore, various checkpoint molecules were universally co-expressed in these TCIP tumors including PD1, CTLA4, LAG3, PDL-2, and IDO, as shown in gene expression analysis.[147] Altogether these data support a role for the PD-1:PD-L1 pathway in T cell exhaustion leading to both persistence of HPV infection and malignant progression in HNC patients. It is then possible that LAG-3 may also play a role in virally induced T cell exhaustion in these patients. Gastric cancer is another exploratory tumor suitable for T cell-directed therapy based on preliminary objective responses observed in patients treated with anti-PD-L1 antibody therapy.[152] In addition, LAG-3 expression ≥ 1% by immunohistochemistry has been documented in ~35% of gastric cancer samples (BMS-986016 Investigator Brochure v03. Document Control No. 930071620). A subtype of gastric cancer is also associated with Epstein-Barr virus (EBV) infection.[148] This subtype is characterized by massive lymphocyte infiltration, better prognosis than EBV-negative tumors, and worldwide distribution, particularly in Asia. So, similar to HNC, the expression of checkpoint inhibitors may be leading to the persistence of EBV infection and/or malignant progression of these tumors which could be halted by T cell-directed therapy.

These data argue strongly that dual blockade of the PD-1 and LAG-3 pathways could be a promising combinatorial strategy for viral positive tumors.

Relatlimab is a fully human antibody specific for human LAG-3 that was isolated from immunized transgenic mice expressing human immunoglobulin genes. It is expressed as an IgG4 isotype antibody that includes a stabilizing hinge mutation (S228P) for attenuated Fc receptor binding in order to reduce or eliminate the possibility of antibody- or complement-mediated target cell killing. Relatlimab binds to a defined epitope on LAG-3 with high affinity (Kd, 0.25-0.5 nM) and specificity and potently blocks the interaction of LAG-3 with its ligand, MHC class II (IC50, 0.7 nM). The antibody exhibits potent in vitro functional activity in reversing LAG-3-mediated inhibition of an antigen-specific murine T cell hybridoma overexpressing human LAG-3 (IC50, 1 nM). In addition, Relatlimab enhances activation of human T cells in superantigen stimulation assays when added alone or in combination with nivolumab (anti-PD-1 antibody).

1.1.11 Rationale to Support Dose/Schedule of Nivolumab Combined with Relatlimab

Based on the available nonclinical combination data and the preliminary clinical data from study CA224-020, a combined dosing regimen of nivolumab 240 mg Q2W and BMS-986016 80 mg Q2W (Combo C) is selected for the metastatic cohort nivolumab plus BMS-986016 combination.

Overall, the safety profile of BMS-986016 in combination with nivolumab is manageable, with no MDT reached at the tested doses up to 80 mg BMS-986016 and 240 mg nivolumab (flat dose, 2qw), and with evaluation of 240 mg BMS-986016 and 240 mg nivolumab combination dose based on clinical cut-off of 29-Jun-2016.[153] Important examples of durable tumor regressions, as well as manageable immune-mediated adverse events provide evidence of immune activation in the subjects treated up to 80 mg BMS-986016/240 mg nivolumab. The clinical findings are supported by the preliminary pharmacokinetic (PK) and receptor occupancy (RO) findings. Peripheral CD8+ T-cell RO data measured at trough monotherapy BMS-986016 treatment shows a linear increase with dose: 74% RO at 20 mg, 84% RO at 80 mg, and 94% RO at 240 mg. A preliminary PK analysis indicates that BMS-986016 exposure parameters are generally proportional across the dose range evaluated (20 to 800 mg) and were not altered by combination with nivolumab.

Taken together, the preliminary data suggest that 80 mg BMS-986016 in combination with 240 mg nivolumab is safe and well tolerated, and there will be no drug-drug interaction expected from this combination. Therefore, a combined dosing regimen of nivolumab 240 mg Q2W and BMS-986016 80 mg Q2W is recommended for investigation in this study.

Additional details are provided in the current version of the BMS-986016 IB.[154]

Relatlimab Adverse Event Management Guidelines

In order to standardize the management of IO AEs across all novel IO treatment combinations and given that nivolumab is the backbone of therapy, nivolumab AE algorithms are recommended for AE management (see Appendix 2 for Nivolumab Adverse Event Management Guidelines for details).

1.1.12 Rationale for Nivolumab plus Daratumumab Combination Therapy

The tumor microenvironment is believed to be important in determining whether a patient can make an effective immune response to his/her tumor. Tumor cells can induce an immunosuppressive microenvironment through multiple tolerogenic factors and expression of inhibitory surface receptors that create a shield around the tumor, resulting in evasion of the immune response. Two such mechanisms include (1) expression of PD-L1 in tumor or infiltrating cells, which triggers PD-1 on T cells, inhibiting T cell activation and expansion of previously activated T cells; and (2) recruitment of immunosuppressive cell types such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) into the tumor. Individual tumors may use more than one means to evade the immune system. Therefore using more than one method to unleash the immune response may show synergistic effects.

Nivolumab, which blocks the PD-1 pathway, has demonstrated single agent clinical efficacy resulting in a survival benefit in patients with metastatic melanoma, squamous and non-squamous NSCLC, advanced RCC and has an approved label in these indications. Nivolumab has also demonstrated significant response rates in other solid tumor malignancies including small-cell lung cancer, head and neck cancer, bladder cancer. The combination of nivolumab with other therapies, such as ipilimumab, has also demonstrated meaningful response rates and progression-free survival in multiple solid tumor indications and is approved for metastatic melanoma in the US.

Daratumumab is a human immunoglobulin G1 (IgG1) monoclonal antibody that targets CD38, inducing tumor cell death through multiple mechanisms, including antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity, and antibody dependent cellular phagocytosis (ADCP).[155,156] Daratumumab has shown promising anti-myeloma activity in 2 clinical studies (GEN501 and SIRIUS) in patients with relapsed and refractory MM, resulting in remarkable response rates that include stringent complete responses (sCRs) and prolonged clinical responses in heavily pretreated patients.[157,158] Based on these data, daratumumab was approved by the US Food and Drug Administration for patients with MM who have received ≥ 3 prior lines of therapy.[159] The target of daratumumab is CD38, which is highly and uniformly expressed on all malignant MM cells and expressed at relatively low levels on lymphoid or myeloid cells and in some tissues of non-hematopoietic origin.[160] CD38 is a type II transmembrane glycoprotein with ectoenzymatic activity involved in the catabolism of extracellular nucleotides.[160,161] Other functions ascribed to CD38 include receptor-mediated adhesion by interacting with CD31 or hyaluronic acid, regulation of migration, and signaling events[160,161,162] Daratumumab induces killing of MM cells and other CD38+ expressing cell types via the activation of potent cytotoxic immune effector functions, including antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC)[155,163] Another mechanism of action is induction of apoptosis upon secondary crosslinking.[164] In addition, during daratumumab therapy, an increase in CD4+ T cells and CD8+ T cells has been demonstrated. These T cells are possibly involved in a host-anti-MM immune response. This increase can be related to cross presentation of tumor antigens by antigen-presenting cells after phagocytosis of daratumumab-coated MM cells in combination with killing of CD38-positive suppressor cells such Tregs, Bregs, and myeloid-derived suppressor cells (MDSCs)[165]

In the current study, the combination of daratumumab to nivolumab is expected to deplete CD38+ immunosuppressive cells from the tumor microenvironment, thus alleviating the immunosuppression so that the nivolumab activated T cells can mount an effective immune response to the tumor. This trial will test whether simultaneous blockade of PD-1 with nivolumab and the immunoregulatory effects with daratumumab will result in enhanced anti-tumor responses in patients with solid tumors.

Following a full review of all available relevant data for daratumumab in combination with nivolumab, a safety signal that would cause a significant risk for patients was not validated based

on the absence of a pattern of severe AEs that could not be accounted for by underlying disease or prior therapy.

The cumulative efficacy data in more than 100 patients in different solid tumor cohorts does not demonstrate an efficacy signal that would warrant continuation of the combination treatment in these solid tumor trials. Therefore, additional enrollment and continued treatment in this cohort have been discontinued. At the discretion of the principal investigator, alternative treatment options will be considered and/or subject(s) may continue treatment with nivolumab monotherapy.

1.1.13 Rationale for Nivolumab Combined with Daratumumab in Patients with HPV Positive and Negative or Unknown SCCHN

Per Revised Protocol 06, enrollment and treatment in this cohort have been terminated. This study will investigate the combination of daratumumab and nivolumab in patients with HPV positive, negative, or unknown SCCHN. Nivolumab, which blocks the PD-1 pathway, has demonstrated single agent clinical efficacy in numerous tumor types. However, there are still a significant number of patients that do not respond to single-agent checkpoint inhibition possibly due to other immunosuppressive mechanisms present in the tumor microenvironment. This presence of immunosuppressive cell types such as Tregs and MDSCs in the tumor microenvironment actively dampen the anti-tumor response.

Daratumumab a human immunoglobulin G1 (IgG1) monoclonal antibody that targets CD38 has shown promising anti-myeloma activity in 2 clinical studies (GEN501 and SIRIUS) in patients with relapsed and refractory MM. Responding patients also demonstrated increased T-cell responses to viral- and alloantigens, suggesting a revival of anti-tumor immune response from an immune suppressive state.[165] The fact that CD38 is expressed on Treg and suppressive cells of myeloid lineage, plus the observed immune stimulatory activity of daratumumab in the clinic, suggest that daratumumab may exhibit immune-stimulatory activities by targeting CD38+ Treg. Data mining of TCGA data indicates that CD38 mRNA expression is present in tumor biopsies from SCCHN subjects and these biopsies have also shown to have all Treg gene based signature. This supports the hypothesis of targeting CD38+ Treg populations in SCCHN to reverse immunosuppression and up regulate anti-tumor immunity. Such immunity will be further enhanced through the combination treatment with nivolumab, by co-targeting CD38+ Treg and PD-1 immune checkpoint. This immuno-modulatory role of daratumumab for reversing the immunosuppressive tumor microenvironment has prompted a clinical evaluation of the combination of daratumumab with the immune checkpoint inhibitor, nivolumab in patient with HPV positive, negative or unknown SCCHN.

1.1.14 Rationale to Support Dose/Schedule of Nivolumab Combined with Daratumumab

Per Revised Protocol 06, enrollment and treatment in this cohort have been terminated. For the nivolumab/daratumumab combination cohort, nivolumab will be administered at 240 mg Q2W, an approved nivolumab dosing regimen for NSCLC and RCC indications. Daratumumab will be administered at 16 mg/kg QW from Week 1 to 8, Q2W from Week 9 to 24, and Q4W from Week 25 and for a maximum of 24 months, or until disease progression, unacceptable toxicity, or

withdrawal of consent, whichever comes first. As nivolumab 480 mg Q4W dosing regimen would produce similar exposures to that of 240 mg Q2W dosing regimen based on PPK modeling and simulation, nivolumab will be administered at 480 mg Q4W starting from Week 25 for the convenience to patients.

Dosing of daratumumab in subjects with multiple myeloma is recommended at 16 mg/kg (weekly for 8 weeks, then every 2 weeks for 16 weeks, then every 4 weeks thereafter) administered via IV until disease progression or unacceptable toxicity. The dose selection was based on an acceptable safety profile, maximal clinical activity, and pharmacokinetics consistent with saturation of the target. The data supporting the selection of a 16 mg/kg dose for the treatment of multiple myeloma are as follows:

- Safety: Clinical safety data demonstrated that daratumumab is well-tolerated, with clinically manageable side effects, highlighted by the fact that no subject treated with 16 mg/kg daratumumab monotherapy discontinued treatment as a result of a daratumumab related adverse event.
  - For doses above 4 mg/kg, there was no dose dependent toxicity pattern observed.
- Clinical efficacy: Clinical response data derived from Study GEN501 and Study MMY2002 show robust activity among subjects treated at 16 mg/kg with ORRs of 36% and 29%, respectively.
  - The response rates were consistently and significantly higher and deeper at the 16 mg/kg dose level as compared to various schedules at the 8 mg/kg dose level.
- Pharmacokinetics: Daratumumab exhibits target-mediated drug disposition. Daratumumab binds to CD38 receptors in the body and the complex with daratumumab is rapidly cleared. As the dose is increased or after repeated administration, CD38 becomes saturated, and the impact of target binding clearance is minimized and PK data can indicate target saturation.
  - Population pharmacokinetic and exposure-response analyses suggested that 16 mg/kg is the lowest tested dose at which the majority (approximately 80%) of subjects achieved serum concentrations above the model-predicted 99% target saturation threshold and 90% of the maximum effect on ORR threshold.
  - Lowering the dose would likely result in reduced efficacy, whereas increasing the dose may not provide further improvement of the benefit-risk profile.
  - The initial weekly dosing schedule rapidly established efficacious concentrations. The every 2 week and every 4 week dosing frequencies were sufficient to produce serum concentration levels that maintained target saturation; thus reducing the risk of disease progression.

Daratumumab is associated with high infusion-related reactions requiring treatment with steroid. In GEN501 study, a phase 1/2 study of daratumumab in relapsed/refractory MM subjects, infusion-related reactions were the most frequent adverse events, occurred in 71% of patients. The majority of these reactions included grade 1 and 2, and characterized by rhinitis, cough, headache, pyrexia, and dyspnea. Most infusion-related reactions occurred during the first daratumumab infusion and only few patients (<10%) had infusion-related reactions with more than one infusion. The SIRIUS (MMY2002) study confirmed the results from GEN501 study that demonstrated single agent

activity of daratumumab with a favorable toxicity profile.[157,158] Among one hundred six patients who had a median of 5 prior lines of therapy (95% refractory to lenalidomide and bortezomib) and received daratumumab monotherapy at a dose of 16 mg/kg, 43% of the patients experience infusion-related reactions, which were predominantly grade 1 and 2, and could be managed with interruption of the infusion or extra corticosteroids and antihistamines. Therefore, to mitigate the increased risk of infusion-related reactions for nivolumab/daratumumab combination cohort, nivolumab 240 mg Q2W administration will start with the third daratumumab infusion and corticosteroids will be administered before and after treatment.

Historically, clinical trials with nivolumab have prohibited the use of high dose steroids before and during the study due to the potential interference with the immune activation mechanism of checkpoint inhibition. Specifically, in the nivolumab registrational trials, patients requiring treatment with systemic corticosteroids (greater than 10 mg daily prednisone equivalents) within 14 days of study drug administration were excluded. However, there have been exceptions to eligibility criteria for certain subjects which have not appeared to impact the efficacy of the therapy including prophylactic high dose steroids for contrast dye allergy and non-autoimmune conditions such as delayed-type hypersensitivity reaction. Furthermore, high dose systemic corticosteroids and other immunosuppressants are commonly used to treat immune-related adverse reactions. This concomitant steroid use to manage immune related AEs does not appear to impair the efficacy of nivolumab and these conclusions have been shared with the regulatory authorities. Pre-treatment with steroids has also been allowed in nivolumab trials where corticosteroids are part of standard of care. High doses of dexamethasone have been administered with nivolumab therapy for patients with hematological malignancies where both lenalidomide and bortezomib require administration with standard doses of dexamethasone. In 1L NSCLC studies with nivolumab and pembrolizumab, steroid pre-medication is mandated with some chemotherapies and this has not appeared to impact overall response rates (reference KN-021 study, CM 012 CSR). In GBM studies, corticosteroid treatment for symptomatic brain lesions is considered standard of care and therefore allowed in these trials. Furthermore, the inclusion of steroid treatment in the clinical trials with daratumumab did not impact the pharmacodynamic effect of expansion of activated T cells that was observed, suggesting that T cell activation and expansion still occurs in the presence of systemic steroid treatment. Taken together, the low likelihood that steroid premedication would compromised safety with, and the evidence that efficacy is not impacted by steroid premedication, support evaluation of nivolumab in combination with daratumumab given with appropriate steroid premedication.

Based on the well-established safety profiles of daratumumab and nivolumab, it is not anticipated that the combination treatment will result in overlapping toxicities. The clinical experience of the combination treatment is being investigated in patients enrolled in the CA209-039 study (Multiple Phase 1 Safety Cohorts of Nivolumab Monotherapy or Nivolumab Combination Regimens Across Relapsed/Refractory Hematologic Malignancies), that were treated with nivolumab and daratumumab at the doses that will be administered in this study. As of the database lock of 15-May-2017, 7 patients have been dosed in CA209039: 3 in the nivolumab and daratumumab (ND) arm and 4 in the nivolumab and daratumumab with pomalidomide (ND-Pd) arm. The first study

drug dose was given on 30 Dec 2016; 2 subjects received 4 cycles of therapy, 1 subject received 3 cycles of therapy, 2 subjects received 2 cycles of therapy, and 2 subjects received 1 cycle of therapy. One patient was discontinued from the study due to disease progression, after completing 3 cycles of therapy.

Related cytopenias were reported in the ND-Pd arm, which aligns with the expected safety profiles of daratumumab and pomalidomide and the underlying disease. The daratumumab and pomalidomide dosing was held for the Grade 3-4 neutropenia events, and treatment was resumed upon recovery to the protocol defined blood counts.

There were 2 daratumumab related infusion related reactions, one in each treatment arm, which resolved and the full dose was administered in both cases (after the infusion was interrupted and appropriate medication was administered).

Three related SAEs were reported. A Grade 4 blood bilirubin increase in the ND arm was reconsidered by the investigator as an unrelated event, indicative of disease progression. This SAE was revised after the database lock. The Grade 1 pneumonitis SAE in the ND arm was related to nivolumab, and resolved in 8 days after treatment was held, per the nivolumab management algorithm. The Grade 3 respiratory syncytial virus bronchitis in the ND-Pd arm was related to daratumumab and pomalidomide, and at the time of onset (C1D8) the patient had not started nivolumab dosing yet.

All safety data from the daratumumab/nivolumab cohort in the current study will be regularly monitored by the study physician, the protocol study team, and the BMS medical safety teams.

Starting from Week 25, subjects in the present study will be switched from nivolumab 240 mg Q2W to nivolumab 480 mg Q4W, which provides a more convenient dosing regimen for subjects. Based on PK modeling and simulations, nivolumab 480 mg Q4W is predicted to provide Cavgss similar to 240 mg Q2W. While 480 mg Q4W is predicted to provide greater (approximately 20%) maximum steady state concentrations and lower (approximately 10%) steady state trough concentrations, these exposures are predicted to be within the exposure ranges observed at doses up to 10 mg/kg Q2W used in the nivolumab clinical program, and are not considered to put subjects at increased risk. Similar to the nivolumab 240 mg Q2W dosing regimen, the exposures predicted following administration of nivolumab 480 mg Q4W, are on the flat part of the exposure-response curves for previously investigated tumors in melanoma and NSCLC, and are not predicted to affect efficacy. Based on these data, nivolumab 480 mg Q4W is expected to have similar efficacy and safety profiles to nivolumab 240 mg Q2W.

1.1.15 Duration of Treatment with Nivolumab Monotherapy or Combination Therapy

The optimal duration of immunotherapy is an important question and continues to be investigated. Clinical trials across different tumors types in the nivolumab and ipilimumab development program indicate that most of the responses occur early, with a median time to response of 2-4 months, and emerging data suggests that benefit can be maintained in the absence of continued treatment. A recent analysis in a melanoma study suggests the majority of patients who discontinue

nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment.[166] Furthermore, a limited duration of ipilimumab, including only 4 induction doses, resulted in long term survival in patients with metastatic melanoma, with a sustained plateau in survival starting around 2 years after the start of treatment.[167]

Accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long term benefit. CA209003, a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in patients with previously treated advanced solid tumors (including 129 subjects with NSCLC), specified a maximum treatment duration of 2 years. Among 16 subjects with non-small cell lung cancer (NSCLC) who discontinued nivolumab after completing 2 years of treatment, 12 subjects were alive >5 years and remained progression-free without any subsequent therapy (2) In the CA209003 NSCLC cohort, the overall survival (OS) curve begins to plateau after 2 years, with an OS rate of 25% at 2 years and 18% at 3 years.[168] These survival outcomes are similar to phase 3 studies in previously treated NSCLC, in which nivolumab treatment was continued until progression or unacceptable toxicity (2 year OS rates of 23% and 29%, and 3 year OS rates of 16%-18% for squamous and non-squamous NSCLC respectively).[169]

Similar results have been reported in clinical studies of pembrolizumab, another PD-1 inhibitor. Keynote-010 was a randomized phase 3 trial of pembrolizumab (at either 2 mg/kg or 10 mg/kg every 3 weeks) versus docetaxel in subjects with previously treated, PD-L1-positive, advanced NSCLC which specified a maximum treatment duration of 2 years for pembrolizumab. OS was significantly longer with both pembrolizumab 2 mg/kg (HR 0.72, $p = 0.00017$) and pembrolizumab 10 mg/kg (HR 0.60, $p < 0.00001$) compared to docetaxel, with an OS plateau developing beyond 2 years in both pembrolizumab arms. Among 690 patients who received pembrolizumab, 47 patients completed 2 years of pembrolizumab and stopped treatment. Most were able to maintain their response, including those with stable disease, with only 2 patients (4%) having confirmed progression after stopping at 2 years.[170]

Keynote-006 was a randomized phase 3 study of pembrolizumab versus ipilimumab in patients with advanced melanoma, which also specified a maximum 2 year duration of pembrolizumab treatment. 104 (19%) of 556 patients randomized to pembrolizumab completed 2 years of treatment. With a median follow-up of 9 months after completion of pembrolizumab, the estimated risk of progression or death was 9% in these patients.[171]

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

In contrast, a shorter duration of nivolumab of only 1 year was associated with increased risk of progression in previously treated patients with NSCLC, suggesting that treatment beyond 1 year is likely needed. In CA209153, patients with previously treated advanced NSCLC who completed 1 year of nivolumab therapy were randomized to either continue or stop treatment, with the option of retreatment upon progression. Among 163 patients still on treatment at 1 year and without

progression, those who were randomized to continue nivolumab had significant improvement in progression-free survival (PFS) compared to those who were randomized to stop treatment, with median PFS (post-randomization) not reached vs 10.3 months, respectively; HR=0.42 (95% CI, 0.25 to 0.71). With a median follow-up of 14.9 months post-randomization, there also was a trend for patients on continued treatment to live longer (OS HR = 0.63 [95% CI: 0.33, 1.20]). Of note, the PFS curves in both groups plateau approximately 1 year after randomization (i.e., 2 years after treatment initiation), suggesting that there may be minimal benefit in extending treatment beyond a total of 2 years.[172]

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

1.2 Research Hypothesis

Research Hypothesis (A): Nivolumab, in the neoadjuvant 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 either ipilimumab, BMS-986016 (relatlimab), 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.

1.3 Objectives(s)

1.3.1 Primary Objectives

- 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
  - Merkel Cell Carcinoma
  - Cervical, vaginal, or vulvar cancers
- In the metastatic cohort (nivolumab monotherapy), to evaluate the investigator-assessed objective response rate (ORR) in subjects with the following diseases:
  - Metastatic or recurrent nasopharyngeal carcinoma (NPC)
  - Metastatic or recurrent EBV related gastric cancer
  - Metastatic or recurrent Merkel Cell Carcinoma
  - Metastatic or recurrent cervical, vaginal, or vulvar cancers
  - Metastatic or recurrent HPV positive squamous cell cancer of the head and neck (SCCHN)
- In the metastatic cohort combination therapy (nivolumab combined with either ipilimumab [Combo A or B], or BMS-986016 (relatlimab) [Combo C]), to evaluate the investigator-assessed objective response rate (ORR) in subjects with the following diseases:
  - Metastatic or recurrent nasopharyngeal carcinoma (NPC)
  - Metastatic or recurrent Merkel Cell Carcinoma
  - Metastatic or recurrent cervical cancers

- Metastatic or recurrent HPV positive squamous cell cancer of the head and neck (SCCHN) (with prior 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 squamous cell cancer of the head and neck (SCCHN) (without prior I-O therapy exposure)

1.3.2 Secondary Objectives

- Metastatic cohort (monotherapy and combination therapy): To evaluate the duration of response, progression-free survival and overall survival.

1.3.3 Exploratory Objective(s)

Neoadjuvant Cohort

- To determine the percent change from baseline of select 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-3L questionnaire.
- To evaluate cancer specific health related quality of life as assessed by EORTC QLQ-C30 questionnaire.
- To characterize pharmacokinetics of nivolumab and explore exposure-response relationships.
- To characterize the immunogenicity of nivolumab.

- **Metastatic Cohort (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, daratumumab, or BMS-986016) 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 (recurrent/metastatic monotherapy only) and nasopharyngeal carcinoma.[44,45]
- 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, daratumumab, or BMS-986016) 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, daratumumab, or BMS-986016) 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, daratumumab, or BMS-986016,) and explore exposure-response relationships.
- To characterize the immunogenicity of nivolumab monotherapy and combination therapy (ipilimumab, daratumumab, or BMS-986016).

1.4 Product Development Background

Information for nivolumab (BMS-936558, anti-PD-1 antibody), ipilimumab (YERVOY®; anti-CTLA antibody), daratumumab (anti-CD38 antibody) and BMS-986016 (relatlimab, anti-LAG-3 antibody) is provided in the sections below; additional details are provided in the respective Investigator Brochures.

1.4.1 Nivolumab

1.4.1.1 Summary of Nivolumab Clinical Activity in the Metastatic Setting

The PK, clinical activity, and safety of nivolumab have been assessed in approximately 70 clinical studies sponsored by BMS, Ono Pharmaceutical Co., Ltd. (ONO), or other partners. Approximately 12,300 subjects have received nivolumab in single- or multiple-dose Phase 1/2/3 studies or studies with nivolumab in combination with other therapeutics (ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies).

Nivolumab monotherapy is approved in multiple countries, including the US and EU, for unresectable or metastatic melanoma, previously treated metastatic NSCLC, and previously treated advanced RCC; it is also approved for the treatment of cHL in the US. In addition,

nivolumab has been approved for use in combination with ipilimumab for unresectable melanoma in multiple countries, including the US and EU.

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy and in combination with ipilimumab in several tumor types, including NSCLC, melanoma, RCC, classical Hodgkin's lymphoma (cHL), small cell lung cancer (SCLC), gastric cancer, urothelial cancer, hepatocellular carcinoma, and colorectal cancer. In confirmatory trials, nivolumab as monotherapy demonstrated a statistically significant improvement in OS as compared with the current standard of care in subjects with advanced or metastatic NSCLC, unresectable or metastatic melanoma, advanced RCC, or SCCHN. Nivolumab in combination with ipilimumab improved PFS and ORR over ipilimumab alone in subjects with unresectable or metastatic melanoma. Additional details on the efficacy profile of nivolumab, including results from clinical studies, are available in the nivolumab IB.

1.4.1.2 Summary of Nivolumab Safety in the Metastatic Setting

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 12,300 subjects treated to date.

For monotherapy, the safety profile is similar across tumor types. There is no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. In Phase 3 controlled studies, the safety profile of nivolumab monotherapy is acceptable in the context of the observed clinical efficacy, and manageable using established safety guidelines. A pattern of immune-related adverse events has been defined, for which management algorithms have been developed; these are provided in Appendix 2. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms. For additional material, see the nivolumab Investigator Brochure.

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the nivolumab IB.

1.4.2 Nivolumab Combined with Ipilimumab

1.4.2.1 Nivolumab and Ipilimumab Mechanism of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. The immune surveillance functions by limiting the emergence of tumors as they arise and/or causing tumor shrinkage. Tumor progression may depend upon acquisition of traits that allow cancer cells to evade immune surveillance and an effective immune response. This evasion may occur by exploiting any of the checkpoints that control the regulatory immune response, including display of antigens and control of co-stimulatory pathways that affect the proliferation of cells involved in immunity. Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system, either directly by stimulation of

immune cells by antibodies directed to receptors on T and B cells or indirectly by cytokine manipulation. T-cell stimulation is a complex process involving the integration of numerous positive, as well as negative, co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR). Collectively, these signals govern the balance between T-cell activation and tolerance to antigens.

Programmed death receptor-1 (PD-1, CD279), a 55 kD type I transmembrane protein, is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA-4, ICOS, and BTLA.2 PD-1 contains an intracellular membrane proximal immunoreceptor tyrosine inhibitory motif (ITIM) and a membrane distal immunoreceptor tyrosine-based switch motif (ITSM). Two ligands specific for PD-1 have been identified: PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273). PD-L1 and PD-L2 have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems. PD-1 delivers a negative signal by the recruitment of SHP-2 to the phosphorylated tyrosine residue in the ITSM in its cytoplasmic region. PD-1 is primarily expressed on activated T cells, B cells, and myeloid cells. Further evidence for a negative regulatory role of PD-1 comes from studies of PD-1-deficient mice. PD-1-deficient mice develop various autoimmune phenotypes, including dilated cardiomyopathy, a lupus-like syndrome with arthritis and nephritis, and accelerated diabetes mellitus. The emergence of these autoimmune phenotypes is dependent upon the genetic background of the mouse strain and many of these phenotypes emerge at different times and show variable penetrance. In addition to the phenotypes of null mutations, PD-1 inhibition by antibody-mediated blockade in several murine models has been found to play a role in the development of autoimmune diseases such as encephalomyelitis, graft-versus-host disease, and type I diabetes. Taken together, these results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

Preclinical animal models of tumors have shown that blockade by PD-1 by monoclonal antibodies (mAbs) can enhance the anti-tumor immune response and result in tumor rejection. Antitumor activity by PD-1 blockade functions in PD-L1-positive tumors as well as in tumors that are negative for the expression of PD-L1. This suggests that host mechanisms (ie, expression of PD-L1 in antigen-presenting cells) limit the antitumor response. Consequently, both PD-L1 positive and negative tumors may be targeted using this approach. In humans, constitutive PD-L1 expression is normally limited to macrophage-lineage cells, although expression of PD-L1 can be induced on other hematologic cells as well, including activated T cells. However, aberrant expression of PD-L1 by tumor cells has been reported in a number of human malignancies. PD-L1 expressed by tumor cells has been shown to enhance apoptosis of activated tumor-specific T cells in vitro. Moreover, the expression of PD-L1 may protect the tumor cells from the induction of apoptosis by effector T cells.

Nivolumab (BMS-936558; anti-PD-1 mAb) is a fully human monoclonal immunoglobulin (Ig)G4 antibody that binds to the programmed death-1 (PD-1) cell surface membrane receptor, a negative regulatory molecule expressed by activated T and B lymphocytes. Blockade of the PD-1pathway by nivolumab was studied using the mixed lymphocyte reaction (MLR). PD-1 blockade resulted

in a reproducible enhancement of both proliferation and interferon release in the MLR. The effect of nivolumab on antigen-specific recall response was investigated using a CMV-restimulation assay with human peripheral blood mononuclear cells (PBMCs), and was evaluated by ELISA.

Ipilimumab is a fully humanized IgG1 monoclonal antibody binding to the anti-cytotoxic T-cell lymphoma-4 antigen (CTLA-4). Ipilimumab is an approved therapy for metastatic melanoma and has demonstrated improved overall survival as monotherapy and in combination with dacarbazine.[131,173] It has been studied in combination with multiple standards of care (SOC) therapies including chemotherapy for squamous and non-squamous NSCLC and radiotherapy for hormone resistant prostate cancer.[126] Phase III studies are ongoing in NSCLC, SCLC, and prostate carcinoma.

1.4.2.2 Summary of Nivolumab plus Ipilimumab Safety Data

Several doses of nivolumab and ipilimumab are currently being explored in ongoing clinical trials. Although the optimal doses have not yet been defined across multiple tumor types, the largest studies to date have been done in melanoma at a dose of nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg administered IV every 3 weeks for 4 doses followed by nivolumab 3 mg/kg IV every 2 weeks. These studies include subjects with previously untreated unresectable or metastatic melanoma in CA209067 (313 subjects) and CA209069 (94 subjects) (a total of 407 subjects). Based on the pooled analyses, nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg administered IV every 3 weeks for 4 doses followed by nivolumab 3 mg/kg IV every 2 weeks has an acceptable safety profile, as demonstrated by the frequency, severity, and types of AEs, drug-related deaths, SAEs, and AEs leading to discontinuation as described below. Additional details on safety and clinical activity of nivolumab plus ipilimumab combinations are described in the IB.[131]

The following were the key safety findings for these pooled subjects:

- The most frequently reported drug-related AEs of any grade (≥ 15% of subjects) were diarrhea (43.0%), fatigue (35.4%), pruritus (33.4%), rash (31.0%), nausea (24.8%), pyrexia (18.7%), ALT increased (18.2%), AST increased (16.7%) and decreased appetite (16.2%). The most frequently reported drug-related Grade 3 - 4 AEs (≥ 5% of subjects) were colitis (9.6%), diarrhea (8.80%), ALT increased (8.4%), lipase increased (8.4%), and AST increased (5.9%).
- The majority of drug-related SAEs were Grade 3 - 4 in severity. The most frequently reported drug-related SAEs of any grade (≥ 2% of subjects) were colitis (11.1%), diarrhea (8.8%), pyrexia (3.7%), pneumonitis (2.7%), hypophysitis (2.2%), transaminases increased (2.2%), and adrenal insufficiency (2.0%). The majority of drug-related SAEs were Grade 3 - 4. The most frequently reported drug-related Grade 3 - 4 SAEs (≥ 2% of subjects) were colitis (8.8%), diarrhea (5.7%), and transaminases increased (2.2%).
- Drug-related AEs leading to discontinuation occurred in 36.4% of subjects. The majority of drug-related AEs leading to discontinuation of study drug were Grade 3 - 4 in severity. The most frequently reported drug-related AEs of any grade leading to discontinuation of study drug (≥ 2% of subjects) were colitis (10.1%), diarrhea (7.4%), ALT increased (4.7%), and

AST increased (4.2%). These were also the most frequently reported drug-related Grade 3 - 4 SAEs leading to discontinuation of study drug (≥ 2% of subjects).

- The most frequently reported drug-related select AE categories with nivolumab + ipilimumab combination therapy were skin (61.9%), GI (46.4%), endocrine (29.7%), and hepatic (29.0%). The majority of select AEs were considered by the investigators to be related to study treatment.
- Drug-related select AEs were mostly Grade 1 - 2 in all categories with the exception of hepatic select AEs where the majority were Grade 3 - 4.
- Across categories, the majority of high-grade events subsequently resolved, including those for which immunosuppressive medication was not initiated.
- The majority of deaths (80/105) were due to disease progression. Study drug toxicity was considered responsible for 2 deaths; 1 subject died of ventricular arrhythmia within 30 days of the last dose and the other died of pneumonitis between 31 and 100 days of the last dose.
- Abnormalities in select hematology assessments and liver/kidney function tests were primarily Grade 1 - 2 in severity.
- The immunogenicity of nivolumab was low and not clinically meaningful.

In general, the frequency of adverse events was lowest across AE categories in the nivolumab monotherapy group and highest in the nivolumab + ipilimumab group. However, the types and frequency of AEs reported in the nivolumab + ipilimumab group were as expected based on the mechanism of action of the two agents and were consistent with previously reported data. Additional toxicity, including a higher frequency of Grade 3 - 4 AEs, was observed in the nivolumab+ipilimumab group relative to the ipilimumab group, leading to a higher frequency of discontinuation from study treatment. The most frequently reported select AE categories were skin, GI, endocrine, and hepatic. Select AEs belonging to these categories were reported more frequently in the nivolumab+ipilimumab group than the ipilimumab group. The majority of events were manageable. In summary, results to date suggest that the safety profile of nivolumab+ipilimumab combination therapy is consistent with the mechanisms of action of nivolumab and ipilimumab. The nature of the AEs is similar to that observed with either agent used as monotherapy; however, both frequency and severity of most AEs are increased with the combination.[174]

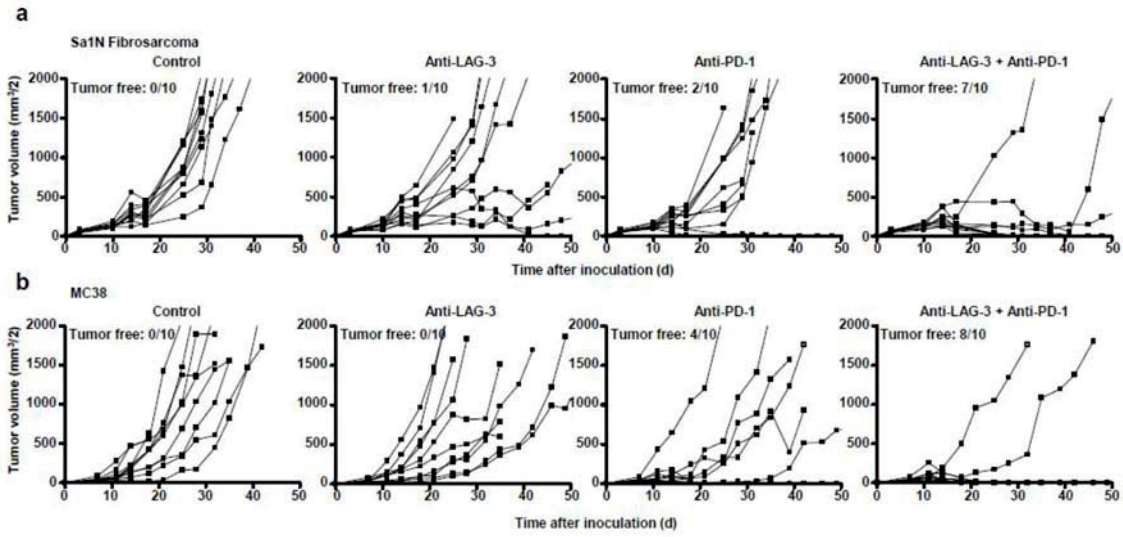
1.4.3 Nivolumab Combined with BMS-986016

1.4.3.1 Nonclinical Pharmacology Studies Utilizing Murine Anti-PD-1 and Anti-LAG-3 Antibodies

The importance of LAG-3 as an immunotherapy target was validated in murine in vivo models using 2 surrogate antibodies specific for mouse LAG-3. These studies evaluated tumor growth inhibition in syngeneic tumor models (Sa1N fibrosarcoma and MC38 colon adenocarcinoma) and monitored acceleration of autoimmunity in the non-obese diabetic (NOD) model. Anti-LAG-3 antibody administration resulted in both overall tumor growth inhibition and an increase in the number of tumor-free (TF) mice in those treatment groups (Figure 1.4.3.1-1).

Anti-LAG-3 antibody administered in combination with anti-PD-1 antibody provided enhanced antitumor activity above the activity of either agent alone. For example, in multiple Sa1N tumor models, anti-LAG-3 antibody resulted in 20%-30% TF mice compared to control and anti–PD-1 antibody-treated mice (0%–10% TF mice), while the combination of anti–LAG-3 and anti–PD-1 antibodies resulted in 60%–90% TF mice. In the MC38 model, anti–LAG-3 antibody showed modest tumor growth inhibition alone but when administered in combination with anti-PD-1 antibody, resulted in enhanced antitumor activity above that observed for anti-PD-1 antibody alone (80% vs. 40% TF mice, respectively).

Figure 1.4.3.1-1: Antitumor Activity of Anti-LAG-3 and Anti-PD-1 Antibodies in Murine Models



1.4.3.2 Nonclinical Toxicology

The nonclinical toxicology package for relatlimab consists of the following studies:

- Four-Week Intermittent (QW) Intravenous Exploratory Combination Pharmacodynamic and Toxicity Study in Cynomolgus Monkeys with Anti-LAG3.1 Antibody (a precursor of the anti-LAG3.5 antibody) and Nivolumab.
- GLP-Compliant Four-Week Intravenous Combination Toxicity Study in Cynomolgus Monkeys with a 6-Week Recovery with BMS-986016 and Nivolumab.

The key results were as follows:

- Single-agent BMS-986016 administered at up to 100 mg/kg/week did not result in adverse changes.
- Combined administration of BMS-986016 and nivolumab (100 and 50 mg/kg/week, respectively) resulted in moribundity of 1 male out of 9 monkeys on study Day 29. From Days 26 to 29, this monkey presented with elevated body temperature, shivers, red or clear nasal discharge, fecal changes (unformed, scant or absent feces), decreased feeding

behavior, mild dehydration, sneezing, decreased activity, and hunched posture. After 2 days of veterinary care and antibiotic treatment, this animal did not show any improvement and was euthanized on Day 29 for poor clinical condition. There were no remarkable gross necropsy findings. Histopathological findings in this monkey included: slight lymphoplasmacytic inflammation of the choroid plexus; minimal to moderate lymphohistocytic inflammation of the vasculature of the brain parenchyma, meninges, spinal cord (cervical and lumbar); and minimal to moderate mixed cell inflammation of the epididymes, seminal vesicles and testes. Clinical pathology changes indicated decreases in red blood cell count, hemoglobin concentration and hematocrit whose cause was unclear, and an increase in fibrinogen correlating with the inflammation observed in the central nervous system (CNS) and male reproductive tract.

- Additional histopathological findings upon combination administration of BMS-986016 and nivolumab (100 and 50 mg/kg/week, respectively) were limited to minimal to slight non-reversible lymphoplasmacytic inflammation of the choroid plexus in the brain in 7 of 8 remaining monkeys, and minimal lymphohistiocytic inflammation of the vasculature of the brain parenchyma in 1 of 8 remaining monkeys, whose reversibility could not be assessed.
- NOAEL for single-agent BMS-986016 was considered to be 100 mg/kg/week (mean AUC[0-168h] = 474,000 μg•h/mL); NOAEL for single-agent nivolumab was considered to be 50 mg/kg/week (mean AUC[0-168h] = 193,000 μg•h/mL); NOAEL for combination of BMS-986016 and nivolumab was not determined.
- However, the combination therapy was generally well tolerated and clinical signs of toxicity were observed in only 1 of 9 monkeys (approximately 10%). Therefore, 100/50 mg/kg/week BMS-986016/nivolumab (mean BMS-986016 AUC[0-168h] = 514,000 μg•h/mL; mean nivolumab AUC[0-168h] = 182,000 μg•h/mL) was considered the STD10.
- The doses administered (100 mg/kg BMS-986016 and 50 mg/kg nivolumab) are ≥ 10 times higher than the maximum doses proposed for the current study.

- GLP-Compliant Tissue Cross Reactivity Study in Human and Select Cynomolgus Monkey Tissues with BMS-986016.
  - Positive staining with BMS-986016-FITC was observed in the plasma membrane or plasma membrane granules of mononuclear leukocytes of most human tissues, including lymphoid tissues and hematopoetic cells of the bone marrow. In addition, staining with BMS-986016-FITC was observed in the cytoplasm of the human pituitary endocrine cell epithelium. Although BMS-986016 is not expected to have access to the cytoplasmic compartment in vivo and the repeat-dose toxicology studies in monkeys showed no effects on the pituitary gland, these findings may be of clinical significance and will be monitored.
  - In Vitro Cytokine Release and Lymphocyte Activation Assessment with BMS-986016 using Human Peripheral Blood Mononuclear Cells.
  - BMS-986016 did not induce cytokine release when presented to human PBMCs regardless of concentration, donor, or incubation time. The levels of cytokines observed were either at or near the assay lower limits of quantification with no evidence of dose-dependence or pattern across donors (IL-1β, IL-2, IL-5, IL-10, IL-12p70, and IFN-γ) or were generally overlapping with cytokine levels from PBMCs incubated with negative controls (IL-6, IL-8, TNF-α).

- Consistent with the lack of cytokine release, there was no evidence that BMS-986016 induced T or NK cell activation, as measured by surface expression of CD25 and CD69. Expression levels of these markers on T and NK cells following stimulation with BMS-986016 were similar to those observed upon stimulation with negative controls.
- Overall, these data indicate that BMS-986016 does not possess agonistic potential to induce either T or NK cellular activation or cytokine release.

1.4.3.3 Nonclinical Pharmacokinetics

Relatlimab demonstrated favorable PK properties in cynomolgus monkeys. From both single-dose and repeat-dose IV PK studies, relatlimab decayed bi-exponentially and the exposure was approximately dose-proportional. The systemic clearance (CLTp) ranges from 0.12 to 0.22 mL/h/kg and a terminal half-life (T-HALF) 133 to 414 hours. Co-administration with nivolumab did not appear to affect exposure to relatlimab. The volume of distribution at steady state (Vss) was 62 to 72 mL/kg, suggesting limited distribution outside the plasma. Anti-BMS-986016 antibodies were detected in some monkeys but the presence of anti-BMS-986016 antibodies appeared to have no impact on BMS-986016 exposure.

1.4.3.4 Clinical Pharmacology

The current Phase 1 clinical program is evaluating advanced solid tumors (special focus in non-small cell lung cancer [NSCLC], renal cell carcinoma, and malignant melanoma) in Study CA224-020 and relapsed refractory hematological malignancies (Hodgkin and non-Hodgkin lymphomas) in Study CA224-022. As of 29-Jun-2016, 89 subjects have been treated with relatlimab in these 2 ongoing studies assessing PK, clinical activity, and safety. An interim determination of relatlimab multiple dose PK was carried out using all available serum concentrations data from Studies CA224 020 and CA224 022. In general, the Cmax and area under the concentration versus time curve over the dosing interval (AUC[TAU]) values over the first dosing interval increased approximately equal to the increment in the relatlimab dose. The PK of BMS 986016 and nivolumab was not altered when given in combination. Relatlimab concentration time data were reasonably described by population PK model with linear, 2 compartment, zero-order IV infusion model with first order elimination. The model estimated mean T-HALF was 19 days, and the typical CLT was 13.7 mL/h. The population PK model will be used to understand the source of variability in relatlimab PK and effect of intrinsic and extrinsic factors.

Currently available data suggest that relatlimab monotherapy exhibits a low level of immunogenicity, with 6 out of 42 subjects having at least 1 post-baseline positive anti-drug antibody (ADA) samples. There are limited data available in combination cohort to make inference on immunogenicity rate.

1.4.3.5 Clinical Safety Combination Therapy (Nivolumab plus Relatlimab)

For details on clinical safety, see Section 1.1.11 and the BMS-986016 IB.

1.4.4 Daratumumab

1.4.4.1 Summary of Daratumumab Clinical Pharmacology

Daratumumab is a first-in-class immunoglobulin G1 kappa (IgG1κ) human monoclonal antibody (mAb) that specifically binds to the CD38 protein expressed on the surface of multiple myeloma tumor cells and other cell types at various levels. In vitro, daratumumab can induce tumor cell lysis through complement dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis in malignancies expressing CD38.

The population pharmacokinetic (PK) analysis included patients with multiple myeloma who received daratumumab. Over the dose range from 1 to 24 mg/kg, AUC increases more than dose-proportionally. Clearance decreases with increasing dose and repeated dosing, indicating target-mediated pharmacokinetics. Following the recommended dose and schedule, the Cmax at the end of weekly dosing is 2.9-fold higher than following the first infusion. Daratumumab steady state is achieved approximately 5 months into the every 4-week dosing period and the Cmax at steady-state to Cmax after the first dose is 1.6. The mean (SD) linear clearance and mean (SD) central volume of distribution are estimated to be 171.4 (95.3) mL/day and 4.7 (1.3) L, respectively. The mean (SD) estimated terminal half-life associated with linear clearance is approximately 18 (9) days. Population PK analyses indicated that the central volume of distribution and clearance of daratumumab increase with increasing body weight, supporting the body weight-based dosing regimen. Population PK analyses also show that age (31-84 years), gender, mild to severe renal impairment (15 to 89 mL/min) and mild hepatic impairment do not have clinically important effects on the pharmacokinetics of daratumumab.

Exposure-response analyses for efficacy and safety were conducted using data from trials GEN501 and MMY2002. The exposure-efficacy analysis shows that ORR increases with increasing daratumumab concentration, with a plateau achieved at daratumumab maximal pre-infusion concentrations (Cpre-infusion, max) ≥ 270 μg/mL. Furthermore, the median progression free survival (PFS) appears shorter in patients with daratumumab Cpre-infusion,max < 270 μg/mL (1.9 month) and longer (6.6 months) in those with daratumumab concentrations > 270 μg/mL. However, this analysis was confounded by baseline risk factors such as disease severity. There was no exposure-safety relationship for infusion related reactions (IRR), thrombocytopenia, anemia, neutropenia and lymphopenia within the exposure range from 0.1 to 24 mg/kg studied in trials MMY2002 and GEN501.

1.4.4.2 Summary of Daratumumab Clinical Activity

Based on the preclinical activity of daratumumab, a phase 1/2 study was initiated in MM patients with relapsed/refractory disease (GEN501 study).[157] In the first-in-human dose-escalation part of the study the maximum-tolerated dose was not reached with dose levels up to 24 mg/kg. In the phase 2 part of the study, patients with a median of 4 prior lines of therapy (majority refractory to lenalidomide and bortezomib) were treated with daratumumab at a dose of 8 mg/kg or 16 mg/kg. The overall response rate (at least PR) was 36% in the 16 mg/kg cohort and 10% in the 8 mg/kg group. Remarkably, in this extensively pretreated group of patients, 2 out of 42 patients treated with 16 mg/kg daratumumab achieved a first complete response. The median PFS in the 8 mg/kg

and 16 mg/kg groups were 2.4 and 5.6 months, respectively. The 12-month survival was 77% for both groups. The most frequent adverse events were infusion-related reactions, which occurred in 71% of patients. The majority of these reactions included grade 1 and 2, and characterized by rhinitis, cough, headache, pyrexia, and dyspnea. Most infusion-related reactions occurred during the first daratumumab infusion and only few patients (<10%) had infusion-related reactions with more than one infusion.

The SIRIUS (MMY2002) study confirmed the results from GEN501 study that demonstrated single agent activity of daratumumab with a favorable toxicity profile.[158] One hundred six patients, with a median of 5 prior lines of therapy (95% refractory to lenalidomide and bortezomib), received daratumumab monotherapy at a dose of 16 mg/kg. At least a PR was achieved in 29% of patients with stringent CR in 3%. The median duration of response was 7.4 months. The median progression-free survival was 3.7 months and 1-year overall survival was 65%. Notably, subgroup analysis showed that in the group of patients who were refractory to lenalidomide, pomalidomide, bortezomib and carfilzomib, PR or better was achieved in 21% of these patients. Infusion-related reactions were observed in 43% of the patients and were predominantly grade 1 and 2, and could be managed with interruption of the infusion or extra corticosteroids and antihistamines. In conclusion, results from these studies show that daratumumab is well tolerated and that in the 16 mg/kg cohort at least a partial response can be achieved in 29-36% of the patients.[157,175,176] Virtually all patients with PR or CR, achieved 50% reduction in tumor load within 3 months after start of therapy.

Based on preclinical evidence showing potential benefit of combining daratumumab with lenalidomide.[177,178,179] another phase 1/2 study is currently evaluating the combination of daratumumab plus lenalidomide and dexamethasone in relapsed/refractory MM (GEN503; NCT01615029). Preliminary safety data show a manageable toxicity profile and high efficacy of this three-drug regimen.[180,181]

Daratumumab has also been shown to be safe, tolerable and efficacious when combined with other immunomodulatory agents in two separate Phase 3 trials combining daratumumab with 1) lenalidomide and dexamethasone (POLLUX) and pomalidomide and dexamethasone (CASTOR). In the POLLUX trial, lenalidomide-dexamethasone was combined with or without daratumumab in patients with relapsed/refractory myeloma with 1-3 previous lines of therapy (patients with lenalidomide-refractory disease were excluded).[182] In this study the daratumumab treated patients had a significantly higher CR rate and an unprecedented improvement in the PFS (HR: 0.37). There was no additional toxicity when daratumumab was added to lenalidomide-dexamethasone, except for infusion-related reactions, which occurred in approximately half of the patients mostly during the first infusion. Another phase 3 trial compared bortezomib-dexamethasone with or without daratumumab (CASTOR).[183] Also in this study there was a significant improvement in CR rate, leading to a significant improvement of the PFS (HR: 0.39). Also in the CASTOR study daratumumab did not add toxicity to bortezomib-dexamethasone, except for infusion-related reactions occurring in approximately half of the patients, mostly during the first infusion of daratumumab.

1.5 Overall Risk/Benefit Assessment

There is a significant unmet medical need for subjects with virus positive tumors including nasopharyngeal carcinoma, gastric, Merkel cell carcinoma, cervical/vulvar/vaginal/anal canal/penile, or SCCHN as outlined in Section 1.1. Virus positive tumors may have distinct patterns of immune responses and tumor immune microenvironments (Section 1.1.4); 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. 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.

Extensive details on the safety profile of nivolumab are available in the Investigator Brochure, and will not be repeated herein.

Overall, the safety profile of nivolumab monotherapy as well as in combination with ipilimumab is manageable and generally consistent across completed and ongoing clinical trials with no MTD reached at any dose tested up to 10 mg/kg. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level.

A pattern of immune-related adverse events has been defined, for which management algorithms have been developed; these are provided in Appendix 2. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the nivolumab IB.

The **combination of nivolumab plus relatlimab** has the potential for increased benefit compared to monotherapy targeting the PD-1 pathway, ie, nivolumab monotherapy. In the nonclinical GLP toxicology study, lymphoplasmacytic infiltration in the choroid plexus (and spinal cord) was reported at the highest doses of anti-PD-1 antibody (3/6 animals) and the anti-LAG-3 + anti-PD-1 antibody combination (5/6). Importantly, these findings were not reported with anti-LAG-3 antibody alone either the 30 mg/kg or 100 mg/kg (highest dose).

These are nonspecific histopathology changes, without clinical manifestations in all but one of the animals treated with combination therapy, which have been observed in other studies with antibodies and small molecules in monkeys. Three subjects have experienced treatment related and immune mediated aseptic meningitis that have responded to immunosuppressive therapy. Vigilance regarding the communication and evaluation of potential neurologic toxicity remains an ongoing priority.

Therapy with relatlimab and nivolumab is investigational and it is possible that a higher incidence of immune mediated-adverse events may occur with the combination of 2 antibodies targeting T cells. The immune-related grade 5 myocarditis event prompted closer monitoring of subjects with ECGs and troponins, as well as tighter eligibility criteria regarding baseline ejection fraction and history of cardiovascular disease. Unanticipated side effects events may also occur, like the Grade

4 VF that was also reported in combination therapy, Part B. There were several confounding factors in this case but, in the absence of a clear etiology, the event was considered treatment-related. In the setting of troponin surveillance three cases of grade 1 myocarditis have been documented and managed without progression to subsequent cardiac dysfunction. Adverse events and SAEs will continue to be reviewed expeditiously by the Medical Monitor, investigators and the Pharmacovigilance group to monitor safety. With 243 subjects treated with combination therapy as of the clinical cut-off date, the overall safety profile of relatlimab + nivolumab currently appears similar to nivolumab monotherapy.

The potential direct benefit to subjects who participate in the CA224020 study is that both single-agent and combined therapy with these investigational agents may result in a greater proportion of subjects with stabilization of disease, objective response, or increased duration of response than those observed with nivolumab monotherapy. It is also possible that combination therapy may reverse LAG-3-mediated T cell exhaustion and achieve responses in 1) tumor types known to be unresponsive to nivolumab; 2) tumors refractory to anti-CTLA4 and anti PD-1 or anti PD L1 antibody therapy; and/or 3) virally-associated tumors. In fact, multiple RECIST1.1 defined partial responses have been observed with relatlimab monotherapy and in combination with nivolumab, both in the immunotherapy naive, as well as the anti-PD-1 resistant setting. More specifically, first disclosure of the initial efficacy at ASCO 2017 showed an ORR of 12.5% in advanced melanoma subjects that have progressed on prior anti-PD1/PDL1 with an even more encouraging ORR of 20% in subjects with significant LAG-3 expression in tumor associated immune cells. Thus, the potential for direct benefit in subjects with few if any alternative treatment options has been initially demonstrated, warranting continued evaluation of the combination across tumor types while extending testing in the melanoma prior IO population.

Based on preliminary data as of the clinical cutoff date of 15-Jun-2017, the safety profile of relatlimab in combination with nivolumab is manageable, with no maximum tolerated dose (MTD) reached at the tested doses up to 160 mg relatlimab and 240 mg nivolumab (flat dose, every 2 weeks [Q2W]), with evaluation of the 240 mg relatlimab/240 mg nivolumab combination dose-level ongoing. At the time of the clinical cutoff date (15-Jun-2017) one dose-limiting toxicity (DLT) of Grade 5 myocarditis was observed at the 240 mg relatlimab/240 mg nivolumab combination dose level among five evaluable subjects. There was no dose relationship between the incidence, severity, or causality of adverse events (AEs) to combination therapy. In the nine expansion cohorts, a total of 262 subjects were treated with 80 mg relatlimab and 240 mg nivolumab Q2W. Most AEs were low grade (Grade 1 to Grade 2) with a total of 26 subjects experiencing a drug-related serious adverse event (SAE). All AEs, except for one Grade 5 myocarditis and one Grade 4 drug-induced liver injury (DILI), were reversible and manageable by withholding study drug administration providing standard medical care, and/or following immune-related AE algorithms. In summary the safety profile of the combination of relatlimab and nivolumab appears similar to nivolumab monotherapy in terms of both frequency and severity of AEs.

A pattern of immune-related adverse events has been defined for treatment with nivolumab monotherapy and nivolumab in combination with other immune-targeting agents such as

relatlimab. Management algorithms have been developed for these events and are provided in Appendix 2. Most high-grade events are manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

Myocarditis has been observed with nivolumab monotherapy treatment (see nivolumab IB Section 5.6.2). Given the grade 5 myocarditis event in the CA224020 study, and the known nonclinical mouse double LAG-3/PD-1 knockout myocarditis phenotype, increased cardiac surveillance with troponin measurements were instituted. As of the clinical cutoff date of 15-Jun-2017 there have been four grade 1 myocarditis cases (asymptomatic troponin elevations with imaging correlate of myocardial inflammation but without evidence of cardiac dysfunction). Treatment was delayed in all cases, and precautionary steroid treatment was given without any of the participants developing evidence of cardiac dysfunction.

Additional safety measures for cardiovascular risks implemented for subjects receiving combination treatment with Combo C have been added to the protocol:

- Exclusion of subjects with history of myocarditis, regardless of etiology.
- Exclusion Criteria under significant cardiac events: history of 2 or more myocardial infarctions (MIs) OR 2 or more coronary revascularization procedures.
- Screening left ventricular ejection fraction (LVEF) assessment (if not performed in the last 6 months) with documented LVEF $\geq$ 50% by either transthoracic echocardiogram or multiple gated acquisition scan (transthoracic echocardiogram being the preferred test) for subjects.
- Increased emphasis in clinical monitoring of subjects for signs and symptoms of cardiovascular toxicities during training meetings and safety teleconferences.
- Addition of pre-dose ECG testing.
- Addition of troponin laboratory testing.

Daratumumab induces antimyeloma effects via multiple mechanisms of action. An additional mechanism of action has been proposed in which treatment with daratumumab eliminates a population of highly immunosuppressive CD38+ Tregs, T-cell MDSCs, and Bregs and thus stimulates T-cell effector functions.[165] This immunomodulatory effects of daratumumab, specifically its ability to promote T-cell expansion and activation, are expected to potentiate the effect of anti-PD-1 antibody. The **combination of nivolumab plus daratumumab** is expected to potentiate the effect of nivolumab by sensitizing the bone marrow T cells to PD-1 blockade, which would translate in augmented clinical benefit.

Daratumumab is approved as monotherapy for third line treatment of MM patients who failed prior therapies.[157,158] Recent reported results demonstrated safety and efficacy when combined with other immunomodulatory therapies in second line MM, including lenalidomide and dexamethasone.[175]

Daratumumab's primary adverse events includes infusion reactions, which are reported to be uncommon with nivolumab alone (Nivolumab IB). However, infusion related reactions to daratumumab occur in close to 50% of the patients, largely with the first infusion. According to

the currently approved United States Prescribing Information (USPI), daratumumab infusions should be interrupted for infusion reactions of any severity, and drug should be permanently discontinued in case of life-threatening infusion reactions. Pre-infusion and post-infusion medication should be administered to all patients, per the currently approved USPI. Severe infusion related reactions have been reported in less than 1% of subjects in clinical trials with nivolumab, with overall rates of infusion related reactions of any grade ranging from 1% to 6%. The risk of infusion reactions is greater with the first and second infusions with daratumumab and decreases for subsequent doses. Therefore, to minimize the likelihood of infusion related reactions to the nivolumab and daratumumab combinations, the first nivolumab dose is administered at week 3 (ie, after the first two doses of daratumumab at weeks 1 and 2). Further, on each dosing day when nivolumab is administered with daratumumab, the required pre-infusion medication for daratumumab is administered first, followed by infusion of nivolumab then infusion of daratumumab and then administration of daratumumab post-infusion medications.

Other AEs of any grade reported in a high frequency (>25%) of daratumumab treated subjects include low grade fatigue and nausea which have been associated with nivolumab treatment. Only one severe AEs (Grade 3/4) of pneumonia has been reported with daratumumab (>5% frequency). Pneumonia is considered uncommon with nivolumab as reported in the USPI; however, severe cases have been reported. The hematological AEs that have been reported following treatment with daratumumab (anemia, thrombocytopenia, neutropenia, lymphopenia), which are common in subjects with hematological malignancies, are not expected to be observed in subjects with solid tumors. In contrast to nivolumab, there have been no cases of immune related AEs, including pneumonitis, reported in the label for daratumumab. Based on the above assessment, the potential benefit of combining nivolumab and daratumumab appears to outweigh the potential risk. The overall risk/benefit assessment supports the evaluation of these combinations in this setting.

It is possible that unforeseen or unanticipated AEs may occur. In order to minimize the overall risks to participating subjects, the protocol has inclusion-exclusion criteria appropriate to the population, and specific follow-up safety assessments. Routine safety monitoring for all the AEs described above will be implemented in the protocol to ensure that we are monitoring the potential for overlapping toxicities.

Adverse events and SAEs will continue to be reviewed expeditiously by the Medical Monitor, investigators and the Pharmacovigilance group to monitor safety.

For subjects with local or locally advanced virus-positive tumors that are amenable to therapies with curative intent (**neoadjuvant cohort** of this study), there are multiple treatment options including perioperative chemotherapy, radiation, and/or observation post-resection depending on the disease stage and intraoperative findings. To minimize any delay to receiving treatment with curative intent, only two doses of nivolumab will be administered q2 week. This will coincide with the time when subjects are being scheduled for surgery and other perioperative treatments; therefore, minimal delays are expected. Furthermore, based on the known safety and tolerability profile of nivolumab, it is unlikely that adverse events from neoadjuvant administration will risk delaying surgery or receipt of standard of care. Prior precedent for the safety of perioperative

checkpoint inhibition has been established in a Phase I bladder cancer study with ipilimumab (see Section 1.1.3). In addition, to minimize the risk of potential delays, a two stage approach will be taken to stop enrollment if there are delays to surgery or chemotherapy/radiation due to a nivolumab-related adverse event as specified in the label in the region of treatment in more than 2 of the first 10 subjects treated within each tumor type. Lastly, although there are no efficacy data on neoadjuvant administration of nivolumab, there is potential for some clinical benefit as objective responses have been observed in clinical trials within weeks of initial treatment.

There is risk associated with tumor biopsies, including bleeding, infection, and pain. While there is no direct benefit to subjects who undergo these procedures, there is a potential that data generated from these samples will guide the further development of these compounds and may be of direct benefit for others with advanced solid tumors.

In summary, based on the manageable safety profile of nivolumab and nivolumab in combination with ipilimumab, the observed clinical activity of nivolumab and nivolumab in combination with ipilimumab across multiple tumor types, and the rationale for immune checkpoint inhibition for patients with virus-associated tumors, it is felt that the overall benefits to subjects outweigh the potential risks in the neoadjuvant or metastatic/recurrent settings. Furthermore, the potential direct benefit to subjects who participate in this study of combined therapy with nivolumab plus relatlimab may result in a greater proportion of subjects with stabilization of disease, objective response, or increased duration of response than those observed with nivolumab monotherapy. It is also possible that combination therapy may reverse LAG-3–mediated T cell exhaustion and achieve responses in virus-associated tumors.

Additionally, because nivolumab and daratumumab have some overlapping toxicity profiles (i.e. infusion related reaction, diarrhea), it is possible that a higher incidence of adverse events may occur with the combination of 2 drugs. Based on the above assessment, the potential benefit of combining nivolumab and daratumumab appears to outweigh the potential risk. The overall risk/benefit assessment supports the evaluation of these combinations in this setting. Per Revised Protocol 06, enrollment and treatment in this cohort have been terminated.

Depending on the clinical activity, results could form the basis for regulatory filings. Additional combination arms based on a nivolumab backbone, and/or expansion of existing cohorts, may be added in future amendments.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

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

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

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

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

2.2 Institutional Review Board/Independent Ethics Committee

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

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

2.3 Informed Consent

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

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

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

Investigators must:

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

5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

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

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

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

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is an open label, multi-center, phase 1/2 trial to investigate the safety and efficacy of nivolumab as a single agent or in combination with either ipilimumab, BMS-986016 (relatlimab, anti-LAG3 antibody), or daratumumab in viral positive and viral negative tumor types of the following tumor types: Epstein Barr Virus (EBV) positive gastric cancer, EBV positive nasopharyngeal cancer (NPC), cervical cancer, HPV positive and negative squamous cell cancer of the head and neck (SCCHN), anogenital HPV associated cancers (vaginal, vulvar, anal canal, penile), and Polyomavirus positive Merkel cell cancer (pMCC).

On the basis of eligibility and tumor type, patients will be enrolled into the neoadjuvant or recurrent/metastatic monotherapy, or assigned or randomized into the recurrent/metastatic combination therapies cohorts (A, B, and D). Upon approval of Revised Protocol 05, all Metastatic Combination Cohorts A, B, and D will enroll patients concurrently, and enrollment will be closed for Combination Cohort C.

Combination B SCC of the cervix cohort is being expanded to add approximately 70 patients to further confirm the efficacy signal. Approximately 50 patients will be added to receive Combination B study drug as first-line treatment of their recurrent/metastatic disease if unfit or unsuitable to receive platinum based therapy; and approximately 20 patients will be added to receive study drug as second-line treatment of their recurrent/metastatic SCC of the cervix.

Treatments for each cohort are as follows:

Neoadjuvant cohort:

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

Metastatic Monotherapy Cohorts:

- 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.

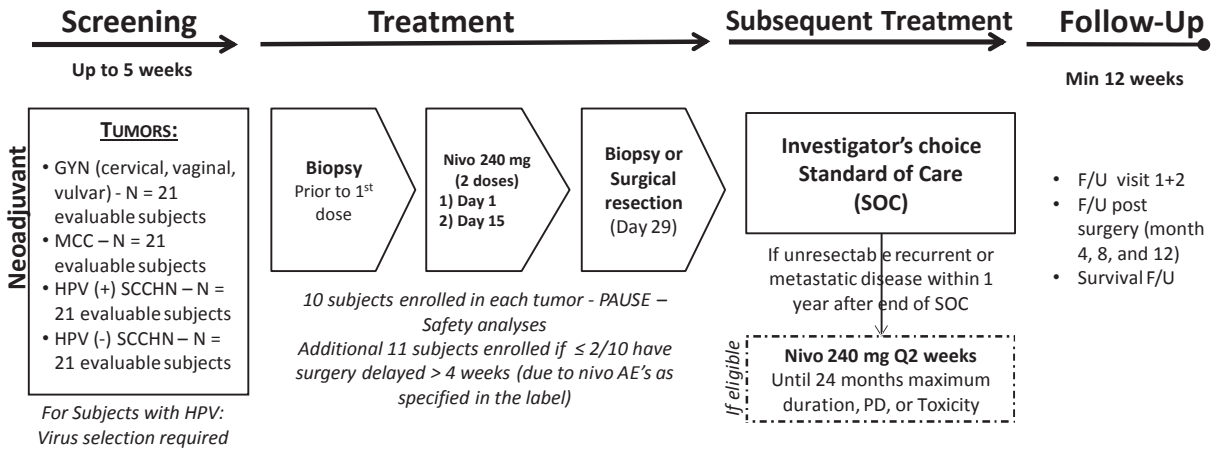
Metastatic Combination Cohorts (Combinations A, B, C, and D):

- 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 240 mg over 30 minutes every 2 weeks plus Anti-Lag3 (BMS-986016) 80 mg for a maximum of 24 months or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first.
- 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.[184]

The tumor types for the neoadjuvant cohort and the study design schematic for the neoadjuvant cohort (Figure 3.1-1) are presented below:

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

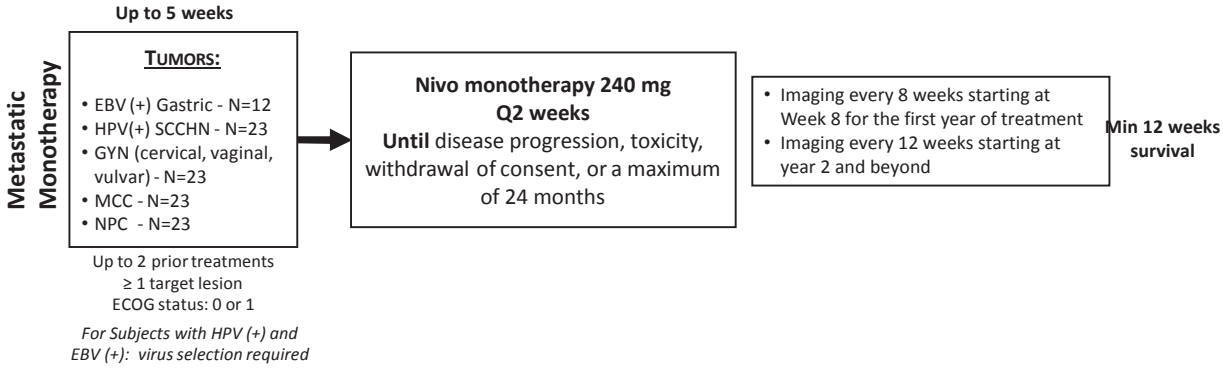
Figure 3.1-1: Study Design Schematic for the Neoadjuvant Cohort:



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 3.1-2 are presented below:

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

Figure 3.1-2: 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 3.1-3 and Figure 3.1-4.

- 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 3.1-3: Study Design Schematic for the Metastatic Cohort Combination Therapies A and B and Combo B SCC of the Cervix Expansion

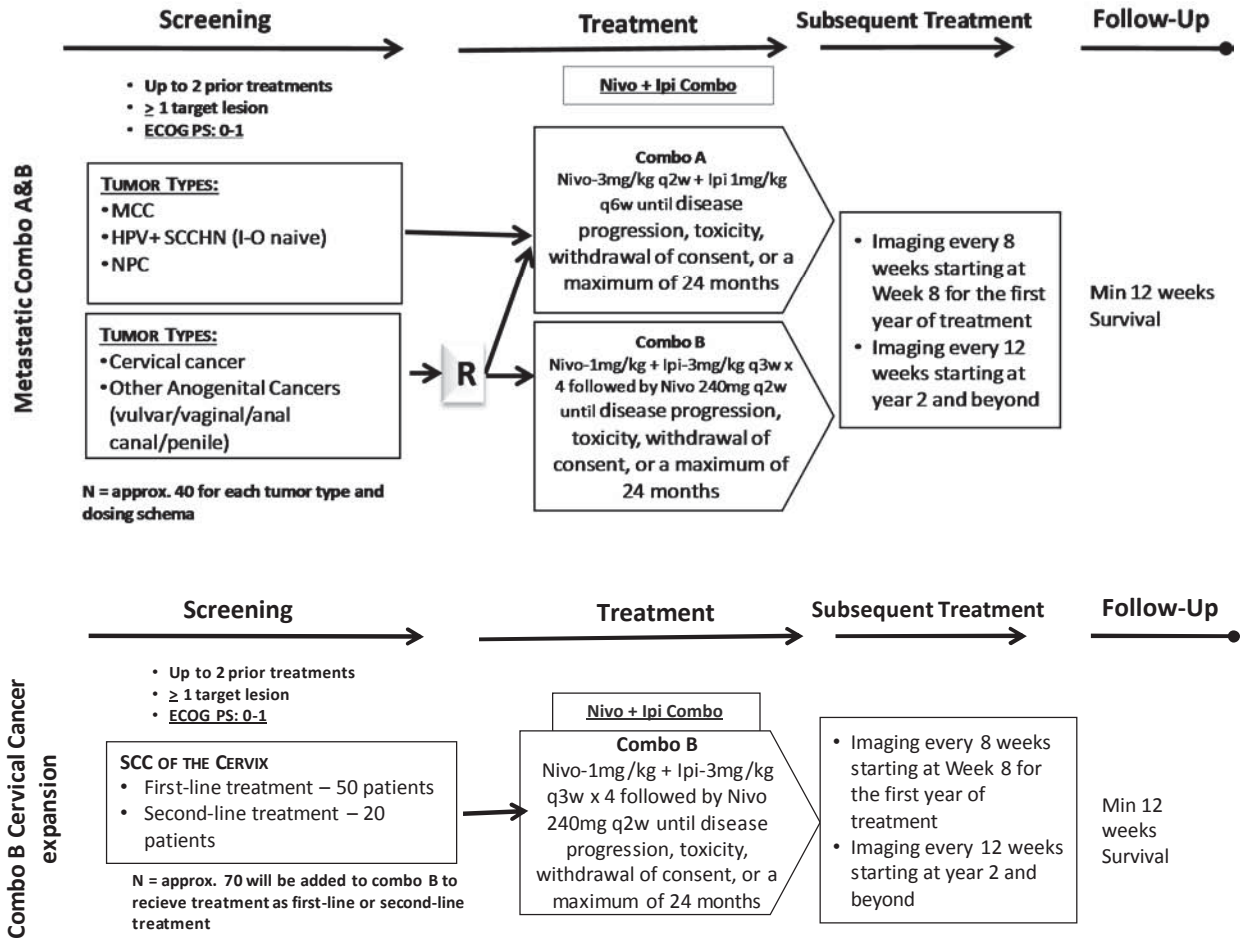
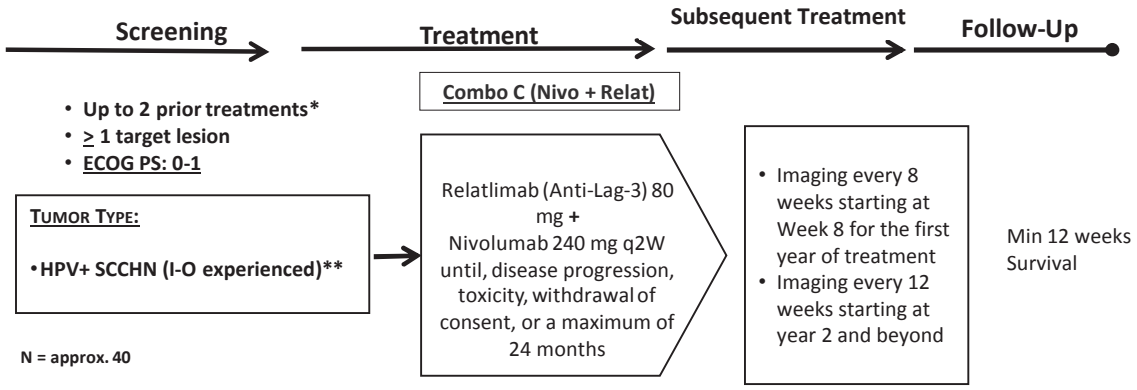


Figure 3.1-4: Study Design Schematic for the Metastatic Cohort Combination Arm C



*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 3.1-5: 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 3.1-5: Study Design Schematic for the Metastatic Cohort Combination Therapy D: Tumor Type SCCHN HPV positive, negative or unknown I-O naive.

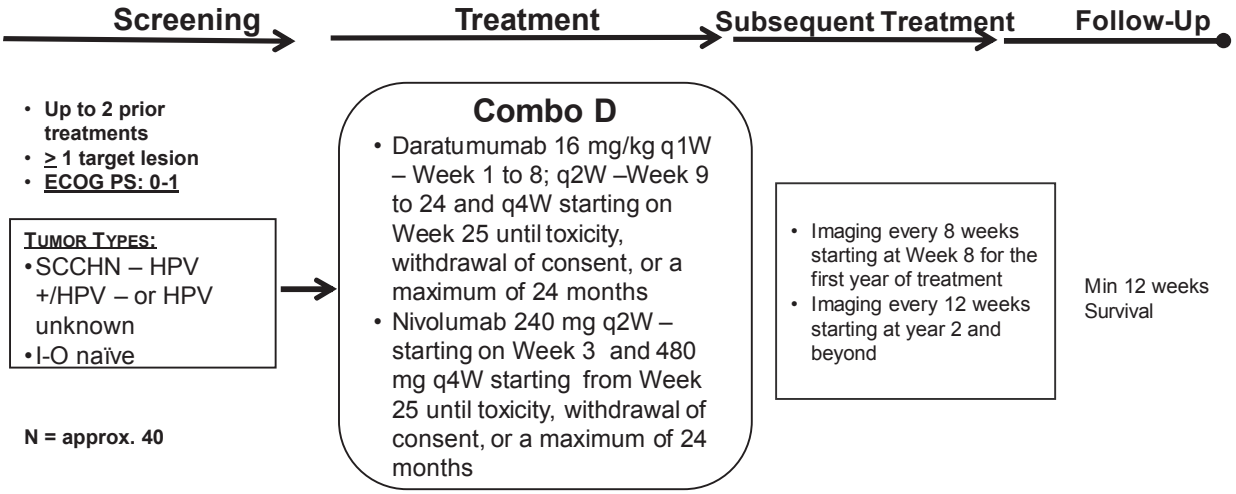


Table 3.1-1: Tumor Types by Cohort

Tumor Type	Cohort
• GYN (cervical, vaginal, vulvar) • MCC • HPV (+) SCCHN • HPV (-) SCCHN	Neoadjuvant Cohort
• EBV (+) Gastric • HPV(+) SCCHN • GYN (cervical, vaginal, vulvar) • MCC • NPC	Metastatic Monotherapy Cohort
• MCC • HPV+ SCCHN • NPC • Cervical cancer • Other anogenital cancers (vulvar/vaginal/anal/penile)	Metastatic Combination Cohort A
• Cervical cancer • Other Anogenital Cancers (vulvar/vaginal/anal canal/penile)	Metastatic Combination Cohort B
• HPV+ SCCHN (I-O experienced)	Metastatic Combination Cohort C
• HPV +/HPV – or unknown SCCHN (I-O naïve)	Metastatic Combination Cohort D

All subjects will complete 3 periods of the study: **Screening**, **Treatment**, **Follow-up**, including survival follow-up.

Duration of Study: The last visit will be defined as the latest survival visit included in the final analysis of OS (ie, the latest subject death, loss to follow up, or withdrawal of consent) for a tumor type within each cohort. Additional survival follow-up may continue for up to 5 years from the time of this analysis. The study will end once survival follow-up collection has concluded.

3.1.1 Viral Status Determination Prior to Entry

The study will enroll prospective subjects diagnosed with gastric cancer in the Metastatic Monotherapy Cohort. 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.

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.

The requirement for viral status for each tumor type by cohort is described below and in Table 3.1.1-1.

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. 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. Gastric subjects must be EBV positive, and SCCHN subjects must be HPV positive to enroll in this cohort. 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. Subjects will be treated with nivolumab 240 mg IV every 2 weeks until disease progression, unacceptable toxicity, or 24 months of treatment. Viral positivity will be tested retrospectively for MCC, NPC, and Gyn tumor types.

Metastatic combination therapy cohort - Combo A, Combo B, and Combo C: SCCHN subjects will be tested for HPV viral status prior to study drug assignment. Viral positivity will be

tested retrospectively for subjects with MCC, NPC, cervical cancer and anogenital HPV associated tumors (vaginal, vulvar, anal canal, and penile); confirmation of viral positivity will not require viral screening prior to study entry.

Approximately 40 subjects with each of the following tumor types will be enrolled into **Combo A and Combo B** into a 1:1 ratio: cervical cancer and anogenital HPV associated tumors (vaginal, vulvar, anal canal, and penile). Additionally, 40 subjects with each of the following tumor types will be enrolled into **Combo A:** MCC, HPV+ SCCHN, and NPC**.** With Revised Protocol 06, no new subjects will be randomized in the anogenital HPV associated tumors cohorts.

Approximately 40 subjects with SCCHN [prior anti-PD-1 or anti-PD-L1 antibody therapy] will be enrolled into **Combo C**. As of Revised Protocol 05, enrollment will close.

Combo D: Approximately 40 subjects with HPV positive, negative or unknown SCCHN [I-O naive] will be enrolled into **Combo D**. On 26-May-2018 enrollment was closed. Subsequently, the administration of daratumumab in combination with nivolumab was terminated.

Table 3.1.1-1: Testing for Viral Status Prior to Treatment

Cohort	Tumor Type	Viral status required prior to study drug (Testing)
Neoadjuvant	SCCHN	YES (p16 IHC)
	Gyn	NO
	MCC	NO
Metastatic Monotherapy	EBV+ Gastric	Yes In situ hybridization EBV RNA (EBER)
Metastatic Combination Therapy	HPV+/- SCCHN	YES (p16 IHC) (except for Combo D)
	Cervical and other HPV associated anogenital tumors (vulvar, vaginal, anal canal, penile)	NO
	MCC	NO
	NPC	NO

Gyn = cervical, vaginal, vulvar

HPV positive, negative or unknown, I-O naive SCCHN patients may participate in Combo D

All subjects (if clinically feasible) in each cohort will receive pre-treatment and on-treatment tumor biopsies. Primary analysis for the Neoadjuvant, Metastatic monotherapy, and Metastatic combination therapy cohorts will be conducted separately after a minimum of at least six months after the first treatment of the last patient for a tumor type enrolled in each cohort. All analyses will be performed independently by cohort and by tumor type.

3.1.2 Neoadjuvant Cohort

The primary objective of the neoadjuvant cohort is to evaluate the safety and tolerability of neoadjuvant nivolumab administration in subjects with select tumor types.

For subjects in the neoadjuvant cohort, radiographic tumor assessments will occur at the following time points (see Table 5.4.1-2).

- Screening to ensure the subject has resectable disease.
- Within 7 days and prior to the planned surgery or chemotherapy/radiation
- Post-surgery (SCCHN, MCC, Gyn) or post-chemotherapy/radiation (Gyn cohort when appropriate) at indicated Follow-Up visit times.

All subjects must have tumor amenable to pre-treatment biopsy (core needle); post-treatment biopsy will consist of the operative specimen or core needle biopsy for the cervical/vaginal/vulvar subjects.

Treatment within the **neoadjuvant** cohort will consist of:

- A pre-treatment, core-needle, biopsy for all subjects. (Four core-needle biopsies, as described in the laboratory manual, are suggested.)
- Two doses of nivolumab will be administered at 240 mg IV on Day 1 and Day 15
- Surgical resections (SCCHN, MCC, Gyn), or biopsy followed by chemotherapy/radiation (where appropriate for Gyn patients only) will occur on Day 29 (± 7 days). No other pre-surgical therapy is allowed.
- After neoadjuvant nivolumab treatment followed by surgical resection or biopsy, subjects will receive standard of care (observation, chemo and/or RT, according to physician's choice).
- Subjects who develop unresectable recurrent or metastatic disease within 1 year of surgery or chemotherapy/radiation completion may receive nivolumab at 240 mg IV every 2 weeks until 24 months of treatment, toxicity, or disease progression, if medically eligible, ie, meet eligibility criteria for metastatic cohort. Written approval from the sponsor's medical monitor is required for subject to be considered eligible. Nivolumab can be administered no earlier than 4 weeks after the last standard of care treatment.
- Enrollment for each tumor type in the neoadjuvant cohort will pause after the first 10 subjects are treated to assess safety and determine the number of subjects with chemotherapy/radiation or surgical delays beyond 4 weeks from the planned surgery date or planned start date for chemoradiation. If ≥ 3 of the first 10 subjects for a single tumor type have delays beyond 4 weeks from the planned surgery date or planned start date for chemoradiation due to a nivolumab immune-related adverse event(s) specified in the label in the region of treatment, that specific tumor cohort will close. The remaining tumor types in the neoadjuvant cohort will not close enrollment should a tumor type(s) close due to a delay in surgery due to nivolumab. If the first 8 patients treated for a single tumor type experience no delay, a pause in enrollment will not be required.

Details regarding the procedures associated with the neoadjuvant cohort can be found in Table 5.1-4. Details regarding procedures required for subjects who develop unresectable recurrent or metastatic disease within 1 year of surgery or chemotherapy/radiation and receive nivolumab can be found in Table 5.1-2.

3.1.3 Subjects in the Metastatic Monotherapy Cohort

For subjects without resectable disease, nivolumab will be administered at 240 mg every 2 weeks until toxicity, disease progression, withdrawal of consent, or 24 months of treatment, whichever comes first. For subjects in the metastatic cohort, radiographic tumor assessments by CT (preferred)/MRI will begin 8 weeks (± 1 week) after the start of therapy and will continue every 8 weeks (± 1 week) for the first year of treatment. CT (preferred)/MRI will continue every 12 weeks (± 2 weeks) for the second year and beyond. Tumor assessments will follow the above schedule until disease progression is documented. If the subject discontinues treatment prior to disease progression, tumor assessment will continue per protocol as described in Table 5.4.1-1. Disease progression is defined by investigator-assessed RECIST 1.1 criteria. The primary endpoint of this cohort is objective response rate (ORR) based on investigator assessments, using RECIST 1.1 criteria. Exploratory endpoints include complete and partial remission rates and durations based on radiological assessments. Individual tumors types will be analyzed separate from each other.

In all subjects for each tumor type, biopsy and submission of fresh tumor tissue, or submission of archived tumor tissue, is mandatory for all subjects. Subjects with accessible lesions where biopsy is deemed safe by the Investigator should undergo biopsy per protocol.

3.1.4 Subjects in the Metastatic Combination Cohorts

Upon approval of Revised Protocol 05, all Metastatic Combination Cohorts A, B, and D will enroll patients concurrently, and enrollment in Cohorts C will be closed.

Subjects with SCCHN, MCC or NPC enrolled in Combo A will be treated with nivolumab 3mg/kg every 2 weeks plus ipilimumab 1mg/kg every 6 weeks (Combo A) for a maximum of 24 months or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first.

Subjects with cervical cancer and anogenital HPV associated tumors (vulvar/vaginal/anal canal/penile) will be randomized (1:1) to treatment with either Combo A - nivolumab 3mg/kg every 2 weeks plus ipilimumab 1mg/kg every 6 weeks or Combo B - nivolumab 1mg/kg plus ipilimumab 3mg/kg every 3 weeks for 4 doses followed by nivolumab 240 mg every 2 weeks for a maximum of 24 months, or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first. With Revised Protocol 06, no new subjects will be randomized in the anogenital HPV associated tumors cohorts.

Subjects with HPV+ SCCHN with prior PD-1/PD-L1 treatment who are enrolled in Metastatic Combination Cohort (Combo C) will be treated with BMS-986016 (relatlimab) 80 mg plus nivolumab 240 mg q2w for a maximum of 24 months until disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first.

Subjects with HPV negative, positive, or unknown SCCHN who are I-O naive will be enrolled into the metastatic SCCHN Combo D (nivolumab plus daratumumab).

For subjects in the metastatic cohorts, radiographic tumor assessments by CT (preferred)/MRI will begin 8 weeks (± 1 week) after the start of therapy and will continue every 8 weeks (± 1 week) for the first year of treatment. CT (preferred)/MRI will continue every 12 weeks (± 2 weeks) for the second year and beyond. Tumor assessments will follow the above schedule until disease progression is documented. If the subject discontinues treatment prior to disease progression, tumor assessment will continue per protocol as described in Table 5.4.1-1. Study treatment will be administered until unacceptable toxicity, 24 months of treatment, or disease progression which is defined by investigator assessed RECIST 1.1 criteria. The primary endpoint of this cohort is objective response rate (ORR) based on investigator assessments, using RECIST 1.1 criteria. Exploratory endpoints include complete and partial remission rates and durations based on radiological assessments. Individual tumors types will be analyzed separate from each other.

In all subjects for each tumor type, biopsy and submission of fresh tumor tissue, or submission of archived tumor tissue, is mandatory for all subjects. Subjects with accessible lesions where biopsy is deemed safe by the Investigator should undergo biopsy per protocol.

3.2 Post Study Access to Therapy

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study drug for the maximum treatment duration specified in Section 3.1. Study drug will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS. BMS reserves the right to terminate access to BMS supplied study drug if any of the following occur: a) the marketing application is rejected by responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

3.3 Study Population

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

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

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

b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests, and other requirements of the study.

2. Target Population

a) Histopathologic confirmation of the following tumor types

i) Merkel Cell Carcinoma

(1) MCPyV status will be determined after enrollment

ii) EBV-Positive Gastric or Gastro-Esophageal junction carcinoma (including adenocarcinoma arising from the lower esophagus)

(1) For subjects in the metastatic monotherapy cohort with gastric tumor types, EBV positivity is defined by EBER in situ hybridization. Testing for EBV positivity will be performed prior to study drug assignment using the EBER1 DNP probe from Ventana in a properly certified lab. Samples interpreted as (+) if nuclear staining of any intensity above the background in tumor cells, provided the negative internal controls (adjacent normal tissue) are negative.

iii) Nasopharyngeal Carcinoma

(1) For subjects in the metastatic cohorts (monotherapy and combination) with nasopharyngeal carcinoma tumor types, EBV positivity is as defined by EBER in situ hybridization as specified above. Virus testing will be performed retrospectively only if results from prior accepted testing are not available.

iv) Squamous cell carcinoma of the cervix, vagina, vulva, penile or anal carcinoma

(1) For subjects in the neoadjuvant and metastatic (monotherapy and combination) cohorts with gynecological tumors, HPV positivity is defined by FDA approved tests (Cobas HPV Test; Digene Hybrid Capture 2 High-Risk HPV DNA Test; Cervista™ HPV HR and Genfind™ DNA Extraction Kit; Cervista™ HPV 16/18; APTIMA® HPV Assay) or other well validated commercially available tests (such as Ventana Inform HPV ISH test) comprising in situ hybridization, real-time PCR, or immunohistochemistry (IHC). High-risk HPV positivity includes the following subtypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68. Virus testing will be performed retrospectively only if results from prior accepted testing are not available.

v) Squamous cell carcinoma of the Head and Neck

(1) For subjects in the neoadjuvant and metastatic (monotherapy and combination) cohorts HPV positivity is defined by p16INK4a (p16) IHC employing clone E6H4 from MTM (Roche). The p16 IHC should be interpreted as positive if > 70% strong and diffuse nuclear and cytoplasmic staining is specific to tumor cells. Testing for p16 will be performed prior to study drug assignment using an appropriately validated test.

(2) HPV positive status can be obtained from either the primary tumor or metastatic lymph node.

(3) For subjects in the virus negative neoadjuvant cohort, HPV status should be documented as defined above. The p16 IHC should be interpreted as negative if < 70% strong and diffuse nuclear and cytoplasmic staining is specific to tumor cells.

b) For subjects in the neoadjuvant cohort

i) Squamous cell carcinoma of the Head and Neck for whom surgical resection is planned.

(1) Subjects must have newly diagnosed, histologically or cytologically confirmed squamous cell carcinoma or undifferentiated carcinoma of the oral cavity, pharynx and larynx. Subjects must have been determined to have resectable disease.

(2) Subjects must have tumor amenable to pre-treatment biopsy. Post-treatment biopsy will consist of the operative specimen. Excisional, incisional or core needle samples are acceptable. Fine needle aspirates are prohibited. See Section 5.6.9 for further details. The biopsy may have been obtained from the primary tumor or metastatic lymph node.

(3) Subjects must have:

a. T1 or greater primary lesions, AND

b. N1 or greater nodal disease,

ii) Squamous cell cervical, vulvar, or vaginal cancer

(1) Stage II to IVA cervical cancer who have planned surgical staging or chemotherapy/radiation treatment

(2) Stage II to IVA vulvar or vaginal cancer who have planned curative intent surgery or chemotherapy/radiation treatment

(3) Subjects must have tumor amenable to pre-treatment biopsy. Post-treatment biopsy will consist of the operative specimen. Excisional, incisional or core needle samples are acceptable. Fine needle aspirates are prohibited. See Section 5.6.9 for further details.

iii) Merkel Cell Carcinoma:

(1) Subjects must have tumor amenable to pre-treatment biopsy. Post-treatment biopsy will consist of the operative specimen. Excisional, incisional or core needle samples are acceptable. Fine needle aspirates are prohibited. See Section 5.6.9 for further details.

(2) Resectable disease of the following tumor types. Subjects must have one of the following Stages of disease

a. Stage II A-IIIB:

i. Primary tumor ≥ 2 cm, or

ii. Primary tumor of any size with palpable regional lymph node metastases or resectable in-transit metastases.

b. Stage IV disease with resectable limited metastasis

c. Local/Regional recurrent disease as defined as total burden ≥ 1 cm diameter with resectable disease defined by local or institutional surgical practices

c) For subjects in the metastatic cohorts (monotherapy and combination)

i) Progressive metastatic or recurrent disease treated with no more than 2 prior systemic therapies or regimens in the metastatic setting.

ii) Measurable disease by CT or MRI per RECIST 1.1 criteria (Appendix 3) (radiographic tumor assessment must be performed within 35 days prior to first dose).

iii) Subjects who actively refuse chemotherapy or other standard therapies for the treatment of unresectable or metastatic disease (advanced Stage III or Stage IV), despite being informed by the investigator about the treatment options may enroll. The subject's refusal must be thoroughly documented. The investigator will discuss each individual subject refusing chemotherapy with the sponsor's medical monitor or study director to confirm eligibility. Written approval from the sponsor's medical monitor is required for eligibility.

iv) The following tumor types

(1) Histologically confirmed Gastric or Gastro-Esophageal Junction Carcinoma (monotherapy cohort only) (including adenocarcinoma arising from the lower esophagus) who are EBV positive, as defined above.

(2) Histologically confirmed HPV positive (monotherapy and Cohorts A and C) or HPV negative or unknown **(Combo D only)**, as defined above, Squamous Cell Carcinoma of the Head and Neck (oral cavity, pharynx, larynx) not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy).

a. Histologically confirmed HPV positive or HPV negative or unknown -subjects naive to I-O

i. Subjects cannot have had prior exposure to IO therapies such as, but not limited to, other anti-CD38 therapies, anti-CTLA-4, anti-PD-1, combination of PD-1/CTLA-4 antibody, anti-PD-L1, anti-PD-L2, anti-KIR, anti-CD137, or anti-OX40 antibodies.

b. Histologically confirmed HPV positive subjects progressing while on or after therapy with anti-PD-1 or anti-PD-L1 antibody as most recent therapy, defined as Squamous Cell Carcinoma of the Head and Neck (oral cavity, pharynx, larynx) not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy). **(Combo C only)**

i. Cannot have had therapy discontinued due to serious and/or life-threatening anti-PD-1; anti-PD-L1 or anti-CTLA-4 antibody-related toxicity (e.g., dose-limiting toxicity in prior study) per Investigator's assessment in consultation with the BMS Medical Monitor.

ii. Last dose of antibody therapy must have been received ≥ 30 days of first dose of study medication

iii. Cannot have had prior exposure to other IOs, such as, but not limited to, anti-CTLA-4 anti-PD-L2, anti-KIR, anti-CD137, or anti OX40 antibodies.

iv. anti-PD-1/PD-L1/CTLA-4 does not need to be considered a 1 of the previous lines of therapy.

(3) Histologically confirmed cervical, vulvar, or vaginal cancer, as defined above. If the viral results are known prior to enrollment, and they are viral negative, the patient would be ineligible.

(4) Histologically confirmed Merkel Cell Carcinoma

a. Subjects with no prior systemic treatment will be allowed to enroll

(5) Histologically confirmed Nasopharyngeal Carcinoma, as defined above. If the viral results are known prior to enrollment, and they are viral negative, the patient would be ineligible.

a. HPV associated NPC is excluded in this cohort

b. Keratinizing squamous cell carcinoma (WHO Type I) is excluded in this cohort due to the low prevalence of EBV infection in this population.

(6) Histologically confirmed anal canal or penile carcinoma. If the viral results are known prior to enrollment, and they are viral negative, the patient would be ineligible. (Metastatic Combination Cohorts only).

v) Recurrent/metastatic SCC of the cervix subjects not amenable to curative treatment with surgery and/or radiation therapy who are unsuitable for platinum-based therapy (ie, creatinine clearance of less than 60 mL/min or have experienced toxicity from prior platinum-based therapy) may enroll in the cervical cancer Combination B expansion cohort.

d) For both neoadjuvant and metastatic (monotherapy and combination)cohorts

i) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

ii) Men and women of age 18 or older.

iii) Subject willing to comply to provide tumor tissue for PD-L1 expression analysis and other biomarker correlative studies. See Section 5.6.9 for further details. Biopsy should be excisional, incisional or core needle. Fine needle aspirates are prohibited.

e) All baseline laboratory requirements will be assessed and should be obtained within -14 days of first dose (unless otherwise specified in Table 5.1-1). Screening laboratory values must meet the following criteria:

i) WBCs ≥ 2000/µL

ii) Neutrophils ≥ 1500/µL

iii) Platelets ≥ 100 x 10^3/µL

iv) Hemoglobin ≥ 9.0 g/dL

v) Creatinine Serum creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥ 40 mL/minute (using Cockcroft/Gault formula)

vi) AST ≤ 3 x ULN

vii) ALT ≤ 3 x ULN

viii) Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome who can have total bilirubin < 3.0 mg/dL)

ix) Cardiac Troponin T (cTnT) or I (cTnI) ≤ 2 × institutional ULN. Subjects with cTnT or cTnI levels between > 1 to 2 × ULN will be permitted if repeat levels within 24 hours are ≤ 1 ULN **(Combo C only)**

(1) If cTnT or cTnI levels are >1 ULN at 24 hours, the subject may undergo a cardiac evaluation and be considered for treatment, following a discussion with the BMS Medical Monitor or designee.

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

g) LVEF assessment with documented LVEF ≥ 50% by either TTE or MUGA (TTE preferred test) within 6 months from first study drug administration **(Combo C only)**

3. Age and Reproductive Status

a) Men and women, ages ≥ 18 years of age

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

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception from the time of enrollment for the duration of treatment with study drug(s) plus approximately 5 half-lives of study drug(s) plus 30 days (duration of ovulatory cycle) for a total of 5 months post treatment completion.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) plus approximately 5 half-lives of study drug(s) plus 90 days (duration of sperm turnover) for a total of 7 months post-treatment completion.

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

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

At a minimum, subjects must agree to the use one highly effective method of contraception as listed in Appendix 4.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Active brain metastases or leptomeningeal metastases. Subjects with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for at least 4 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (>10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.

2. Medical History and Concurrent Diseases

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

b) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured or successfully resected, such as basal or squamous cell skin cancer, superficial bladder cancer, or gastric cancer, or carcinoma in situ of the prostate, cervix, or breast.

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

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

e) Subjects with primary tumor or nodal metastasis fixed to the carotid artery, skull base or cervical spine.

f) Prior therapy with experimental anti-tumor vaccines; any T cell co-stimulation or checkpoint pathways, such as anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, including ipilimumab; or other medicines specifically targeting T cell co-stimulation or checkpoint pathways is also prohibited. **Exception**: **Combo C** SCCHN prior anti-PD-1/anti-PD-L1/anti-CTLA-4 exposure tumor types.

g) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of study drug. Subjects with toxicities attributed to prior anti-cancer therapy which are not expected to resolve and result in long lasting sequelae, such as neuropathy after platinum based therapy, are permitted to enroll.

h) Treatment with any chemotherapy, radiation therapy, biologics for cancer, or investigational therapy within 28 days of first administration of study treatment (subjects with prior cytotoxic or investigational products < 4 weeks prior to treatment might be eligible after discussion between investigator and sponsor, if toxicities from the prior treatment have been resolved to Grade 1 (NCI CTCAE version 4).

i) active neurological disease or confirmed history of encephalitis, meningitis, or uncontrolled seizures in the year prior to informed consent for **Combo C only**

j) Uncontrolled or significant cardiovascular disease including, but not limited to, any of the following (**Combo C only)**:

   i) Myocardial infarction (MI) or stroke/transient ischemic attack (TIA) within the 6 months prior to consent

   ii) Uncontrolled angina within the 3 months prior to consent

iii) Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes)

iv) QTc prolongation > 480 msec

v) History of other clinically significant cardiovascular disease (i.e., cardiomyopathy, congestive heart failure with New York Heart Association [NYHA] functional classification III-IV, pericarditis, significant pericardial effusion, significant coronary stent occlusion, deep venous thrombosis, etc.)

vi) Cardiovascular disease-related requirement for daily supplemental oxygen

vii) History of two or more MIs OR two or more coronary revascularization procedures

viii) Subjects with history of myocarditis, regardless of etiology

k) For **Combo D** only

i) Known history of stage 3 or 4 chronic obstructive pulmonary disease (COPD).

ii) Known moderate or severe persistent asthma within the past 2 years, or uncontrolled asthma of any classification. Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed to participate in the study.

iii) Screening 12-lead ECG showing a baseline QT interval as corrected (QTc) >480 msec

l) Treatment with botanical preparations (eg herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to randomization/treatment. Refer to Section 3.4.1 for prohibited therapies.

m) For the expansion cohort for subjects with SCC of the cervix and for subjects eligible to receive study drug (Combo B) as first-line treatment for their recurrent/metastatic disease, must not have been treated previously with chemotherapy except when used concurrently with radiation therapy.

3. Physical and Laboratory Test Findings

a) Any positive test result for hepatitis B virus (e.g. surface antigen [HBV sAg, Australia antigen] positive) or hepatitis C virus (Hepatic C antibody [anti-HCV] positive, except if HCV-RNA negative.

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

4. Allergies and Adverse Drug Reaction

a) History of allergy to study drug components.

b) History of severe hypersensitivity reaction to any monoclonal antibody.

5. Sex and Reproductive Status

a) WOCBP who are pregnant or breastfeeding

b) Women with a positive pregnancy test at enrollment or prior to administration of study drug

6. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated

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

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

3.3.3 Women of Childbearing Potential

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

See Appendix 4 for more details.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study:

- Immunosuppressive agents (except to treat a drug-related adverse event)
- Immunosuppressive doses of systemic corticosteroids (> 10 mg daily prednisone equivalent), except as stated in Section 3.4.2 or to treat a drug-related adverse event.
- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, radiation therapy except for palliative radiation therapy described in Section 3.4.2 or standard or investigational agents for treatment of cancer).
- Any botanical preparation (eg herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally.
- LAG-3 targeting agents.

Supportive care for disease-related symptoms may be offered to all subjects on the trial.

3.4.1.1 Restricted Treatments

Restricted therapies are not prohibited but are not recommended; consult BMS medical monitor/designee if the following are clearly medically indicated:

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

3.4.2 Permitted Therapy

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

Oral Prophylaxis for herpes zoster reactivation is recommended during the Treatment Phase. Initiate antiviral prophylaxis within 1 week after starting daratumumab, and continue for 3 months following treatment discontinuation (**Combo D only**).

Subjects must receive pre-infusion and post-infusion medications with each dose of daratumumab, per the daratumumab Investigators Brochure; additional details are provided in Section 4.7.7.

Palliative (limited-field) radiation therapy and palliative surgical resection are permitted if the following criteria are met:

- The subject is considered to have progressed at the time of palliative therapy and meets criteria to continue with treatment beyond progression (Section 4.7.8).
- The case is discussed with the BMS medical monitor.
- Palliative therapy must be clearly documented as such in the study record.

The potential for overlapping toxicities with radiotherapy and nivolumab alone or in combination with either ipilimumab, BMS-986016 (relatlimab), or daratumumab currently is not known. Therefore, palliative radiotherapy is not recommended while receiving study drug. If palliative radiotherapy is required, then study drug should be withheld for at least 1 week before, during and 1 week after radiation. Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs considered related to radiotherapy should resolve to Grade ≤ 1 prior to resuming study drug.

Only non-target lesions included in the planned radiation field or CNS lesions may receive palliative radiotherapy. Details of palliative radiotherapy should be documented in the source records and electronic case report form (eCRF). Details in the source records should include: dates of treatment, anatomical site, dose administered and fractionation schedule, and adverse events. Subjects receiving limited field palliative radiation therapy will be considered to have unequivocal

progression of disease in the non-target lesion. Symptoms requiring palliative radiotherapy should be evaluated for objective evidence of disease progression. Administration of additional study drug to subjects who received limited field palliative radiation should follow guidelines specified in Section 4.7.8 Treatment Beyond Disease Progression.

3.4.3 Surgical Resection Following Initial Response

Investigators may choose to resect solitary lesions in subjects with residual disease and render the subject free of macroscopic disease. Subjects treated in this study may have lesions surgically resected only following consultation with the Medical Monitor and following the Week 25 tumor imaging assessments. If additional tumor shrinkage is noted compared to the tumor imaging assessments at Week 17, it is highly encouraged that surgical resection be delayed until subsequent scans fail to demonstrate further shrinkage. Subjects with a confirmed PR who go on to have surgical resection of remaining disease will be considered a PR. Subjects with SD who go on to have surgical resection of remaining disease will be considered a SD. Subjects may continue treatment after surgery. Tumor tissue of any resected solitary lesion should be submitted to BMS (see Section 5.6.9). Detailed instructions of the obtaining, processing, labeling, handling, storage and shipment of these specimens will be provided in a separate Procedure Manual at the time of study initiation.

3.4.4 Other Restrictions and Precautions

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

It is the local imaging facility's responsibility to determine, based on subject attributes (eg, allergy history, diabetic history and renal status), the appropriate imaging modality and contrast regimen for each subject. Imaging contraindications and contrast risks should be considered in this assessment. Subjects with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate. Specific to MRI, subjects with severe renal insufficiency (ie, estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this subject population. In addition, subjects are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc.

The ultimate decision to perform MRI in an individual subject in this study rests with the site radiologist, the investigator and the standard set by the local Ethics Committee.

Blood typing (**Combo D only**).

Blood Type, Rh, and IAT should be done before the first dose of daratumumab. Subject RBC phenotyping (standard or extended) is an alternative option to the IAT test, if locally required. Either method must be completed prior to first daratumumab infusion. Daratumumab interferes with the Indirect Antiglobulin Test (IAT), which is a routine pre-transfusion test performed to identify a patient's antibodies to minor antigens so that suitable donor blood can be given for

transfusion. Daratumumab does not interfere with ABO/RhD typing. CD38 is expressed at very low levels on erythrocytes. Daratumumab binds to the CD38 on erythrocytes, which results in a positive IAT (Indirect Coombs Test). This positive result masks the detection of antibodies to minor antigens and may prevent or delay blood banks from issuing donor blood for transfusion. This effect occurs during daratumumab treatment and for up to 6 months after treatment ends. Subjects will receive a patient identification wallet card for the study that includes the blood profile (ABO, Rh, and IAT or phenotyping) determined before the first infusion of daratumumab along with information on the IAT interference for healthcare providers/blood banks. Subjects are to carry this card throughout the treatment period and for at least 6 months after treatment ends. Blood banks can eliminate the daratumumab IAT interference with IAT by treating reagent RBCs with dithiothreitol (DTT).[185]

Possible methods for blood banks to provide safe RBCs for transfusion to subjects receiving daratumumab include:

a) Providing ABO/RhD compatible, phenotypically (standard or extended phenotyping) or genotypically matched units

b) Providing ABO/RhD compatible, K-negative units after ruling out or identifying alloantibodies using DTT-treated reagent RBCs

Uncrossmatched, ABO/RhD compatible RBC units should be administered if transfusion is needed emergently as per local blood bank practice. Despite daratumumab binding to CD38 on erythrocytes, no indication of clinical significant hemolysis has been observed in daratumumab studies.

3.5 Discontinuation of Subjects following any Treatment with Study Drug

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

- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- For discontinuation criteria related to nivolumab-and/or ipilimumab, BMS-986016 (relatlimab) or daratumumab-related adverse events, please refer to Section 4.7.6.

Follow-up begins when the decision to discontinue a subject from study therapy is made (no further treatment with study therapy).

- Subjects will have two follow-up visits for safety. Follow-up visit 1, 35 days from the last dose or from the date decision is made to discontinue subject from the study (only

applicable for early treatment discontinuation) (± 7 days) and follow-up visit 2 80 days (± 7 days) after follow-up visit 1. After follow-up visit 2, subjects will be followed every 3 months for ongoing drug-related adverse events until resolved, return to baseline or deemed irreversible, or until lost to follow-up, withdrawal of study consent, or start of a subsequent anti-cancer therapy.

- Subjects who discontinue study therapy for reasons other than disease progression will continue to have radiographic assessments as per defined schedule until disease progression, lost to follow-up, or withdrawal of study consent.
- PK and immunogenicity samples will be collected at the first 2 follow-up visits.

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. Please contact the Sponsor or designee within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

All subjects who discontinue study drug should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

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

This study will end when analysis of the primary endpoint is complete. Additional survival analysis may be conducted for up to 5 years beyond analysis of the primary endpoint.

3.6 Post Study Drug Study Follow-up

In this study, overall survival is a key endpoint of the study. Post study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

BMS may request that survival data be collected on all treated/randomized subjects outside of the protocol defined window (refer to Section 5.1). At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contacts or is lost to follow-up.

3.6.1 Withdrawal of Consent

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

authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-up

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

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 STUDY DRUG

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

- All products, active or placebo, being tested or used as a comparator in a clinical trial.
- Study required premedication, and
- Other drugs administered as part of the study that are critical to claims of efficacy (eg, background therapy, rescue medications)
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection.

Table 4.-1: Product Description: Treatment Period

Product Description / Class and Dosage Form	Potency	IP/ Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
BMS-936558-01 (Nivolumab) Solution for Injection[a]	100 mg (10 mg/mL)	IP	Open Label	Various packaging configurations	Refer to the label on container and/or pharmacy manual
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	IP	Open Label	Various packaging configurations	Refer to the label on container and/or pharmacy manual
BMS-986016-01[b] Injection	80 or 100 mg (10 mg/mL)	IP	Open Label	Various packaging configurations	Refer to the label on container and/or pharmacy manual
Daratumumab Injection[c]	100 mg (20 mg/mL) and/or 400 mg (20 mg/mL)	IP	Open Label	Various packaging configurations	Refer to the label on container and/or pharmacy manual

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

[b] Designated as BMS-986016 or relatlimab in the protocol

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

4.1 Investigational Product

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

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

In this protocol, the investigational product is: nivolumab for the neoadjuvant and metastatic monotherapy cohorts.

For the metastatic combination therapy cohort, the investigational products are nivolumab and ipilimumab for combination therapy Combo A and B, nivolumab and BMS-986016 (relatlimab) for combination therapy Combo C, and nivolumab and daratumumab for combination therapy Combo D.

4.2 Non-investigational Product

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

Standard of care treatment will be procured by the investigator.

4.3 Storage and Dispensing

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

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

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

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

Please refer to the current version of the Investigator Brochure and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information for nivolumab, ipilimumab, BMS-986016 (relatlimab), and daratumumab.

Nivolumab is to be administered as an IV infusion. Nivolumab infusion must be promptly followed by a flush of diluent to clear the line. For Combo A and B, ipilimumab is to be administered as an approximately 30-minute IV infusion. At the end of the infusion, flush the line with a sufficient quantity of normal saline or 5% dextrose solution. When both study drugs (nivolumab and ipilimumab) are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a flush of diluent to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be ipilimumab, and will start after the infusion line has been flushed, filters changed and patient has been observed to ensure no infusion reaction has occurred. The time in between infusions is expected to be approximately 30 minutes after completion of the nivolumab infusion.

For Combo C, where both nivolumab and BMS-986016 (relatlimab) are administered, nivolumab will be administered first, as an approximately 30-minute IV infusion. At the end of the infusion, flush the line with a sufficient quantity of normal saline or 5% dextrose solution. When both study drugs (nivolumab and BMS-986016) are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the BMS-986016 infusion. The second infusion will be BMS-986016 and will start after the infusion line has been flushed, filters changed and patient has been observed to ensure no infusion reaction has occurred. BMS-986016 infusion will start within 60 minutes after completion of the nivolumab infusion. Further details regarding preparation and administration will be provided separately in site/pharmacy training materials.

For Combo D, daratumumab injection for IV infusion is considered IMP for this study. Daratumumab is an immunoglobulin G1 kappa human monoclonal antibody against CD38 antigen, produced in a mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology. The molecular weight of daratumumab is approximately 148 kDa. Daratumumab is supplied as a colorless to pale yellow preservative-free solution for intravenous infusion in single-dose vials. Starting on week 3, when both nivolumab and daratumumab are administered, nivolumab will be administered first followed by daratumumab by at least 30 minutes after completion of nivolumab infusion.

Pre-infusion medications should be administered before starting daratumumab infusions. On days when nivolumab and daratumumab are both administered, daratumumab pre-medications may be administered before the start of the nivolumab infusion. Post-infusion medications should be administered upon completion of the daratumumab infusion.

Therefore, the sequence of administration on days when nivolumab and daratumumab are administered should be as follows:

- Daratumumab pre-infusion medications
- Nivolumab infusion
- Daratumumab infusion
- Daratumumab post-infusion medications

Daratumumab Infusion solution will be prepared as a 1,000-mL (first dose) or 500-mL (second and subsequent doses) dilution of daratumumab in sterile, pyrogen-free 0.9% NaCl. Preparation of infusion bags should be done on the day of the planned infusion. Daratumumab must be administered as an IV infusion given through a well-functioning IV catheter by using an infusion pump. The study drug must be filtered by using an inline filter (0.2 μM) during the infusion. The infusion rates for the first, second, and subsequent daratumumab infusions should closely follow the specifications of the currently approved (USPI)/pharmacy reference manual.[184] Pharmacy manuals with detailed descriptions for preparation and administration of daratumumab will be supplied to each pharmacy and site.

Because of this high risk of infusion related reactions daratumumab infusions will be administered per the Investigator's Brochure by a healthcare professional, with immediate access to emergency equipment and appropriate medical support to manage infusion reactions if they occur, and all subjects will receive pre-infusion and post-infusion medication per the descriptions in Section 4.7.7 of the protocol.

Before administration the drug product should be stored and prepared as per the instructions in pharmacy manual. Daratumumab (dose) will be administered as an IV infusion. Each subject's dose will be calculated based on the subject's weight at Cycle 1 Day 1 rounded to the nearest kilogram. The dose of daratumumab to be administered to a subject will be calculated by multiplying the subject's weight (kg) by 16 mg/kg. The dose of daratumumab will remain constant throughout the study, unless the subject's weight changes more than 10% from Cycle 1 Day 1. All infusions will be planned as outpatient visits. Subjects will receive pre-infusion medications and post-infusion medications as detailed in the protocol (Section 4.7.7).

The infusion start and stop time will be recorded in the CRF. If the infusion is stopped mid-session for any reason, the stop/start time must be recorded together with an explanation.

The dilution volumes, initial infusion rates, and increment for the first, second, and subsequent doses are provided in Table 4.3-1. The infusion rates for the first, second, and subsequent daratumumab infusions should closely follow the specifications of the currently approved (USPI)/pharmacy reference manual. The maximum infusion rate for all infusions is 200 mL/hour. Additional details for administration times and rates, as well as pre-infusion medications, will be provided in the pharmacy manual.

Table 4.3-1: Daratumumab Infusion Rates

	Dilution Volume	Initial Infusion Rate (first hour)	Increments of Infusion Rate	Maximum Infusion Rate
First infusion	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second infusion[a]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusions[b]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

[a] Modified rates should only be used if the first infusion of daratumumab was well tolerated as defined by an absence of > Grade 1 infusion-related reactions during the first 3 hours.

[b] Modified rates should only be used if the first 2 infusions of daratumumab were well tolerated as defined by an absence of > Grade 1 infusion-related reactions during a final infusion rate of ≥ 100 mL/hr.

For subjects with a higher risk of respiratory complications (eg, subjects with mild asthma or subjects with stage 2 COPD who have a known FEV1 <80% at screening or developed FEV1 <80% during the study without any medical history) the following post infusion medications should be considered:

- Antihistamine (diphenhydramine or equivalent)
- Leukotriene inhibitor (montelukast or equivalent)
- Short-acting β2 adrenergic receptor agonist such as salbutamol aerosol
- Control medications for lung disease (eg, inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for subjects with COPD)

In addition, these at-risk subjects may be hospitalized for monitoring for up to 2 nights after an infusion. If subjects are hospitalized, then their spirometry test (FEV1) should be performed before discharge. If these subjects are not hospitalized, then a follow up telephone call should be made to monitor their condition within 48 hours after all infusions. If no infusion-related reaction has occurred, the follow-up telephone call 48 hours after the infusion is not required. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event. Investigators may prescribe bronchodilators, H1-antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after subjects are released from the hospital/clinic. If an at-risk subject experiences no major infusion-related reactions, then these post-infusion medications may be waived after 4 doses at the investigator's discretion.

Any post-infusion medication will be administered after the infusion has completed.

4.4 Method of Assigning Subject Identification

The subject number will be assigned through an interactive response technology (IRT) system once the subject has signed the informed consent form and is registered. Every subject that signs

the informed consent form must be assigned a subject number in IRT. Specific instructions for using IRT will be provided to the investigational site in a separate document.

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

- Confirm that informed consent was obtained
- Date of birth
- Gender at birth
- Subject Identification Method
- Which cohort the subject will be enrolled (Neoadjuvant or Metastatic)
- Tumor type for subject

Once enrolled subjects have met all eligibility criteria the IRT must be contacted again for treatment assignment, drug vial (nivolumab, nivolumab plus ipilimumab, nivolumab plus BMS-986016, nivolumab plus daratumumab), and to confirm that the Cohort/Tumor Type that the subject would qualify for is not closed for the study.

Upon approval of Revised Protocol 05, enrollment will be concurrent for metastatic/recurrent combinations A, B, and D, and enrollment in Cohorts C will be closed.

The following information is required for drug vial assignment:

- Subject number
- Date of birth
- Confirmation of viral status (for Neoadjuvant Cohort: SCCHN subjects, and Metastatic Cohorts: Gastric and SCCHN subjects, see Table 3.1.1-1)

Confirmation of viral status will be required prior to study drug assignment for EBV gastric cancer and HPV SCCHN tumor types in the metastatic cohorts. Confirmation of viral status will also be required prior to study drug assignment for SCCHN subjects enrolled in the neoadjuvant cohort. Subjects with gastric cancer or SCCHN tumor types will provide consent, via pre-screening informed consent, for determination of viral status.

Results will be entered into the IRT by sites at the screening visit, or results will be transferred from the central laboratory to the IRT via an automated feed. After positive test result confirmation, consent for demographic and further eligibility will be collected. If the viral status result cannot be confirmed for EBV gastric cancer and HPV SCCHN tumor types in the metastatic cohorts, and HPV SCCHN tumor types in the neoadjuvant cohort, those subjects will not be able to enter the treatment phase of the study and will be considered enrollment failures.

If the Cohort/Tumor Type that the subject would qualify for has already met the maximum number of subjects, the subject will not be able to enter the treatment phase of the study and will be considered an enrollment failure.

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

4.5 Selection and Timing of Dose for Each Subject

Table 4.5-1: Study Drug Dosing

Cohort	Drug	Dose	Frequency of administration	Route of administration	Duration
Neoadjuvant	Nivolumab	240 mg flat dose	Day 1, Day 15	30 minute Intravenous (IV) infusion	Two doses
Metastatic Monotherapy	Nivolumab	240 mg flat dose	every 2 weeks	30 minute Intravenous (IV) infusion	Maximum of 24 months or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first
Neoadjuvant Subjects Treated with Study Drug Post-Standard of Care	Nivolumab	240 mg flat dose	every 2 weeks	30 minute Intravenous (IV) infusion	Maximum of 24 months or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first
Metastatic Combination Cohort Combo A	Nivolumab	3 mg/kg	every 2weeks	30 minute Intravenous (IV) infusion	Maximum of 24 months or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first
	Ipilimumab	1 mg/kg	every 6week	30 minute Intravenous (IV) infusion	
Metastatic Combination Cohort Combo B (Cervical cancer and anogenital HPV associated tumors only)	Nivolumab	1 mg/kg	every 3 weeks for 4 doses	30 minute Intravenous (IV) infusion	Maximum of 24 months or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first
		240 mg flat dose	then every 2 weeks		
	Ipilimumab	3 mg/kg	every 3weeks for 4 doses	30 minute Intravenous (IV) infusion	
Metastatic Combination Cohort Combo C	Nivolumab	240 mg flat dose	every 4weeks (every 2 weeks)	30 minute Intravenous (IV) infusion	Maximum of 24 months or until disease progression, unacceptable toxicity, or withdrawal of
	BMS-986016 (relatlimab)	(80 mg)	(every 2 weeks)	60 minute Intravenous (IV) infusion	

Table 4.5-1: Study Drug Dosing

Cohort	Drug	Dose	Frequency of administration	Route of administration	Duration
					consent, whichever comes first discontinuation from study
Metastatic Combination Cohort Combo D	Nivolumab	240 mg flat dose	Every 2 weeks starting at Week 3	30 minute Intravenous (IV) infusion	Maximum of 24 months or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first
		480 mg flat dose	then every 4 weeks starting at Week 25		
		Nivolumab will be administered before daratumumab when both study drugs are administered on the same day.			
	Daratumumab	16 mg/kg	Every week (Wks 1-8) then every 2 weeks (Wks 9-24), then every 4 weeks starting at Week 25	Intravenous (IV) infusion See Section 4.3	

Neoadjuvant Cohort subjects will receive two doses of nivolumab administered at 240 mg IV on Day 1 and on Day 15 (+1 week). A delay of the 2nd dose of nivolumab is acceptable for up to 1 week (up to Day 22); however, the 2nd dose of nivolumab should not be administered after Day 22 in order to avoid postponing surgery/biopsy beyond Day 29 and subsequent standard of care.

Metastatic Monotherapy Cohort subjects will receive treatment with nivolumab on Day 1 of a treatment cycle every 2 weeks (14 days).

Metastatic Combination Cohort subjects will be assigned to receive one of the following dosing schema (starting Day 1) based on tumor type and randomization:

- Combo A: nivolumab 3 mg/kg q2 weeks + ipilimumab 1 mg/kg q6 weeks: ± 1 week (no less than 5 weeks between doses)
- Combo B: nivolumab 1 mg/kg + ipilimumab 3 mg/kg, q3 weeks x4, followed by nivolumab 240 mg q2 weeks: +/-3 days (no less than 18 days between doses)
- Combo C: nivolumab 240 mg + BMS-986016 160 mg, q4 weeks: ± 2 days.
- Combo D: daratumumab q1 week x8, q2 weeks (Weeks 9-24); q4 weeks starting at Week 25 + nivolumab 240 mg q2 weeks (starting at Week 3); 480 mg q4 weeks starting at Week 25. Nivolumab will be administered before daratumumab on study days when both drugs are administered on the same day. Dosing windows for daratumumab are as follows:

Weeks 1-8: -1 and +3 days; Weeks 9-24: ± 1 week; Week 25+: up to 14 days delayed. For nivolumab, no less than 12 days between dosing is allowed.

Subjects who complete the neoadjuvant portion of the study and complete standard of care treatment post-surgery/biopsy who develop unresectable recurrent or metastatic disease within 1 year of surgical resection, or completion of standard of care (whichever is later), may receive treatment with nivolumab monotherapy, if eligible. Eligibility assessments are detailed in Table 5.1-5.

Please refer to the Pharmacy Manual for more detail. There are no pre-medications recommended on the first cycle, **except for Combo D**. All subjects in Combo D will receive pre-infusion and post-infusion medication per the descriptions in Section 4.7.7 of the protocol. If an acute infusion reaction is noted, subjects should be managed according to Section 4.7.7.

Dosing modifications:

There will be no dose modifications allowed for the management of toxicities of individual subjects.

Dosing window:

When nivolumab is administered alone and in combination with BMS-986016 (relatlimab), subjects may be dosed no less than 12 days between doses during Q2 week dosing. For ipilimumab (Combo A), subjects may be dosed within a ± 1-week window and no less than 5 weeks from the previous dose. For subjects in Combo B, when nivolumab is administered in combination with ipilimumab, subjects may be dosed within a ± 3-day window and no less than 18 days from the previous dose. A dose given more than 3 days after the intended dose date will be considered a delay, except for subjects receiving ipilimumab in Combo A. A maximum delay of 6 weeks between doses is allowed, except for subjects in the Neoadjuvant cohort.

Daratumumab will be administered at a dose of 16 mg/kg as an IV infusion every week for the 8 doses (-1 and +3 days window is allowed), every two weeks from weeks 9 to 24 (can be delayed up to 1 week) and every four weeks from weeks 25 onwards (can be delayed up to 14 days) until toxicity or disease progression.

4.6 Blinding/Unblinding

Not applicable.

4.7 Treatment Compliance

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

4.7.1 Premedications

Antiemetic medications should not be routinely administered prior to dosing of nivolumab, ipilimumab, and BMS-986016 (relatlimab). See Section 4.7.7 for subsequent premedication recommendations following a study drug-related infusion reaction.

See Section 4.3 for post-infusion medications for subjects at higher risk of respiratory complications (**Combo D only**). All subjects in Combo D will receive pre-infusion and post-infusion medication per the descriptions in Section 4.7.7 of the protocol.

4.7.2 Management Algorithms for Immuno-oncology Agents

Immuno-oncology (I-O) agents are associated with adverse events that can differ in severity and duration than adverse events caused by other therapeutic classes. Nivolumab, ipilimumab, BMS-986016 (relatlimab), and daratumumab are considered immuno-oncology agents in this protocol. Early recognition and management of adverse events associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of adverse events:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathies
- Skin
- Neurological

The safety management algorithms are provided in Appendix 2 of this protocol.

4.7.3 Dose Delay Criteria

Study drug administration (nivolumab, ipilimumab, and BMS-986016) should be delayed for the following:

- Grade 2 non-skin, drug-related adverse event, except for fatigue.
- Grade 3 skin, drug-related adverse event
- Grade 2 drug-related creatinine, AST, ALT, and/or total bilirubin
- Grade 3 drug-related fatigue, nausea, vomiting, and anemia (Combination Cohort C only)
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require a dose delay
  - Grade ≥ 3 AST, ALT, or total bilirubin will require dose discontinuation (Section 4.7.6)
- All troponin elevations require a dose delay to allow for prompt cardiac evaluation (Combo C only)
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study drug.
- Subjects receiving ipilimumab or BMS-986016 in combination with nivolumab that have drug-related toxicities that meet the criteria for dose delay, should have both drugs (nivolumab and either ipilimumab, or BMS-986016) delayed until retreatment criteria are met.
- Subjects who require delay of study treatment should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met.

For subjects receiving Combo D treatment, daratumumab dose should be delayed if any of the following criteria below are met, to allow for recovery from toxicity related to daratumumab. For subjects whose dose delay is not related to nivolumab, treatment with nivolumab may continue:

- Grade 4 hematologic toxicity, except for grade 4 lymphopenia
- Grade 3 or higher thrombocytopenia with bleeding
- Febrile neutropenia
- Neutropenia with infection, of any grade
- Grade 3 or higher non-hematologic toxicities with the following exceptions:
  - Grade 3 nausea that responds to antiemetic treatment within 7 days
  - Grade 3 vomiting that responds to antiemetic treatment within 7 days
  - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
  - Grade 3 fatigue that was present at baseline or that lasts for <7 days after the last administration of daratumumab
  - Grade 3 asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab

Table 4.7.3-1: Daratumumab Dose Delay Guidance

Week	Frequency	Dose Held	Dosing Re-start
1-8	Weekly (q1wk)	>3 days	next planned weekly dosing date
9-24	Biweekly (q2wks)	>7 days	next planned biweekly dosing date
25+	Every 4 weeks (q4wks)	>14 days	next planned every 4 weeks dosing date

- Subjects experiencing a Grade 3 infusion reaction related to daratumumab must permanently discontinue daratumumab.
- Any adverse event deemed to be related to daratumumab that requires a dose hold of more than 3 consecutive planned doses will result in permanent discontinuation of daratumumab. If a dose delay occurs, then pharmacokinetic and pharmacodynamic assessments should be performed on the actual day of study drug administration, not on the original scheduled administration day
- Subjects who miss ≥3 consecutive planned doses of daratumumab for reasons other than toxicity should be withdrawn from study drug, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon. Subjects who are withdrawn from daratumumab may continue to receive nivolumab.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study drug.

Doses of daratumumab may be delayed up to 4 weeks during Weeks 1-24 or up to 6 weeks from Week 25 and beyond. Any adverse event deemed to be related to daratumumab that requires a dose hold longer than those specified above will result in permanent discontinuation of daratumumab. If a dose delay occurs, then pharmacokinetic and pharmacodynamic assessments

should be performed on the actual administration day of daratumumab, not on the original scheduled administration day.

Administration of daratumumab may be restarted upon recovery from toxicity to Grade 2 or baseline, with the exception that Grade 2 laryngeal edema or Grade 2 bronchospasm must be fully recovered.

If daratumumab administration does not commence within the prespecified window (Table 4.7.3-1) of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date. A missed dose will not be made up.

Rescheduling (Combo A or B):

- Nivolumab may be delayed until the next planned ipilimumab dose if the next ipilimumab dose is scheduled within the next 12 days. This will permit periodic ipilimumab dosing to be synchronized with nivolumab dosing.
- Ipilimumab should be dosed at the specified interval regardless of any delays in intervening nivolumab doses. However, in order to maintain periodic synchronized dosing of ipilimumab and nivolumab, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted +/- 3 day window, as long as consecutive nivolumab doses are given at least 12 days apart. Ipilimumab may be delayed beyond the 3 day window if needed to synchronize with the next nivolumab dose.
- A dose delay of ipilimumab which results in no ipilimumab dosing for > 12 weeks requires ipilimumab discontinuation, with exceptions as noted in Section 4.7.6.

4.7.4 Dose Reductions

There will be no dose reductions for nivolumab, ipilimumab, BMS-986016 or daratumumab.

4.7.5 Criteria to Resume Dosing

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

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- For participants with Grade 2 AST, ALT and/or Total Bilirubin Abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the BMS Medical Monitor.
- Subjects who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≤ 10 mg/day.

- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
- Troponin elevations will require the participant to undergo a cardiac evaluation. Following this evaluation, determination of further treatment will be based on the discussion with the BMS medical monitor/designee.
- Dose delay of nivolumab, BMS-986016 and ipilimumab (Combo B), which results in treatment interruption of > 6 weeks requires treatment discontinuation, with exceptions as noted in Section 4.7.6.
- Dose delay of ipilimumab in Combo A, which results in treatment interruption of > 12 weeks requires treatment discontinuation, with exceptions as noted in Section 4.7.6.
- Ipilimumab may not be resumed sooner than 6 weeks (+/- 3 days) after the prior ipilimumab dose for Combo A.
- In general, subjects who meet criteria to resume ipilimumab will also have met criteria to resume nivolumab, so it should be feasible to synchronize dosing of both drugs when resuming ipilimumab. In order to facilitate this, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted +/- 3 day window, as long as consecutive nivolumab doses are given at least 12 days apart.
- One exception to note is when ipilimumab and nivolumab doses are delayed due to drug-related Grade 3 amylase or lipase abnormalities not associated with symptoms or clinical manifestations of pancreatitis. If the investigator assesses the Grade 3 amylase or lipase abnormality to be related to ipilimumab and not related to nivolumab, nivolumab may be resumed when the amylase or lipase abnormality resolves to Grade < 3 but ipilimumab may only be resumed when the amylase or lipase abnormality resolves to Grade 1 or baseline. Investigator attribution of this toxicity to the ipilimumab dosing must be clearly noted in the subject's medical chart. The BMS Medical Monitor should be consulted prior to resuming nivolumab in such subjects.
- Subjects may resume treatment with daratumumab in Combo D, when the toxicity has resolved to Grade 2 or baseline, with the exception that Grade 2 laryngeal edema or Grade 2 bronchospasm must be fully recovered. If the daratumumab administration does not commence within the pre-specified window of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date.

4.7.6 Discontinuation Criteria

Treatment with study drug should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days or recurs, with the following exceptions for laboratory abnormalities, diarrhea, colitis, neurologic toxicity, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, myocarditis, infusion reactions, and endocrinopathies:

  - Grade 3 drug-related diarrhea, colitis, neurologic toxicity, uveitis, pneumonitis, bronchospasm, myocarditis, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
      - Grade ≥ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation. Note: * In most cases of Grade 3 AST or ALT elevation, study drug(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug(s), a discussion between the investigator and the BMS Medical Monitor/designee must occur.
      - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin), except for the following events, which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy adverse events such as hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (steroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.
- Daratumumab treatment should be permanently discontinued for the following reasons:
  - Grade 4 infusion reactions related to daratumumab.
  - For Grade 3 infusion reactions related to daratumumab: Once reaction symptoms resolve, consider restarting the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience additional symptoms, resume infusion rate escalation at increments and intervals as outlined in Table 4.3-1. Repeat the procedure above in the event of recurrence of Grade 3 symptoms. Permanently discontinue daratumumab upon the third occurrence of a Grade 3 or greater infusion reaction
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued study drug dosing.

- Any event that leads to delay in dosing lasting > 6 weeks for Combo B and C, and > 12 weeks for Combo A from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
  - Dosing delays lasting > 6 weeks (Combo A and C) or >12 weeks (Combo A) from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor.

For Combo A, B, and C, prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks (Combo B and C) and > 12 weeks (Combo A), the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

The assessment for discontinuation of study drug should be made separately considering each study drug. If discontinuation criteria are attributed with only one drug used in this trial, once the subject meets criteria to resume therapy, the subject may continue dosing with the remaining study drug not attributed to criteria for discontinuation. In the nivolumab and BMS-986016 (relatlimab) combination (Combo C), if discontinuation criteria are met, both drugs (nivolumab and BMS-986016) will be discontinued regardless of the assessment of attribution to a particular study drug.

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

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

4.7.7 Treatment of Study Drug-related Infusion Reactions

Since nivolumab, ipilimumab, and BMS-986016 (relatlimab) contain only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (version 4) guidelines.

For subjects in the combination cohorts A, B and C when ipilimumab or BMS-986016 (relatlimab) are scheduled to be administered on the same day as nivolumab, if a subject has an infusion reaction with nivolumab, the ipilimumab or BMS-986016 (relatlimab) infusion can be given (without prophylactic medications) if the infusion reaction resolves within 3 hours. For scheduling purposes after a nivolumab infusion reaction, the ipilimumab or BMS-986016 (relatlimab) infusion may be given the next day. Prophylactic pre-infusion medications should be given prior to all subsequent nivolumab infusions.

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

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

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

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

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

The following prophylactic premedications are recommended for future infusions:

- Diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

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

- Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a

1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Study drug will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms.

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

Guidelines for prevention and management of daratumumab infusion-related reactions

Prevention of Daratumumab Infusion related reactions:

- Pre-infusion medication to be administered to all subjects approximately 1 hour prior to every daratumumab infusion (can be administered before the nivolumab infusion):
  - IV corticosteroid (methylprednisolone 100 mg, or equivalent dose of an intermediate acting or long-acting corticosteroid). Following the second infusion, the dose of corticosteroid may be reduced (methylprednisolone 60 mg IV), PLUS
  - Oral antipyretics (acetaminophen 650 to 1000 mg), PLUS
  - Oral or IV antihistamine (diphenhydramine 25 to 50 mg or Leukotriene Inhibitor (optional) on Cycle 1 Day 1: montelukast 10 mg PO, or equivalent).
- Post-infusion medication to be administered to all subjects to reduce the risk of delayed infusion reactions:
  - Oral corticosteroid (20 mg methylprednisolone or equivalent dose of a corticosteroid in accordance with local standards) on the first and second day after all infusions
  - At the investigator discretion, for subjects with a history of obstructive pulmonary disorder, short and long-acting bronchodilators and inhaled corticosteroids can be administered. Following the first 4 infusions, if subjects experience no major infusion reactions, these additional inhaled post-infusion medications may be discontinued.

Subjects should be carefully monitored for infusion reactions during daratumumab administration. Trained study staff at the clinic should be prepared to intervene in case of any infusion reactions, and resources necessary for resuscitation must be available. All subjects should have blood pressure monitored before and after all infusions. For the first two infusions, blood pressure should also be monitored during the infusion. There will be no dose escalations or reductions of daratumumab allowed. Doses of daratumumab may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment.

If an acute infusion reaction is noted, subjects should be managed according to the Investigator's Brochure and as summarized below.

Management of Daratumumab Infusion related reactions:

Per Revised Protocol 06, enrollment and treatment in this cohort have been terminated. Subjects should be carefully observed during daratumumab infusions. Trained study staff at the clinic should be prepared to intervene in case of any infusion reactions, and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilator, also medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at bedside. Attention to staffing should be considered when multiple subjects will be dosed at the same time.

Interrupt the daratumumab infusion for infusion-related reactions of any severity. Management of infusion reactions may require further reduction in the rate of infusion, or treatment discontinuation of daratumumab.

Subjects who experience adverse events during the infusion must be treated according to the investigator's judgment and best clinical practice. Subjects should be treated with acetaminophen, antihistamine, and/or corticosteroids as needed. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, subjects may require vasopressors.

If an infusion is interrupted, then a longer-than-anticipated infusion time may occur. Overnight stays at the hospital because of slow infusion times should not be reported as serious adverse events. However, if the underlying cause of the delayed infusion time is an adverse event or serious adverse event, then that should be reported as such.

Infusion-related reactions of grade 1 or grade 2: Once reaction symptoms resolve, resume the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience any further reaction symptoms, infusion rate escalation may resume at increments and intervals as appropriate as outlined in Table 4.3-1.

Grade 3 (severe): Once reaction symptoms resolve, consider restarting the infusion at no more than half the rate at which the reaction occurred. If the subject does not experience additional symptoms, resume infusion rate escalation at increments and intervals as outlined in Table 4.3-1. Repeat the procedure above in the event of recurrence of Grade 3 symptoms. Permanently discontinue daratumumab upon the third occurrence of a Grade 3 or greater infusion-related reaction.

Grade 4 (life threatening): Permanently discontinue daratumumab treatment.

4.7.8 Treatment Beyond Disease Progression

Accumulating clinical evidence indicates some subjects treated with immune system stimulating agents may develop progression of disease (by conventional response criteria) before demonstrating clinical objective responses and/or stable disease. This phenomenon was observed in approximately 10% of subjects in the Phase 1 study of nivolumab and also with ipilimumab

monotherapy.[186] Two hypotheses have been put forth to explain this phenomenon. First, enhanced inflammation within tumors could lead to an increase in tumor size which would appear as enlarged index lesions and as newly visible small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease leading to overt signs of clinical improvement. Alternatively, in some individuals, the kinetics of tumor growth may initially outpace anti-tumor immune activity. With sufficient time, the anti-tumor activity will dominate and become clinically apparent. Therefore, subjects will be allowed to continue study therapy after initial investigator-assessed RECIST 1.1 defined progression as long as they meet the following criteria:

1) Investigator-assessed clinical benefit, and do not have rapid disease progression
2) Tolerance of study drug as defined by the investigator
3) Stable performance status
4) Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
5) Subject provides a new written informed consent prior to receiving any additional study drug using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment.

Patients enrolled to the nivolumab monotherapy, the nivolumab plus ipilimumab, nivolumab plus BMS-986016 (relatlimab), or the nivolumab plus daratumumab combination arms may be allowed to continue treatment beyond initial progression for up to a maximum of 24 months from the date of first dose. In this instance, subjects may continue therapy with assigned treatment.

All decisions to continue treatment beyond initial progression must be discussed with the BMS Medical Monitor and documented in the study records. **Subjects will be re-consented with an ICF describing any reasonably foreseeable risks or discomforts.**

Subjects should discontinue study therapy upon further evidence of further progression, defined as an additional 10% or greater increase in tumor burden volume from time of initial progression (including all target lesions and new measurable lesions).

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

For statistical analyses that include the investigator-assessed progression date, subjects who continue treatment beyond initial investigator-assessed, RECIST 1.1-defined progression will be

considered to have investigator-assessed progressive disease at the time of the initial progression event.

4.8 Destruction of Study Drug

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

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

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

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

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

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

4.9 Return of Study Drug

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

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

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline for All Subjects (CA209358)

Procedure	Screening Visit[a]	Notes
Eligibility Assessments		
Informed Consent	X	Register in Interactive Response Technology (IRT) system to obtain subject number. Pre-screening informed consent will be obtained to perform viral testing for Gastric and SCCHN subjects. Register subject in IRT. Once viral status is confirmed positive, informed consent will be obtained for full eligibility assessments. See Viral Testing row below in this table for additional details.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to first dose
Medical History	X	
Serious Adverse Event Assessment	X	Serious Adverse Events from time of consent. See Section 6.
Prior Systemic Therapy	X	
Safety Assessments		
Physical Examination	X	Within 14 days prior to first dose
Physical Measurements	X	Include Height and Weight Within 14 days prior to first dose
Vital Signs	X	Temperature, BP and HR Within 72 hours of first dose
Performance Status (ECOG)	X	Within 14 days prior to first dose See Appendix 1 for ECOG scale
Echocardiogram	X (see notes)	**For Combo C only**: LVEF assessment with documented LVEF ≥ 50% by either TTE or MUGA (TTE preferred test) within 6 months from first study drug administration

Table 5.1-1: Screening Procedural Outline for All Subjects (CA209358)

Procedure	Screening Visit[a]	Notes
ECG	X	Within 14 days prior to first dose
Assessment of Signs and Symptoms	X	After obtaining Informed Consent, assess all signs and symptoms within 14 days prior to first dose.
Concomitant Medication Collection	X	Within 14 days prior to first dose
Laboratory Tests	X	CBC with differential and platelet count, Chemistry panel including LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, P, glucose, bicarbonate or total CO2 (if locally available), albumin, amylase, lipase, TSH (reflex to free T3, free T4 for abnormal TSH result), hepatitis B surface antigen (HBV sAg, Australia antigen), and hepatitis C antibody (HCV Ab or RNA) Within 14 days prior to first dose. **Combo C only -** Cardiac Troponin Levels: T (cTnT) or I (cTnI)
Viral Testing	X	See Section 5.6.1. Pre-screening informed consent will be obtained prior to viral testing • Confirmation of viral status will be required prior to study drug assignment for EBV gastric cancer and HPV SCCHN tumor types in the metastatic cohorts (monotherapy and combination). • If SCCHN 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. • Confirmation of viral status will be required prior to study drug assignment for SCCHN subjects enrolled in the neoadjuvant cohort. • See the Efficacy/Biomarker Assessment section of this table for additional information regarding other tumor types.
Pregnancy Test	X	Serum or urine pregnancy testing to be done at screening visit and repeated within 24 hours of first dose.
Blood type (ABO, Rh, and indirect antiglobulin testing - Cohort D only)	X	Within 14 days prior to first dose

Table 5.1-1: Screening Procedural Outline for All Subjects (CA209358)

Procedure	Screening Visit[a]	Notes
Efficacy/Biomarker Assessments		
Radiographic Tumor Assessment Spiral CT/MRI of Chest, Abdomen, Pelvis, and any other known sites of disease	X	Should be performed within 35 days prior to first dose. Additional sites of known or suspected disease (including CNS) should be imaged at the screening visit and at subsequent on-study assessments.
Collection of tumor tissue	X	For both the Neoadjuvant and Metastatic Cohorts: Submission of tumor tissue is mandatory. A fresh biopsy is preferred. An archived sample of an FFPE tumor tissue block or 15 unstained slides collected as a standard of care procedure within 90 days prior to obtaining informed consent is acceptable for metastatic cohorts. Fresh Biopsies are mandatory for neoadjuvant cohort patients. Fresh biopsy samples should be excisional, incisional, or core needle. Fine needle aspirates are not acceptable. Tumor biopsies should be placed in formalin for IHC of tumor and TIL, RNALater for gene expression, and media for flow cytometry analysis (neo-adjuvant cohort only) as described in the laboratory manual. If HPV viral status of the gynecological (cervical, vaginal, vulvar) or anogenital HPV associated tumor types (anal canal, penile) is not available, a fresh collection of tumor cells will be required. Please see laboratory manual for details. See Section 5.6.9 for Biomarker Sampling Schedules.
Record Historic mutation/markers of interest	X	EBV gastric (metastatic monotherapy cohort only): EBV status, HER2, CDH1, PIK3CA HPV Head/Neck: HPV status, PIK3CA Cervical, Vaginal, Vulvar, Anal Canal, Penile: HPV status MCC: Polyomavirus status, BRAF (V599), CK20, TFF-1 HPV NPC: HPV Status, KRAS, NRAS, PIK3CA

Table 5.1-1: Screening Procedural Outline for All Subjects (CA209358)

Procedure	Screening Visit[a]	Notes
IRT/Clinical Drug Supplies		
Phone calls to IRT	X	Phone calls must be made to IRT as follows: • For subject number assignment at the time of pre-screening informed consent is obtained (Gastric and SCCHN patients) • For subject number assignment at the time informed consent is obtained. • Prior to dosing for study drug vial assignment (call should be made within 5 days prior to dosing). • Confirmation of viral status will be required prior to study drug assignment for EBV gastric cancer (metastatic monotherapy cohort only) and HPV SCCHN tumor types in the neoadjuvant and metastatic cohorts (monotherapy or Combos A and C). • If SCCHN 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.

[a] Within 35 days prior to first dose

Table 5.1-2: On-Treatment Assessments Metastatic Monotherapy Cohort (CA209358)

Procedure	Cycle 1 Day 1 (C1D1)	Each Cycle (every 2 Weeks) on Day 1 (± 3 days)	Notes
Safety Assessments			
Targeted Physical Examination	X	X	Targeted examination must include at a minimum the following body systems: • Cardiovascular • Gastrointestinal • Pulmonary • Neurological exam for subjects with brain metastases Within 72 hours prior to dosing
Vital Signs	X	X	Temperature, BP, and HR prior to dosing and at any time a subject has any new or worsening respiratory symptoms. Obtain vital signs within 72 hours prior to dosing.
Physical Measurements	X	X	Includes Weight and ECOG performance status See Appendix 1 for ECOG scale Obtain physical measurements within 72 hrs prior to dosing.
Adverse Events Assessment	------ Continuously -------		Assessed using NCI CTCAE version 4.
Review of Concomitant Medications	X	X	
Laboratory Tests	X	X	On-study local laboratory assessments should be done within 72 hours prior to dosing for every cycle and include: CBC with differential and platelet count, BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphorus, chloride, bicarbonate or total CO2 (if locally available), amylase, lipase, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH, albumin. Labs required prior to first dose do not have to be repeated if screening labs were performed within 14 days prior to first dose.
Thyroid Function Testing		See Note	TSH (reflex to free T3 and free T4 if abnormal result) to be performed every 6 weeks (± 1 week).

Table 5.1-2: On-Treatment Assessments Metastatic Monotherapy Cohort (CA209358)

Procedure	Cycle 1 Day 1 (C1D1)	Each Cycle (every 2 Weeks) on Day 1 (± 3 days)	Notes
Pregnancy Test	X	See Note	Serum or urine within 24 hours prior to first dose and then at least once every 4 weeks (+/- 1 week) regardless of dosing schedule.
Efficacy/Biomarker Assessments			
Radiographic Tumor Assessment Spiral CT/MRI of Chest, Abdomen, Pelvis, and any other known sites of disease		See Table 5.4.1-1 for imaging frequency. See Appendix 3 (RECIST 1.1 Guidelines) for details regarding imaging methodology requirements and assessments	
Collection of Tumor Tissue	Collection of tumor tissue (FFPE tumor tissue block or 15 unstained slides) for determination of PD-L1 expression and other exploratory biomarker analysis. Biopsy samples should be excisional, incisional, or core needle. Tumor biopsies should be placed in formalin for IHC of tumor and TIL and RNALater for gene expression. See Table 5.6.9-2 for Biomarker Sampling Schedule		
Serum Plasma PBMC Whole Blood	See Table 5.6.9-2 for Biomarker Sampling Schedule		
PK and Immunogenicity Assessments			
PK samples	See Table 5.5-1 of PK and Immunogenicity Sampling		
Immunogenicity samples	See Table 5.5-1 of PK and Immunogenicity Sampling		
Outcomes Research Assessments			
EORTC QLQ-C30	X	See note	Assessments to be collected every 4 cycles for the first 17 cycles: Day 1 (prior to dosing) of Cycles 5, 9, 13, 17 every 6 cycles thereafter: Day 1 (prior to dosing) of Cycles 23, 29, 35+.
EQ-5D	X	See note	

Table 5.1-2: On-Treatment Assessments Metastatic Monotherapy Cohort (CA209358)

Procedure	Cycle 1 Day 1 (C1D1)	Each Cycle (every 2 Weeks) on Day 1 (± 3 days)	Notes
Clinical Drug Supplies			
Administer Study Drug	X	X	First dose to be administered within 5 days of study drug assignment. Confirmation of viral status will be required prior to study drug assignment for EBV gastric cancer and HPV SCCHN tumor types in the metastatic cohort.

Table 5.1-3: On-Treatment Assessments Metastatic Combination Therapy Cohorts (CA209358)

Procedure	Combo A During Treatment Nivo 3mg q2w + Ipi 1 mg/kg q6w	Combo B During Treatment Nivo 1 mg/kg + Ipi 3 mg/kg q3w x 4, followed by Nivo 240 mg q2w	Combo C During Treatment Nivo 240 mg + BMS-986016 80 mg q2w	Combo D During Treatment Daratumumab q1 week/q2weeks/q4 weeks + Nivo 240 mg q2 weeks/ 480 mg every 4 wks.	Notes See note sections below for dosing windows
Safety Assessments					
Targeted Physical Examination	X	X	X	X	Targeted examination must include at a minimum the following body systems: Cardiovascular Gastrointestinal Pulmonary Neurological exam for subjects with brain metastases Within 72 hours prior to dosing
Neurologic examination			X		Obtain neurological exam (performed by a neurologist) in subjects who experience a study drug related ≥ Grade 2 neurological AE.
Vital Signs	X	X	X	X	Temperature, BP, and HR prior to dosing and at any time a subject has any new or worsening respiratory symptoms. Obtain vital signs within 72 hours prior to dosing.
Physical Measurements	X	X	X	X	Includes Weight and ECOG performance status

Table 5.1-3: On-Treatment Assessments Metastatic Combination Therapy Cohorts (CA209358)

Procedure	Combo A During Treatment Nivo 3mg q2w + Ipi 1 mg/kg q6w	Combo B During Treatment Nivo 1 mg/kg + Ipi 3 mg/kg q3w x 4, followed by Nivo 240 mg q2w	Combo C During Treatment Nivo 240 mg + BMS-986016 80 mg q2w	Combo D During Treatment Daratumumab q1 week/q2weeks/q4 weeks + Nivo 240 mg q2 weeks/ 480 mg every 4 wks.	Notes See note sections below for dosing windows
					Note: a change of +/- 10% of body weight from the prior dosing visit requires recalculation of dose[a] See Appendix 1 for ECOG scale Obtain physical measurements within 72 hrs prior to dosing.
12-lead electrocardiogram (ECG)			X (See Notes)		12-lead ECG to be performed within 72 hrs prior to dosing using site's own ECG machine.
Adverse Events Assessment	------ Continuously -------				Assessed using NCI CTCAE version 4.
Review of Concomitant Medications	X	X	X	X	

Table 5.1-3: On-Treatment Assessments Metastatic Combination Therapy Cohorts (CA209358)

Procedure	Combo A During Treatment Nivo 3mg q2w + Ipi 1 mg/kg q6w	Combo B During Treatment Nivo 1 mg/kg + Ipi 3 mg/kg q3w x 4, followed by Nivo 240 mg q2w	Combo C During Treatment Nivo 240 mg + BMS-986016 80 mg q2w	Combo D During Treatment Daratumumab q1 week/q2weeks/q4 weeks + Nivo 240 mg q2 weeks/ 480 mg every 4 wks.	Notes See note sections below for dosing windows
Laboratory Tests (Cohorts A, C, and D)	X		X	X	On-study local laboratory assessments should be done within 72 hours prior to dosing for every cycle and include: CBC with differential and platelet count, BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphorus, chloride, bicarbonate or total CO2 (if locally available), amylase, lipase, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH, albumin. Labs required prior to first dose do not have to be repeated if screening labs were performed within 14 days prior to first dose. In addition, the following tests at Week 7 and 13, then every 6 weeks (3 cycles of nivolumab): TSH (Reflex to free T3 and free T4 if TSH abnormal. Total T3/T4 are acceptable if free T3/T4 are not available). **Combo C only:** Cardiac Troponin Levels: T (cTnT) or I (cTnI). Labs are performed locally, and may be collected within 72 hours prior to each dosing. Results must be reviewed by the Investigator or appropriate designee prior to dose administration.

Table 5.1-3: On-Treatment Assessments Metastatic Combination Therapy Cohorts (CA209358)

Procedure	Combo A During Treatment Nivo 3mg q2w + Ipi 1 mg/kg q6w	Combo B During Treatment Nivo 1 mg/kg + Ipi 3 mg/kg q3w x 4, followed by Nivo 240 mg q2w	Combo C During Treatment Nivo 240 mg + BMS-986016 80 mg q2w	Combo D During Treatment Daratumumab q1 week/q2weeks/q4 weeks + Nivo 240 mg q2 weeks/ 480 mg every 4 wks.	Notes See note sections below for dosing windows
Laboratory Tests (Cohort B)		X			On-study local laboratory assessments should be done within 72 hours prior to dosing for every cycle and include: CBC with differential and platelet count, BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphorus, chloride, bicarbonate or total CO2 (if locally available), amylase, lipase, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH, albumin. Labs required prior to first dose do not have to be repeated if screening labs were performed within 14 days prior to first dose. In addition, the following tests at Week 7 and 13, then every 6 weeks (3 cycles of nivolumab 240 mg): TSH (Reflex to free T3 and free T4 if TSH abnormal. Total T3/T4 are acceptable if free T3/T4 are not available)
Pregnancy Test (Cohort A, C, and D)	X		X	X	Serum or urine within 24 hours prior to first dose and then at least once every 4 weeks (+/- 1 week) regardless of dosing schedule.
Pregnancy Test (Cohort B)		X			Serum or urine pregnancy test (minimum sensitivity 25 IU/L or

Table 5.1-3: On-Treatment Assessments Metastatic Combination Therapy Cohorts (CA209358)

Procedure	Combo A During Treatment Nivo 3mg q2w + Ipi 1 mg/kg q6w	Combo B During Treatment Nivo 1 mg/kg + Ipi 3 mg/kg q3w x 4, followed by Nivo 240 mg q2w	Combo C During Treatment Nivo 240 mg + BMS-986016 80 mg q2w	Combo D During Treatment Daratumumab q1 week/q2weeks/q4 weeks + Nivo 240 mg q2 weeks/ 480 mg every 4 wks.	Notes See note sections below for dosing windows
					equivalent units of HCG) to be done within 24 hours prior to first dose, and then at Week 4, 7, 10 and every 4 weeks (+/- 1 week), regardless of dosing schedule.
Efficacy/Biomarker Assessments					
Radiographic Tumor Assessment Spiral CT/MRI of Chest, Abdomen, Pelvis, and any other known sites of disease	See Table 5.4.1-1 for imaging frequency. See Appendix 3 (RECIST 1.1 Guidelines) for details regarding imaging methodology requirements and assessments.				
Collection of Tumor Tissue	Collection of tumor tissue (FFPE tumor tissue block or 15 unstained slides) for determination of PD-L1 expression and other exploratory biomarker analysis. Biopsy samples should be excisional, incisional, or core needle. Tumor biopsies should be placed in formalin for IHC of tumor and TIL and RNALater for gene expression. See Table 5.6.9-2 and Table 5.6.9-3 for Biomarker Sampling Schedule				
Serum Plasma PBMC Whole Blood	See Table 5.6.9-2 and Table 5.6.9-3 for Biomarker Sampling Schedule				
PK and Immunogenicity Assessments					
PK samples Immunogenicity samples	See Table 5.5-1 through Table 5.5-8 for PK and Immunogenicity Sampling				

Table 5.1-3: On-Treatment Assessments Metastatic Combination Therapy Cohorts (CA209358)

Procedure	Combo A During Treatment Nivo 3mg q2w + Ipi 1 mg/kg q6w	Combo B During Treatment Nivo 1 mg/kg + Ipi 3 mg/kg q3w x 4, followed by Nivo 240 mg q2w	Combo C During Treatment Nivo 240 mg + BMS-986016 80 mg q2w	Combo D During Treatment Daratumumab q1 week/q2weeks/q4 weeks + Nivo 240 mg q2 weeks/ 480 mg every 4 wks.	Notes See note sections below for dosing windows
Outcomes Research Assessments s					
EORTC QLQ-C30 (Cohorts A, C, and D)	X		X	X	Assessments to be collected at Day 1 Week 1 every 4 cycles for the first 17 cycles: Day 1 (prior to dosing) of Cycles 1, 5, 9, 13, 17; Then every 6 cycles thereafter: Day 1 (prior to dosing) of Cycles 23, 29, 35+.
EORTC QLQ-C30 (Cohort B)		X			Assessments to be collected prior to dosing at Cycle 1 Day 1 and Cycle 4 Day 1, and then every 4 cycles for 16 cycles: Day 1 (prior to dosing) Cycles 1, 4, 8, 12, 16; Then every 6 cycles thereafter: Day 1 (prior to dosing) Cycles 22, 28, 34+
EQ-5D (Cohort A, C, and D)	X		X	X	Assessments to be collected at Day 1 Week 1 every 4 cycles for the first 17 cycles; Day 1 (prior to dosing) of Cycles 1,5, 9, 13, 17; every 6 cycles thereafter; Day 1 (prior to dosing) of Cycles 23, 29, 35+.

Table 5.1-3: On-Treatment Assessments Metastatic Combination Therapy Cohorts (CA209358)

Procedure	Combo A During Treatment Nivo 3mg q2w + Ipi 1 mg/kg q6w	Combo B During Treatment Nivo 1 mg/kg + Ipi 3 mg/kg q3w x 4, followed by Nivo 240 mg q2w	Combo C During Treatment Nivo 240 mg + BMS-986016 80 mg q2w	Combo D During Treatment Daratumumab q1 week/q2weeks/q4 weeks + Nivo 240 mg q2 weeks/ 480 mg every 4 wks.	Notes See note sections below for dosing windows
EQ-5D (Cohort B)		X			Assessments to be collected prior to dosing at Cycle 1 Day 1 and Cycle 4 Day 1, and then every 4 cycles for 16 cycles: Day 1 (prior to dosing) Cycles 1, 4, 8, 12, 16; Then every 6 cycles thereafter: Day 1 (prior to dosing) Cycles 22, 28, 34+

Table 5.1-3: On-Treatment Assessments Metastatic Combination Therapy Cohorts (CA209358)

Procedure	Combo A During Treatment Nivo 3mg q2w + Ipi 1 mg/kg q6w	Combo B During Treatment Nivo 1 mg/kg + Ipi 3 mg/kg q3w x 4, followed by Nivo 240 mg q2w	Combo C During Treatment Nivo 240 mg + BMS-986016 80 mg q2w	Combo D During Treatment Daratumumab q1 week/q2weeks/q4 weeks + Nivo 240 mg q2 weeks/ 480 mg every 4 wks.	Notes See note sections below for dosing windows
Clinical Drug Supplies					
Administer Study Drug (Cohort A)	X[a]				First dose to be administered within 5 days of study drug assignment. Confirmation of viral status will be required prior to study drug assignment for HPV SCCHN tumor types in the metastatic cohort. Dosing Window: +/-1 week Subjects may be dosed no less than 12 days for nivolumab and 5 weeks for ipilimumab.
Administer Study Drug (Cohort B)		X[a]			First dose to be administered within 5 days of study drug assignment. Confirmation of viral status will be required prior to study drug assignment for HPV SCCHN tumor types in the metastatic cohort. Dosing window: ± 3 days Subjects may be dosed no less than 19 days between q3week doses of nivolumab and ipilimumab, and no less than 12 days for nivolumab monotherapy after completion of ipilimumab induction.

Table 5.1-3: On-Treatment Assessments Metastatic Combination Therapy Cohorts (CA209358)

Procedure	Combo A During Treatment Nivo 3mg q2w + Ipi 1 mg/kg q6w	Combo B During Treatment Nivo 1 mg/kg + Ipi 3 mg/kg q3w x 4, followed by Nivo 240 mg q2w	Combo C During Treatment Nivo 240 mg + BMS-986016 80 mg q2w	Combo D During Treatment Daratumumab q1 week/q2weeks/q4 weeks + Nivo 240 mg q2 weeks/ 480 mg every 4 wks.	Notes See note sections below for dosing windows
Administer Study Drug (Cohort C)			X		First dose to be administered within 5 days of study drug assignment. Confirmation of viral status will be required prior to study drug assignment for HPV SCCHN tumor types in the metastatic cohort. Dosing window +/-2 days. Subjects may be dosed no less than 12 days for nivolumab and BMS-986016.
Administer Study Drug (Cohort D)				X	First dose to be administered within 5 days of study drug assignment. Viral testing may be done retrospectively for HPV SCCHN tumor type in the metastatic cohort (Combo D). Please see Table 4.7.3-1 for Daratumumab Dose Delay Guidance. Dosing windows for Daratumumab Wks 1-8: -1/ +3 days Wks 9-24: +/-1 week Wk 25+: up to 21 days delayed Subjects may be dosed no less than 12 days between nivolumab doses through Week 24 (240 mg)

Table 5.1-3: On-Treatment Assessments Metastatic Combination Therapy Cohorts (CA209358)

Procedure	Combo A During Treatment Nivo 3mg q2w + Ipi 1 mg/kg q6w	Combo B During Treatment Nivo 1 mg/kg + Ipi 3 mg/kg q3w x 4, followed by Nivo 240 mg q2w	Combo C During Treatment Nivo 240 mg + BMS-986016 80 mg q2w	Combo D During Treatment Daratumumab q1 week/q2weeks/q4 weeks + Nivo 240 mg q2 weeks/ 480 mg every 4 wks.	Notes See note sections below for dosing windows
					Subjects may be dosed no less than 21 days between nivolumab doses beyond Week 25 (480 mg)

[a] Dosing calculations should be based on the body weight assessed at baseline. It is not necessary to re-calculate subsequent doses if the participant weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded up or to the nearest milligram per institutional standard.

Table 5.1-4: On Treatment Assessments Neoadjuvant Cohort (CA209358)

Procedure	Day 1	Day 15	Pre-Surgery Visit (up to7 days prior to surgery)	Notes
Safety Assessments				
Targeted Physical Examination	X	X	X	Targeted examination must include at a minimum the following body systems: • Cardiovascular • Gastrointestinal • Pulmonary • Neurological exam for subjects with brain metastases • Site of resection of primary tumor Once within 72 hours prior to nivolumab or surgery
Vital Signs	X	X	X	Temperature, BP, and HR at rest and after exertion (also monitor amount of supplemental oxygen if applicable) prior to dosing and at any time a subject has any new or worsening respiratory symptoms. Obtain vital signs within 72 hours prior to dosing.
Physical Measurements	X	X	X	Includes Weight and ECOG performance status See Appendix 1 for ECOG scale
Adverse Events Assessment	---------- Continuously ----------			Assessed using NCI CTCAE version 4
Review of Concomitant Medications	X	X	X	

Table 5.1-4: On Treatment Assessments Neoadjuvant Cohort (CA209358)

Procedure	Day 1	Day 15	Pre-Surgery Visit (up to7 days prior to surgery)	Notes
Laboratory Tests	X	X	X	Laboratory assessments should be done within 72 hours prior to dosing for Day 1 and 15 and the Pre-Surgery Visit and include: CBC with differential and platelet count, BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphorus, chloride, bicarbonate or total CO2 (if locally available), amylase, lipase, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH, albumin. Labs required prior to first dose do not have to be repeated if screening labs were performed within 14 days prior to first dose.
Thyroid Function Testing			X	TSH (reflex to free T3 and free T4 if abnormal result)
Pregnancy Test	X		X	Serum or urine within 24 hours prior to first dose and then at least once every 4 weeks regardless of dosing schedule.
Efficacy/Biomarker Assessments				
Radiographic Tumor Assessment Spiral CT/MRI of Chest, Abdomen, Pelvis, and any other known sites of disease	See Note			Post-Surgery: CT or MRI scan per local practices See Table 5.4.1-2 for imaging frequency See Appendix 3 (RECIST 1.1 Guidelines) for details regarding imaging methodology requirements and assessments

Table 5.1-4: On Treatment Assessments Neoadjuvant Cohort (CA209358)

Procedure	Day 1	Day 15	Pre-Surgery Visit (up to7 days prior to surgery)	Notes
Tumor Assessment (Surgery or Biopsy)			X	Sample sent for biomarkers. Surgery (SCCHN, MCC, Gyn) or biopsy (Gyn pts, where appropriate) on Day 29 ±7 days Collection of tumor tissue (FFPE tumor tissue block or 15 unstained slides) for determination of PD-L1 expression and other exploratory biomarker analysis. Biopsy samples should be excisional, incisional, or core needle. Tumor biopsies should be placed in formalin for IHC of tumor and TIL, RNALater for gene expression, and media for flow cytometry analysis. See Table 5.6.9-1 for Biomarker Sampling Schedule
Additional Exploratory Biomarker Assessments				
Serum Plasma PBMC Whole Blood	See Table 5.6.9-1 for Biomarker Sampling Schedule			
Subsequent therapy	See Note			Postoperative treatment of participants Adjuvant chemotherapy and/or radiation therapy: Postoperative treatment will be administered at the discretion of the treating physician based on established standard indications. Postoperative treatment will start at a time based on the standard of care approach at the institution taking into account postoperative recovery time for the subject. Postoperative treatment should not commence until nivolumab-related toxicity has resolved to < grade 2.

Table 5.1-4: On Treatment Assessments Neoadjuvant Cohort (CA209358)

Procedure	Day 1	Day 15	Pre-Surgery Visit (up to7 days prior to surgery)	Notes
PK and Immunogenicity Assessments				
PK samples	See Table 5.5-2 of PK and Immunogenicity Sampling			
Immunogenicity samples	See Table 5.5-2 of PK and Immunogenicity Sampling			
Outcomes Research Assessments				
EORTC QLQ-C30	X	X		
EQ-5D	X	X		
Clinical Drug Supplies				
Administer Study Drug	X	X		First dose to be administered within 5 days of study drug assignment. Subjects may be dosed no less than 12 days between doses and no more than 7 days from the scheduled 2nd dose. Confirmation of viral status will be required prior to study drug assignment for SCCHN subjects enrolled in the neoadjuvant cohort.

Table 5.1-5: Eligibility Assessments and On-Treatment Assessments - Subjects Receiving Study Drug Post-Standard of Care (CA209358)

Procedure	Cycle 1 Day 1 (C1D1)	Each Cycle (every 2 Weeks) on Day 1 (± 3 days)	Notes
Eligibility Assessments			
Inclusion/Exclusion Criteria	X		Eligibility must be assessed within 72 hours per inclusion/exclusion criteria for metastatic subjects as defined in Section 3.3, with the following exceptions/specificities: • Subjects who completed the neoadjuvant portion of the study must have developed unresectable recurrent or metastatic disease within 1 year of surgery or chemotherapy/radiation completion to be eligible. • Exclusion criterion '2.f' regarding prior therapies is not applicable. Subjects who meet discontinuation criteria at Cycle 1 Day 1 are not eligible to receive nivolumab. See Section 3.5 for discontinuation criteria.
Safety Assessments			
Targeted Physical Examination	X	X	Targeted examination must include at a minimum the following body systems: Cardiovascular Gastrointestinal Pulmonary Neurological exam for subjects with brain metastases Within 72 hours prior to dosing
Vital Signs	X	X	Temperature, BP, and HR prior to dosing and at any time a subject has any new or worsening respiratory symptoms. Obtain vital signs within 72 hours prior to dosing.
Physical Measurements	X	X	Includes Weight[a] and ECOG performance status See Appendix 1 for ECOG scale

Table 5.1-5: Eligibility Assessments and On-Treatment Assessments - Subjects Receiving Study Drug Post-Standard of Care (CA209358)

Procedure	Cycle 1 Day 1 (C1D1)	Each Cycle (every 2 Weeks) on Day 1 (± 3 days)	Notes
			Obtain physical measurements within 72 hrs. prior to dosing.
Adverse Events Assessment	------- Continuously -------		Assessed using NCI CTCAE version 4.
Review of Concomitant Medications	X	X	
Laboratory Tests	X	X	On-study local laboratory assessments should be done within 72 hours prior to dosing for every cycle and include: CBC with differential and platelet count, BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphorus, chloride, bicarbonate or total CO2 (if locally available), amylase, lipase, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH, albumin.
Thyroid Function Testing		See Note	TSH (reflex to free T3 and free T4 if abnormal result) to be performed every 6 weeks (± 1 week).
Pregnancy Test	X	See Note	Serum or urine within 24 hours prior to first dose and then at least once every 4 weeks (+/- 1 week) regardless of dosing schedule.

Table 5.1-5: Eligibility Assessments and On-Treatment Assessments - Subjects Receiving Study Drug Post-Standard of Care (CA209358)

Procedure	Cycle 1 Day 1 (C1D1)	Each Cycle (every 2 Weeks) on Day 1 (± 3 days)	Notes
Efficacy Assessments			
Radiographic Tumor Assessment Spiral CT/MRI of Chest, Abdomen, Pelvis, and any other known sites of disease		See Note	See Table 5.4.1-1 for imaging frequency See Appendix 3 (RECIST 1.1 Guidelines) for details regarding imaging methodology requirements and assessments Should be performed within 35 days prior to first dose or restarting nivolumab. Additional sites of known or suspected disease (including CNS) should be imaged at the screening visit and at subsequent on-study assessments.
Additional Exploratory Biomarker Testing			
Serum Whole Blood Tumor Biopsy PMBC	See Note	See Note	See Table 5.6.9-4 for Biomarker Sampling Schedule
PK and Immunogenicity Assessments			
PK samples	See Note		See Table 5.5-3 of PK and Immunogenicity Sampling
Immunogenicity samples	See Note		See Table 5.5-3 of PK and Immunogenicity Sampling
Outcomes Research Assessments			
EORTC QLQ-C30	X	See Note	Assessments to be collected every 4 cycles for the first 17 cycles; Day 1 (prior to dosing) of Cycles 5, 9, 13, 17 every 6 cycles thereafter; Day 1 (prior to dosing) of Cycles 23, 29, 35+.
EQ-5D	X	See Note	

Table 5.1-5: Eligibility Assessments and On-Treatment Assessments - Subjects Receiving Study Drug Post-Standard of Care (CA209358)

Procedure	Cycle 1 Day 1 (C1D1)	Each Cycle (every 2 Weeks) on Day 1 (± 3 days)	Notes
Clinical Drug Supplies			
Administer Study Drug	X	X	Within 5 days from vial allocation, the subject must receive the first dose of study drug. Subjects may be dosed no less than 12 days between doses and no more than 3 days from the scheduled dose

[a] Dosing calculations should be based on the body weight assessed at baseline. It is not necessary to re-calculate subsequent doses if the participant weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded up or to the nearest milligram per institutional standard.

Table 5.1-6: Follow-Up Assessments - All Subjects (CA209358)

Procedure	X, Follow-Up[a] Visits X01 and X02	Follow-Up Assessments for Neoadjuvant Cohort Subjects 4, 8, and 12 Months Post-Surgery[b]	S, Survival Follow-Up[c] Visits	Notes
Safety Assessments				
Targeted Physical Examination	X			Lymph node areas (eg, submandibular, cervical, supraclavicular, axillary, or inguinal lymph node), and abdominal organs (eg, spleen, liver). To assess for potential late emergent study drug related issues
Adverse Events Assessment	X		X	NSAEs and SAEs must be collected up to 100 days after study drug discontinuation. SAEs that relate to any later protocol specified procedure must be collected.
Review of Medical History and Subsequent Cancer Therapy Information	X	X	X	
Laboratory Tests	X			CBC with differential and platelet count, BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphorus, chloride, bicarbonate or total CO2 (if locally available), amylase, lipase, glucose, AST, ALT, total bilirubin, alkaline phosphatase, LDH, albumin..
Thyroid Function Testing	X			TSH (reflex to free T3 and free T4 if abnormal result)
Pregnancy Test	X			Serum or urine

Table 5.1-6: Follow-Up Assessments - All Subjects (CA209358)

Procedure	X, Follow-Up[a] Visits X01 and X02	Follow-Up Assessments for Neoadjuvant Cohort Subjects 4, 8, and 12 Months Post-Surgery[b]	S, Survival Follow-Up[c] Visits	Notes
Efficacy Assessments				
Radiographic Tumor Assessment Spiral CT/MRI	See Note	X	See note	Only for subjects without progression and no longer on study therapy See Table 5.4.1-1 for Spiral CT/MRI. For subjects in the neoadjuvant cohort, radiographic tumor assessment should be at 4 mo, 8 mo and 12 mo post-surgery.[b] Subjects with a history of brain metastasis may have surveillance MRI approximately every 12 weeks or sooner if clinically indicated
Outcomes Research Assessments				
EORTC QLQ-C30	X			
EQ-5D	X		X	EQ-5D during the survival follow-up will be assessed during a clinic visit or via a phone contact
Pharmacokinetic/Immunogenicity Assessments				
PK Samples	X			See Table 5.5-1, Table 5.5-2, Table 5.5-3, Table 5.5-4, Table 5.5-5, and Table 5.5-8 for PK and Immunogenicity Sampling
Immunogenicity samples	X			

Table 5.1-6: Follow-Up Assessments - All Subjects (CA209358)

Procedure	X, Follow-Up[a] Visits X01 and X02	Follow-Up Assessments for Neoadjuvant Cohort Subjects 4, 8, and 12 Months Post-Surgery[b]	S, Survival Follow-Up[c] Visits	Notes
Additional Exploratory Biomarker Testing				
Serum	See Note.			Collection of Biomarker samples at time of progression is optional. See Table 5.6.9-1, Table 5.6.9-2, and Table 5.6.9-3, and Table 5.6.9-4 for Biomarker Sampling Schedule.
Whole Blood				
Tumor Biopsy				
PMBC				
Plasma				
Subject Status				
Survival Status	X	X	X	Every 3 months after X02; may be accomplished by visit or phone contact, to update survival information and assess subsequent anti-cancer therapy.

[a] X visits occur as follows: X01 = 35 days ± 7 days from last dose or from the date decision is made to discontinue subject from the study (only applicable for early treatment discontinuation), X02 = 80 days ± 7 days from X01. Neoadjuvant cohort subjects will have these visits labeled as E01 (35 days +/ 7 days from last dose) and E02 (80 days +/ 7 days) visits in the CRF. For neoadjuvant cohort subjects receiving nivolumab as part of the post-standard of care, X01 and X02 visits will be completed after the last dose

[b] Follow-Up Assessments for Neoadjuvant Cohort Subjects, 4, 8, and 12 Months Post-Surgery, may occur ±7 days from scheduled time point. 4 Month Post-Surgery may occur ±3 weeks from scheduled time point. Neoadjuvant Cohort. E02 and E03 follow-up can occur at the same time.

[c] S, Survival Follow-Up visits continue every 3 months after X visits.

5.1.1 Retesting During Screening or Lead-in Period

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

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

5.2 Study Materials

- NCI CTCAE version 4
- BMS-936558 (nivolumab) Investigator Brochure
- Ipilimumab Investigator Brochure
- BMS-986016 (relatlimab) Investigator Brochure
- Daratumumab Investigator Brochure
- Pharmacy Binder
- Laboratory manuals for collection and handling of blood (including biomarker and immunogenicity) and tissue specimens
- Site manual for operation of interactive response technology system, including enrollment worksheets
- Manual for entry of local laboratory data
- Pregnancy Surveillance Forms
- Serious Adverse Events (or eSAE) case report forms
- EORTC QLQ-C30 and EQ-5D questionnaires
- CT/MRI/PET Subject Scanning Guide
- CT-MRI Subject Data Transmittal Form
- PET-CT Subject Data Transmittal Form

5.3 Safety Assessments

At baseline, a medical history will be obtained to capture relevant underlying conditions. The baseline examinations should include signs and symptoms, weight, height, ECOG Performance Status, BP, HR, temperature, and respiratory rate should be performed within 14 days prior to first dose except where noted in Table 5.1-1. Concomitant medications will also be collected from within 14 days prior to first dose and through the study treatment period (See Table 5.1-1, Table 5.1-2, Table 5.1-3, Table 5.1-4, and Table 5.1-5).

Baseline safety laboratory assessments should be done within 14 days prior to the first dose and include: CBC with differential and platelet count, Chemistry panel including LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, P, glucose, bicarbonate or total CO2 (if locally available), albumin, amylase, lipase, TSH (reflex to free T3, free T4 for abnormal TSH result), hepatitis B surface antigen (HBV sAg, Australia antigen), and hepatitis C antibody (HCV Ab, RNA) (see Table 5.1-1). Pregnancy testing for WOCBP (done locally) to be done within 24 hours prior to first dose, and then every 4 weeks (± 1 week) regardless of dosing schedule, and at each safety follow up visit. Safety assessments for subjects assigned to Combo C

will also include cardiac troponin levels: T (cTnT) or I (cTnI). If the pre-dose troponin level is above the ULN dosing should be held, subject should undergo prompt cardiac evaluation, and the medical monitor should be notified.

Determination of safety lab results is required prior to dosing. If there are delays with obtaining results for certain tests, please contact the medical monitor to determine clinical significance.

Subjects will be evaluated for safety if they have received any study drug. Toxicity assessments will be performed continuously during the treatment phase. During the safety follow-up phase (Table 5.1-6) toxicity assessments should be done in person. Once subjects reach the survival follow-up phase, either in-person visits or documented telephone calls to assess the subject's status are acceptable.

Adverse events and laboratory values will be graded according to the NCI-CTCAE version 4.

On-study weight and ECOG performance status should be assessed at each on-study visit prior to nivolumab dosing. On treatment vital signs may be performed within 72 hours prior to dose. In addition, vital signs can also be taken as per institutional standard of care prior to; during and after the infusion. The start and stop time of the nivolumab infusion should be documented. Physical examinations are to be performed at treatment visits as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse event page.

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

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

5.4 Efficacy Assessments

5.4.1 Imaging Assessments for the Study

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

Study evaluations will take place in accordance with the flow charts in Section 5.1, Table 5.4.1-1, Table 5.4.1-2, and Appendix 3. For the Neoadjuvant cohort, any images obtained prior to Month 4 as standard of care should also be assessed.

In addition to chest, abdomen, and pelvis, all known sites of disease should be assessed at baseline. Subsequent assessments should include chest, abdomen, and pelvis, and all known sites of disease and should use the same imaging method as was used at baseline. Baseline MRI for brain should be done for known or suspected disease.

Tumor imaging assessments for ongoing study treatment decisions will be completed by the investigator using RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 criteria, see Appendix 3.

All study images will be submitted to an imaging core laboratory for review. Sites should be trained prior to sending in the first image. Image acquisition guidelines and submission process will be outlined in the CA209358 Imaging Manual to be provided by the core imaging laboratory.

Table 5.4.1-1: Schedule of Spiral CT/MRI Tumor Assessments for Metastatic Cohorts (Monotherapy and Combination Therapy), and Subjects Treated with Study Drug Post-Standard of Care Adjuvant Treatment

Time On Study	Assessment Frequency	Assessment Week (Day 1 of Week Shown)	Assessment Window
Metastatic Cohort Subjects During First Year of Treatment	At screening (within 35 days of first dose), then every 8 weeks	Screening, 8, 16, 24, 32, 40, 48	± 1 week
Metastatic Cohort Subjects During Second Year of Treatment and Beyond	Every 12 weeks	60, 72, 84, 96, etc.	± 2 weeks
Neoadjuvant Subjects Treated with Study Drug Post-Standard of Care	Scan documenting progression is required, then every 8 weeks	Screening, 8, 16, 24, 32, 40, 48	± 1 weeks
For Subjects Treated with Study Drug Post-Standard of Care During Second Year of Treatment and Beyond	Every 12 weeks	60, 72, 84, 96, etc.	± 2 weeks

Table 5.4.1-2: Schedule of Spiral CT/MRI Tumor Assessments for Neoadjuvant Cohort

Time On Study	Assessment Frequency	Assessment Window
Screening	At screening (within 35 days of first dose)	Within 35 days of first dose
Pre-Surgery	Day 29 (within 7 days prior to the planned surgery date)	within 7 days prior to the planned surgery date
Post-Surgery	Months 4, 8, and 12[a]	Months 4 (within ±3 weeks), 8, and 12[b]

[a] Any images obtained prior to Month 4 as standard of care should also be assessed.

[b] 4-Month Post-Surgery Assessments for Neoadjuvant Cohort Subjects may occur ± 3 weeks from scheduled time point. Follow-up assessments 8 and 12 Months Post-Surgery may occur ± 7 days from the scheduled time point. Neoadjuvant Cohort E02 and E03 Follow Up may occur at same time.

For the Metastatic Cohorts (monotherapy and combination therapy), baseline tumor assessments should be performed within 35 days prior to the first dose. Subjects will then be evaluated for tumor response beginning 8 weeks from the date of first dose (± 1 wk.), then every 8 weeks (± 1 wk.) thereafter up to 48 weeks, then it will be every 12 weeks (± 2 weeks) until disease progression is documented, or when treatment is discontinued (whichever occurs later).

For the Neoadjuvant Cohort, a Day 29 tumor scan is required for within 7 days prior to the planned surgery date.

For Neoadjuvant Cohort subjects who progress to unresectable recurrent or metastatic disease within 1 year of surgical resection or chemotherapy/radiation and receive nivolumab, a baseline tumor scan documenting progression is required prior to restarting nivolumab. Subjects will then be evaluated for tumor response beginning 8 weeks from the date of first dose of treatment (± 1 wk.), then every 8 weeks (± 1 wk.) thereafter up to 48 weeks, then it will be every 12 weeks (± 2 week) until disease progression is documented, or when treatment is discontinued, (whichever occurs later).

5.4.2 Primary Efficacy Assessment

The investigator objective response rate (ORR) of nivolumab monotherapy is the primary endpoint among all treated subjects in the recurrent/metastatic monotherapy cohort. The investigator objective response rate (ORR) of nivolumab combination therapy (ipilimumab, BMS-986016, daratumumab) is the primary endpoint among all treated subjects in the recurrent/metastatic combination cohort for combination therapies, Combo A, B, C and D.

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 all treated subjects. BOR is defined as the best response designation recorded between the date of first dose and the date of the initial objectively documented tumor progression per investigator assessment using RECIST 1.1 criteria or the date of subsequent therapy, whichever occurs first.

5.4.3 Secondary Efficacy Assessments

Not applicable

5.5 Pharmacokinetic Assessments

Samples for pharmacokinetic and immunogenicity assessments will be collected for all subjects receiving nivolumab as a monotherapy or in combination with ipilimumab, BMS-986016 (relatlimab), or daratumumab. Table 5.5-1, Table 5.5-2, and Table 5.5-3 list the sampling schedule to be followed for pharmacokinetics and immunogenicity of nivolumab. Table 5.5-4 and Table 5.5-5 list the sampling schedule to be followed for pharmacokinetics and immunogenicity of nivolumab and ipilimumab. Table 5.5-6 lists the sampling schedule to be followed for pharmacokinetics and immunogenicity of nivolumab and BMS-986016 (relatlimab). Table 5.5-7 and Table 5.5-8 list the sampling schedule to be followed for pharmacokinetics and immunogenicity of nivolumab and daratumumab, respectively, for nivolumab and daratumumab combination cohort. All time points in nivolumab/ipilimumab and nivolumab/BMS-986016

(relatlimab) combination cohorts are relative to the start of nivolumab infusion. In the nivolumab/daratumumab combination cohort, daratumumab will be administered after nivolumab and predose sample for daratumumab should be drawn with a window of -2 hours before the start of daratumumab dosing. Daratumumab post-dose samples should be drawn within 2 hours after the end of the infusion. All on-treatment PK time points are intended to align with days on which nivolumab is administered. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected, but the dose is subsequently delayed, an additional predose sample should not be collected.

The exact dates and times of blood sampling must be recorded. Refer to the Laboratory Manual for sample collection requirements. Collected samples must be stored under the specified and controlled conditions for the temperatures indicated in the Laboratory Manual. Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

Table 5.5-1: Pharmacokinetic and Immunogenicity Sampling Schedule (Metastatic Monotherapy Cohort)

Study Day	Event (Relative to Start of Infusion/Event)	Time (Relative to Start of Nivolumab Infusion) Hour:Min	Nivolumab PK Blood Sample	Nivolumab Immunogenicity Sample
Cycle 1 Day 1 (Week 1 Day 1)	predose[a]	00:00	X	X
Cycle 5 Day 1(Week 9 Day 1)	predose[a]	00:00	X	X
Cycle 7 Day 1 (Week 13 Day 1)	predose[a]	00:00	X	X
Day 1 of every 8th cycle (every 16 weeks) until discontinuation of study treatment[b]	predose[a]	00:00	X	X
First 2 Follow-up visits- X01 & X02			X	X

[a] Predose samples should be taken just prior to the administration (preferably within 30 minutes). If the infusion is delayed and a pre-dose sample was already collected, there is no need to collect an additional pre-dose sample.

[b] For subjects during second year of treatment and beyond, PK collections will occur every 24 weeks instead of every 16 weeks.

Table 5.5-2: Pharmacokinetic and Immunogenicity Sampling Schedule (Neoadjuvant Cohort)

Study Day	Event (Relative to Start of Infusion/Event)	Time (Relative to Start of Nivolumab Infusion) Hour:Min	Nivolumab PK Blood Sample	Nivolumab Immunogenicity Sample
Cycle 1 Day 1 (Week 1 Day 1)	predose[a]	00:00	X	X
Pre-Surgery Visit (Up to 7 days prior to surgery)	Prior to surgery	00:00	X	X
First 2 Follow-up visits- X01 & X02			X	X

[a] Predose samples should be taken just prior to the administration (preferably within 30 minutes). If the infusion is delayed and a pre-dose sample was already collected, there is no need to collect an additional pre-dose sample.

Table 5.5-3: Pharmacokinetic and Immunogenicity Sampling Schedule (Subjects Receiving Nivolumab Post-Standard of Care)

Study Day	Event (Relative to Start of Infusion/Event)	Time (Relative to Start of Nivolumab Infusion) Hour:Min	Nivolumab PK Blood Sample	Nivolumab Immunogenicity Sample
Cycle 1 Day 1 (Week 1 Day 1)[a]	predose[b]	00:00	X	X
Cycle 5 Day 1(Week 9 Day 1)	predose[b]	00:00	X	X
Cycle 7 Day 1(Week 13 Day 1)	predose[b]	00:00	X	X
Day 1 of every 8th cycle (every 16 weeks) until discontinuation of study treatment[c]	predose[b]	00:00	X	X
First 2 Follow-up visits- X01 & X02			X	X

[a] The day subjects start study drug after standard of care will be considered Cycle 1 Day 1 (Week 1 Day 1).

[b] Predose samples should be taken just prior to the administration (preferably within 30 minutes). If the infusion is delayed and a pre-dose sample was already collected, there is no need to collect an additional pre-dose sample.

[c] For subjects during second year of treatment and beyond, PK collections will occur every 24 weeks instead of every 16 weeks.

Table 5.5-4: Pharmacokinetic and Immunogenicity Sampling Schedule (Nivolumab and Ipilimumab Combination - Combo A)

Study Day[a]	Event (Relative to Start of Infusion/Event)	Time (Relative to Start of Nivolumab Infusion) Hour:Min	PK Blood Sample	Immunogenicity Sample for Nivolumab and Ipilimumab
Week 1 Day 1	predose[b]	00:00	X	X
Week 7 Day 1	predose[b]	00:00	X	X
Week 19 Day 1	predose[b]	00:00	X	X
Day 1 of every 18 weeks after Week 19 until discontinuation of study treatment	predose[b]	00:00	X	X
First 2 Follow-up visits- X01 & X02			X	X

[a] If a subject permanently discontinues both study drug treatments during the sampling period, they will move to sampling at the follow up visits. If ipilimumab is discontinued and nivolumab continues, ipilimumab PK and ADA should be collected only for the next 2 time points (corresponding to nivolumab sample collection) according to the PK table. If nivolumab is discontinued and ipilimumab continues, nivolumab PK and ADA should be collected only for the next 2 time points (corresponding to ipilimumab sample collection) according to the PK table.

[b] Pre-dose samples should be taken just prior to the start of infusion (preferably within 30 minutes). If the infusion is delayed and a pre-dose sample is already collected, there is no need to collect an additional pre-dose sample.

Table 5.5-5: Pharmacokinetic and Immunogenicity Sampling Schedule (Nivolumab and Ipilimumab Combination - Combo B)

Study Day[a]	Event (Relative to Start of Infusion/Event)	Time (Relative to Start of Nivolumab Infusion) Hour:Min	PK Blood Sample	Immunogenicity Sample for Nivolumab and Ipilimumab
Week 1 Day 1	predose[b]	00:00	X	X
Week 4 Day 1	predose[b]	00:00	X	X
Week 7 Day 1	predose[b]	00:00	X	X
On Day 1 every 18 weeks beyond Week 7 until discontinuation of study treatment	predose[b]	00:00	X[c]	X[c]
First 2 Follow-up visits- X01 & X02			X[c]	X[c]

[a] If a subject permanently discontinues both study drug treatments during the sampling period, they will move to sampling at the follow up visits. If ipilimumab is discontinued and nivolumab continues, ipilimumab PK and ADA should be collected only for the next 2 time points (corresponding to nivolumab sample collection) according to the PK table. If nivolumab is discontinued and ipilimumab continues, nivolumab PK and ADA should be collected only for the next 2 time points (corresponding to ipilimumab sample collection) according to the PK table.

[b] Pre-dose samples should be taken just prior to the start of infusion (preferably within 30 minutes). If the infusion is delayed and a pre-dose sample is already collected, there is no need to collect an additional pre-dose sample.

[c] PK and immunogenicity samples will be collected only for nivolumab. For ipilimumab, only week 25 PK and immunogenicity samples will be collected.

Table 5.5-6: Pharmacokinetic and Immunogenicity Sampling Schedule (Nivolumab and Relatlimab Combination - Combo C)

Study Day[a]	Event (Relative to Start of Infusion/Event)	Time (Relative to Start of Nivolumab Infusion) Hour:Min	PK Blood Sample for Nivolumab and Relatlimab	Immunogenicity Sample for Nivolumab and Relatlimab
Cycle 1 Day 1 (Week 1 Day 1)	Predose[b]	00:00	X	X
Cycle 3/5[c] Day 1 (Week 9 Day 1)	predose[b]	00:00	X	X
Cycle 4/7 Day 1 (Week 13 Day 1)[d]	predose[b]	00:00	X	X
Day 1 of every 8th cycle (every 16 weeks) until discontinuation of study treatment or up to 2 years of treatment	predose[b]	00:00	X	X

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

[b] Pre-dose samples should be taken just prior to the start of infusion (preferably within 30 minutes). If the infusion is delayed and a pre-dose sample is already collected, there is no need to collect an additional pre-dose sample.

[c] Cycle 3 pertains to the nivolumab every 4 week (q4w) regimen; Cycle 5 pertains to the nivolumab every 2 week (q2w) regimen.

[d] Cycle 4 pertains to the nivolumab every 4 week (q4w) regimen; Cycle 7 pertains to the nivolumab every 2 week (q2w) regimen.

Table 5.5-7: Pharmacokinetic and Immunogenicity Sampling Schedule for Nivolumab (Nivolumab and Daratumumab Combination - Combo D)

Study Day (1 Cycle = 1 week from Weeks 1-8 1 Cycle -= 2 weeks from Weeks 9-24 1 Cycle = 4 weeks from Week 25)	Event (Relative to Start of Infusion/Event)	Time (Relative to Start of Nivolumab Infusion) Hour:Min	PK Blood Sample for Nivolumab	Immunogenicity Sample for Nivolumab
Cycle 3 Day 1 (Week 3 Day 1)[a]	Predose[b]	00:00	X	X
Cycle 9 Day 1(Week 9 Day 1)	Predose[b]	00:00	X	X
Cycle 11 Day 1(Week 13 Day 1)	Predose[b]	00:00	X	X
Cycle 17 day 1 (Week 25 Day 1)[c]	Predose[b]	00:00	X	X
Day 1 of every 4th cycle (every 16 weeks) until discontinuation of study treatment or up to 2 years of treatment	Predose[b]	00:00	X	X

[a] Nivolumab will start at Week 3.

[b] Pre-dose samples should be taken prior to the start of both nivolumab and daratumumab infusion. If the infusion is delayed and a pre-dose sample is already collected, there is no need to collect an additional pre-dose sample

[c] Starting from Week 25, nivolumab will be given 480 mg Q4W

Table 5.5-8: Pharmacokinetic and Immunogenicity Sampling Schedule for Daratumumab (Nivolumab and Daratumumab Combination - Combo D)

Study Day	Event (Relative to Start of Daratumumab Infusion/Event)[a]	Time (Relative to Start of Daratumumab Infusion) Hour:Min	PK Blood Sample for Daratumumab	Immunogenicity Assessment for Daratumumab (taken from Dara PK sample)[b]
Week 1 Day 1	Predose[a]	00:00	X	X
Week 1 Day 1	Postdose	EOI	X	
Week 5 Day 1	Predose	00:00	X	X
Week 5 Day 1	Postdose	EOI	X	
Week 9 Day 1	Predose[a]	00:00	X	X
Week 13 Day 1	Predose[a]	00:00	X	X

Table 5.5-8: Pharmacokinetic and Immunogenicity Sampling Schedule for Daratumumab (Nivolumab and Daratumumab Combination - Combo D)

Study Day	Event (Relative to Start of Daratumumab Infusion/Event)[a]	Time (Relative to Start of Daratumumab Infusion) Hour:Min	PK Blood Sample for Daratumumab	Immunogenicity Assessment for Daratumumab (taken from Dara PK sample)[b]
Week 25 Day 1	Predose[a]	00:00	X	X
Week 41 Day 1	Predose[a]	00:00	X	
Week 57 Day 1	Predose[a]	00:00	X	X
Week 73 Day 1	Predose[a]	00:00	X	
Week 89 Day 1	Predose[a]	00:00	X	
Week 105 Day 1	Predose[a]	00:00	X	X
Follow-up visit 1	4 weeks (± 1 week) after last dose of dara		X	X
Follow up visit 2	8 weeks (± 1 week) after last dose of dara		X	X

[a] Daratumumab predose PK samples should be drawn before administration of either nivolumab or daratumumab (window of -2 hours before that start of dara dosing). Daratumumab post dose samples should be drawn within 2 hours after the end of the infusion.

[b] Daratumumab immunogenicity will be assessed from an aliquot of the daratumumab PK blood sample – no additional blood draw is required.

5.5.1 Pharmacokinetic Sample Analysis

Serum samples will be analyzed for nivolumab, ipilimumab, BMS-986016 (relatlimab), or daratumumab concentrations by a validated method. In addition, selected samples may be analyzed by an exploratory analytical method that measures nivolumab, ipilimumab, BMS-986016 (relatlimab), or daratumumab for technology exploration purposes; exploratory results will not be reported.

5.6 Biomarker Assessments

Peripheral blood and tumor tissue will be collected prior to therapy and at selected time points on treatment as outlined in the Biomarker Sampling Schedule in Table 5.6.9-1, Table 5.6.9-2, Table 5.6.9-3, and Table 5.6.9-4 unless restricted by local requirements. Detailed instructions of the obtaining, processing, labeling, handling, storage and shipment of specimens will be provided in a separate Procedure Manual at the time of study initiation.

5.6.1 Determination of Tumor's Viral Positivity

Confirmation of viral status will be required prior to study drug assignment for EBV gastric cancer and HPV SCCHN tumor types in the metastatic cohorts. Confirmation of viral status will also be required prior to study drug assignment for SCCHN subjects enrolled in the neoadjuvant cohort and Metastatic Combination Cohorts A and C. For SCCHN subjects in Cohort D and in all other tumor types, viral status will not be required prior to subject enrollment, but will be determined retrospectively if the viral status is not already known. Viral testing determined more than 35 days prior to first dose may be used. Viral status will be determined using an appropriately validated test as described below for each of the tumor types.

EBV Gastric: In situ hybridization EBV RNA (EBER) of FFPE sections. Testing for EBV positivity will be performed prior to study drug assignment using the EBER1 DNP probe from Ventana in a properly certified lab. Samples interpreted as (+) if nuclear staining of any intensity above the background in tumor cells, provided the negative internal controls (adjacent normal tissue) are negative.

HPV Head and Neck: HPV p-16 status should be assessed using the following criteria: p16 IHC should be done with anti-p16INK4a clone E6H4 from MTM labs (Roche). Interpretation as positive if > 70% strong and diffuse nuclear and cytoplasmic staining is specific to tumor cells; p-16 status will be reported as either p-16 positive or p-16 negative. If results acquired according to these criteria are not available, then a sample (tissue on microscopic slides, tissue block or a fresh tissue biopsy in formalin) should be sent to sponsor-contracted laboratory for analysis. HPV 16 in situ hybridization may also be performed retrospectively.

Polyomavirus MCC: Assessment of polyomavirus by IHC will be performed retrospectively at a sponsor-contracted laboratory if the polyomavirus status is unknown. If the polyomavirus status is known, please report this information on the provided case report form.

Cervical, vaginal, vulvar, anal canal and penile: HPV positivity is defined by FDA approved tests (Cobas HPV Test; Digene Hybrid Capture 2 High-Risk HPV DNA Test; Cervista™ HPV HR and Genfind™ DNA Extraction Kit; Cervista™ HPV 16/18; APTIMA® HPV Assay) or other well validated commercially available tests (such as Ventana Inform HPV ISH test) comprising in situ hybridization, real-time PCR, or immunohistochemistry (IHC). High-risk HPV positivity includes the following subtypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. Virus testing will be performed retrospectively only if results from prior accepted testing are not available. If the HPV status is known please report this information on the provided case report form.

EBV Nasopharyngeal: In situ hybridization EBV RNA (EBER) of FFPE sections. Testing for EBV positivity will be performed using the EBER1 DNP probe from Ventana in a properly certified lab. Samples interpreted as (+) if nuclear staining of any intensity above the background in tumor cells, provided the negative internal controls (adjacent normal tissue) are negative.

Soluble Biomarkers: Soluble factors, such as cytokines, chemokines, soluble receptors, and antibodies to tumor antigens may be characterized and quantified by immunoassays in serum. Analyses may include, but not necessarily be limited to, soluble CD25, soluble PD-1, soluble

LAG-3, and CXCL-9. Collected serum samples may also be used for the assessment of tumor antigen-specific responses elicited following treatment with monotherapy to explore which antitumor antibodies are most associated with clinical response. Antibody levels to cancer test antigens will be assessed by multiplex assays and enzyme-linked immunosorbent assay (ELISA).

5.6.2 Viral-related Assessments

Quantification of EBV DNA by PCR, when appropriate, to correlate viral load to response. MHC tetramers assay may be used for analysis of virus-specific T cells. The seropositivity to viral oncoprotein antibodies and anti-viral antibodies may be examined in serum samples. PBMCs and/or lymphocytes isolated from tumors may be used in ELISPOT assays for T cell responses to viral antigens and/or epitope spreading.

5.6.3 HLA Genotyping

HLA typing of peripheral blood samples may be assessed by standard genotyping methods.

5.6.4 Immunophenotyping

The proportion of specific lymphocyte subsets and expression levels of T cell co-stimulatory and inhibitory markers in peripheral blood mononuclear cell (PBMC) preparations may be quantified by cytometry. Analyses may include, but not necessarily be limited to, the proportion of T, B, and NK cells, proportion of memory and effector T cell subsets, and expression levels of PD-1, PD-L1, PD-L2, ICOS, and Ki67. Whole blood samples will also be collected to quantify myeloid-derived suppressor cells (MDSC) before and after treatment.

5.6.5 Ex Vivo Functional Assays

To explore whether nivolumab may restore T cell activation and function, peripheral blood mononuclear cells (PBMCs) will be isolated and cryopreserved. Assays of the functional status of effector T cells may be performed, including but not limited to, assays for interferon-gamma (IFN-ϒ) and CD107.

5.6.6 Peripheral Blood Gene Expression

The expression level of genes and miRNA related to response to nivolumab as monotherapy or in combination with either ipilimumab, BMS-986016 (relatlimab), or daratumumab will be quantified by molecular methods such as nanostring, RNAseq, microarray, and/or quantitative reverse transcription polymerase chain reaction (RT-PCR) analysis of whole blood samples. Analysis may include, but not necessarily be limited to, genes associated with immune-related pathways, such as T cell activation and antigen processing and presentation.

5.6.7 T Cell Repertoire Analysis

Low diversity of the peripheral T cell compartment has been shown to correlate with poor overall survival in metastatic breast cancer.[187] A standing theory in immuno-oncology suggests a diverse and activated immune environment is better adept at eradicating tumor compared to a skewed repertoire of naïve and tolerized T cells. In order to explore whether a diverse T cell repertoire is predictive of response to therapy, next generation, high-throughput, DNA sequencing maybe

performed on DNA isolated from peripheral blood and tumor tissue to quantitate the composition of the T cell repertoire prior to and during monotherapy.

5.6.8 Single Nucleotide Polymorphism (SNP) Analysis

In order to identify potential polymorphisms associated with safety and efficacy of nivolumab, selected genes may be evaluated for single nucleotide polymorphisms (SNP). Analysis may include but will not be limited to sequence polymorphisms linked to genes associated with the PD-1/PD-L1 pathway and activated T cell phenotype, including PD-1, PD-L1, PD-L2, and CTLA-4. A blood sample will be obtained at Day 1, unless restricted by local regulations.

5.6.9 Tumor Samples

Tumor tissue specimen requirements for the Neoadjuvant Cohort are as follows:

- At Baseline (Prior to first dose of study drug): Biopsy and submission of fresh tumor tissue is mandatory for all subjects. Biopsy is indicated for subjects with accessible lesions where biopsy is deemed safe by the Investigator.
- Day 29 (On-treatment) fresh samples obtained via scheduled surgical resection or scheduled biopsy are mandatory.
- Day 29 (On-treatment) samples must be reviewed by pathologist and a copy of the pathology report must be sent to BMS
- All other time points where tumor tissue collections are indicated, aside from baseline and Day 29, are described in Table 5.6.9-1.

Tumor tissue specimen requirements for the Metastatic Cohort (Monotherapy and Combination Therapy) are as follows:

- At Baseline (Prior to first dose of study drug): Biopsy and submission of fresh tumor tissue, or submission of archived tumor tissue, is mandatory for all subjects. Biopsy is indicated for subjects with accessible lesions where biopsy is deemed safe by the Investigator.
- An on-treatment biopsy and submission of fresh tumor tissue is mandatory for subjects in each tumor type in the metastatic cohort to ensure an adequate number of paired samples to perform meaningful analyses to support biomarker objectives. Subjects with accessible lesions where biopsy is deemed safe by the Investigator should undergo biopsy per protocol.
- All other time points where tumor tissue collections are indicated, aside from baseline and the one mandatory on-treatment biopsy, are described in Table 5.6.9-2 and Table 5.6.9-3.

Tumor tissue specimen requirements for Subjects Treated with Study Drug Post-Standard of Care are as follows:

- At Cycle 1 Day 1 biopsy and submission of fresh tumor tissue is strongly encouraged for subjects with accessible lesions where biopsy is deemed safe by the Investigator.
- All other time points where tumor tissue collections are indicated, aside from Cycle 1 Day 1, are described in Table 5.6.9-4.

Submission of fresh tumor tissue collected via biopsy is required for TILs isolation for ex-vivo functional assays (RPMI media preparation), and also for gene expression profiling (RNALater samples). Please refer to Central Lab Manual for detailed sample requirements.

Submission of tissue samples (FFPE tumor tissue block or slides) is required for characterization of tumor infiltrating lymphocytes (TILs) and tumor, utilizing immunohistochemistry (IHC) methods. A minimum of 1 FFPE tumor tissue block (preferred) OR minimum of 15 FFPE unstained sections are required for this purpose. Tissue for this purpose may be obtained during the screening phase, prior to resection, or collected as a standard of care procedure within 90 days prior to obtaining informed consent, and is mandatory. Please refer to Central Lab Manual for detailed sample requirements.

Tissue for protocol purposes should be obtained via excision, incision or core needle. Fine needle aspirates are prohibited.

Tumor samples obtained from bone metastases are not considered acceptable for PD-L1 testing because the PD-L1 assay does not include a decalcification step. For any cases where the only tumor tissue available is from a bone metastasis lesion, please discuss further with the study Medical Monitor.

All subjects may volunteer to undergo tumor biopsies at any time during therapy, if clinically indicated. When tumor biopsy is performed during these times, submission of tumor biopsy is strongly encouraged.

All tumor tissue sample submission upon progression is optional, and can be taken within 7 days at the discretion of the investigator.

Tumor-Based Biomarker Measures

Tumor biopsy specimens will be obtained from consenting subjects prior to administration of study drug to characterize immune cell populations and expression of selected tumor markers. Tumor biopsy collection and submission is mandatory for subjects with accessible lesions prior to therapy. Tumor tissue (obtained during the screening phase or collected as a standard of care procedure within 90 days prior to obtaining informed consent) will be provided for biomarker analysis if accessible and deemed safe by the investigator. For subjects where tumor tissue cannot be provided due to issues related to safety, the reason must be clearly documented in the medical record AND the BMS Medical Monitor must be contacted. Archival tissue should be submitted for these subjects. Submission of archival tissue is also encouraged for all subjects, irrespective of whether fresh biopsy tissue is available.

For cases when a complete response occurs, and an on-treatment biopsy is required but not feasible, these cases must be clearly documented in the medical record AND the BMS Medical Monitor must be contacted.

A tumor biopsy sample of subjects that have confirmed progression is optional, but strongly encouraged for the purposes of understanding mechanisms of resistance to therapy.

Biopsy samples may be used for the following assessments:

Characterization of tumor infiltrating lymphocytes (TILs) and tumor. Immunohistochemistry (IHC) will be used to assess the number and composition of immune infiltrates in order to define the immune cell subsets present within formalin-fixed, paraffin-embedded (FFPE) tumor tissue before and after exposure to therapy. These IHC analyses may include, but not necessarily be limited to, the following markers: PD-L1, PD-L2, PD-1, LAG3, IDO, GITR, T cell and macrophage markers. For the neo-adjuvant arm only TILs may also be assessed in fresh baseline biopsies and surgical resections by cytometry. Analysis of cytokines including but not limited to IFN-g, IL-4, IL-13, IL-10, IL-17, and IL-32g may be done with multiplex qRT-PCR and/or amplified in situ hybridization (ISH) using fixed tumor tissue.

Tumor genotyping, mutational analysis, and tumor antigen profiling

RNA and DNA from tumor samples may be analyzed using whole-exome and transcriptome sequencing or another technology to determine the number of mutations found within a given sample relative to a normal host tissue, such as adjacent non-transformed cells or PBMC. Mutations that are detected will be analyzed for their ability to bind the MHC I and MHC II proteins using prediction algorithms. Evaluating the ability of tumor mutations to bind MHC molecules will provide evidence that these mutations are serving as antigens that are recognized the immune system and are potential rejection antigens.

In addition to viral positivity, chromosomal translocations, aberrant expressions, and epigenetic modifications within tumor cells may be characterized and explored by IHC and RNA/DNA analysis of tumor biopsies. Associations of altered tumor cell genetic structure with nivolumab efficacy will be performed. This includes, but is not limited to, assessments of 9p24 copy number alterations.

Characterization of T cell repertoire. As described above, DNA sequencing may be performed on pre- and post-treatment tumor tissue to assess the composition of the T cell repertoire. DNA may be isolated from either the FFPE tumor block or from RNAlater, or equivalent preparations.

Gene expression profiling. Tumor biopsies that are collected in RNAlater or equivalent fixative maybe examined for mRNA and miRNA gene expression by nanostring, RNAseq, microarray, and/or quantitative real-time polymerase chain reaction (qPCR) to detect expression of selected immune related genes and regulatory pathways.

Ex vivo Functional Assays. To explore whether nivolumab may restore T cell activation and function, Tumor infiltrating Lymphocytes (TILs) will be isolated. Assays for phenotypic characteristic as well as functional status of effector T cells may be performed, including but not limited to, flow cytometry and peptide restimulation.

Table 5.6.9-1: CA209358 Biomarker Sampling Schedule (Neo-Adjuvant Cohort)

Collection Time[a]	Serum	Plasma	PBMC (US and European Sites Only)		Tumor Biopsy	Whole Blood		
Study Day	Soluble Biomarker		Immuno-phenotyping	Ex-vivo Functional		Gene Expression	MDSC	SNP
Screening					X[b]			
Cycle 1 Day 1	X	X	X	X		X	X	X
Cycle 2 Day 1	X		X			X		
Prior to Resection (Day 29)	X		X	X	X[c]	X		
CR Evaluation[c]	X		X		X (optional)[c]	X		
During Treatment (when clinically indicated)					X[c]			
Upon Progression[d]	X (optional)		X (optional)	X (optional)	X (optional)	X (optional)	X (optional)	

[a] Serum, PBMC, Plasma, and Whole Blood samples may be obtained ± 3 days of the indicated time **except** for Cycle 1 Day 1 samples which must be collected prior to treatment.

[b] Submission of fresh tumor tissue collected via biopsy is required for TILs isolation for ex-vivo functional assays (RPMI media preparation), and also for gene expression profiling (RNALater samples).

Submission of tissue samples (FFPE tumor tissue block or slides) is required for characterization of tumor infiltrating lymphocytes (TILs) and tumor, utilizing immunohistochemistry (IHC) methods. Tissue for this purpose may be obtained during the screening phase, prior to resection, or collected as a standard of care procedure within 90 days prior to obtaining informed consent, and is mandatory.

[c] Fresh tumor tissue is required to be collected on Day 29. Day 29 tumor biopsy may be collected ± 7 days. Day 29 biopsy must be reviewed by pathologist and the pathology report must be sent to BMS.

[d] All sample submission upon progression is optional and can be taken at any time after progression at the discretion of the investigator.

Table 5.6.9-2: CA209358 Biomarker Sampling Schedule (Metastatic Monotherapy Cohorts and Metastatic Cohort Combo A and B)

Collection Time[a]	Serum	Plasma	PBMC (US and European Sites Only)		Tumor Biopsy	Whole Blood		
Study Day	Soluble Biomarker		Immuno-phenotyping	Ex-vivo Functional		Gene Expression	MDSC	SNP
Screening					X[b]			
Week 1 Day 1	X	X	X	X		X	X	X
Week 3 Day 1	Mono & Combo A[c]		Mono & Combo A[c]			Mono & Combo A[c]		
Week 4 Day 1	Combo B Only[d]		Combo B Only[d]		Combo B Only	Combo B Only[d]		
Week 5 Day 1	Mono & Combo A[c]		Mono & Combo A[c]		Combo A only X[b]			
Week 7 Day 1	X		X	X		X	X	
Week 19 Day 1	Combo A Only		Combo A Only	Combo A Only		Combo A Only		
CR Evaluation	X		X		X (optional)[e]	X		
During Treatment (when clinically indicated)[e]					X[e]			
Upon Progression[f]	X (optional)		X (optional)	X (optional)	X (optional)	X (optional)	X (optional)	

[a] Serum, PBMC, Plasma, and whole blood samples may be obtained ± 3 days of the indicated time **except** for Cycle 1 Day 1 samples which must be collected prior to treatment.

[b] Submission of fresh tumor tissue is required for gene expression profiling (RNALater samples).

[c] For Monotherapy, and Combo A; excludes Combo B

[d] For cervical cancer and anogenital HPV associated tumors (vulvar/vaginal/anal canal/penile) only

[e] All subjects may volunteer to undergo tumor biopsies at any time during therapy if clinically indicated. When tumor biopsy is performed, submission of tumor biopsy is strongly encouraged.

[f] All sample submission upon progression is optional and can be taken at any time after progression at the discretion of the investigator.

Submission of tissue samples (FFPE tumor tissue block or slides) is required for characterization of tumor infiltrating lymphocytes (TILs) and tumor, utilizing immunohistochemistry (IHC) methods. Tissue for this purpose may be obtained during the screening phase, prior to resection, or collected as a standard of care procedure within 90 days prior to obtaining informed consent. On-treatment tumor biopsies are mandatory. On-treatment tumor biopsy may be collected +/- 7 days.

Table 5.6.9-3: CA209358 Biomarker Sampling Schedule (Metastatic Combination Cohort Combo C and Combo D)

Collection Time[a]	Serum	Plasma	PBMC (US and European Sites Only)		Tumor Biopsy	Whole Blood		
Study Day	Soluble Biomarker		Immuno-phenotyping	Ex-vivo Functional		Gene Expression	MDSC	SNP
Screening					X[b]			
Week 1 Day 1	X	X	X	X		X	X	X
Week 5 Day 1	X		X		X[b]			
Week 9 Day 1	X		X	X		X	X	
CR Evaluation	X		X		X (optional)[c]	X		
During Treatment (when clinically indicated)					X[c]			
Upon Progression[d]	X (optional)		X (optional)	X (optional)	X (optional)	X (optional)	X (optional)	
Upon Drug-Related AE • ≥ Grade 2 drug related neurological AE	X		X	X				

[a] Serum, PBMC, plasma, and whole blood samples may be obtained ± 3 days of the indicated time except for Cycle 1 Day 1 samples which must be collected prior to treatment.

[b] Submission of fresh tumor tissue is required for gene expression profiling (RNALater samples).

[c] All subjects may volunteer to undergo tumor biopsies at any time during therapy if clinically indicated. When tumor biopsy is performed, submission of tumor biopsy is strongly encouraged.

[d] All sample submission upon progression is optional and can be taken at any time after progression at the discretion of the investigator.

Submission of tissue samples (FFPE tumor tissue block or slides) is required for characterization of tumor infiltrating lymphocytes (TILs) and tumor, utilizing immunohistochemistry (IHC) methods. Tissue for this purpose may be obtained during the screening phase, prior to resection, or collected as a standard of care procedure within 90 days prior to obtaining informed consent. On-treatment tumor biopsies are mandatory. On-treatment tumor biopsy may be collected +/- 7 days

Table 5.6.9-4: CA209358 Biomarker Sampling Schedule (Subjects Treated with Study Drug Post-Standard of Care)

Collection Time[a]	Serum	PBMC (US and European Sites Only)		Tumor Biopsy	Whole Blood	
Study Day	Soluble Biomarker	Immuno-phenotyping	Ex-vivo Functional		Gene Expression	MDSC
Cycle 1 Day 1	X	X	X	X[b]	X	X
Cycle 2 Day 1	X	X			X	
Cycle 3 Day 1	X	X				
Cycle 4 Day 1	X	X	X		X	X
CR Evaluation	X	X		X (optional)[c]	X	
During Treatment (when clinically indicated)[c]				X[c]		
Upon Progression[d]	X (optional)	X (optional)	X (optional)	X (optional)	X (optional)	X (optional)

[a] Serum, PBMC and whole blood samples may be obtained ± 3 days of the indicated time except for Cycle 1 Day 1 samples which must be collected prior to treatment.

[b] Submission of tumor tissue is strongly encouraged, if feasible.

[c] All subjects may volunteer to undergo tumor biopsies at any time during therapy if clinically indicated. When tumor biopsy is performed, submission of tumor biopsy is strongly encouraged.

[d] All sample submission upon progression is optional and can be taken at any point after progression at the discretion of the investigator.

5.7 Outcomes Research Assessments

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

The 3-level version of the EQ-5D (EQ-5D-3L) will be used to assess treatment effects on perceived health status and to generate utility data for health economic evaluations. The EQ-5D-3L is a generic multi-attribute health-state classification system by which health is described in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is evaluated using 3 levels: no problems, some problems, and extreme problems. Responses to these 5 dimensions are converted into 1 of 243 unique health state descriptions, which range between no problems in all 5 dimensions (11111) to extreme problems in all 5 dimensions (33333). Using appropriate country-specific value weighting algorithms, a respondent's self-described health state can be converted into a utility representing the societal desirability of his or her own health. In addition, the EQ-5D includes a visual analogue scale (VAS) allowing a respondent to rate his/her health on a scale ranging from 0 to 100 with 0 being the worst health state imaginable and 100 being the best health state imaginable.

The European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30) will be used to assess the effects of disease symptoms on functioning and well-being. The EORTC QLQ-C30 is the most commonly used quality of life instrument in oncology trials. The instrument's 30 items are divided among five functional scales (physical, role, cognitive, emotional, and social), eight symptom scales (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, and diarrhea), a scale measuring financial difficulties, and a global health or quality of life scale. With the exception of two items included in the global health or quality of life scale, for which responses range from 1 (Very poor) to 7 (Excellent), item responses range from 1 (Not at all) to 4 (Very much). Raw scores for the QLQ-C30 and are transformed to a 0-100 metric such that higher values indicate better functioning or QoL or a higher level of symptoms.

5.8 Immunogenicity Assessments

Serum samples collected at time points identified from Table 5.5-1 to Table 5.5-8 will be analyzed by validated immunoassay methods. Additional characterization (ie, neutralizing antibodies) for any detected anti-drug antibodies (ADA) response to study drug may also be performed. All samples collected for detection of anti-drug antibodies will also be assessed for the respective serum drug concentrations to enable interpretation of the antibody data. All on-treatment PK time points are intended to align with days on which nivolumab is administered. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected, but the dose is subsequently delayed, an additional predose sample should not be collected. Selected serum samples may be analyzed by an exploratory method that measures anti-nivolumab, anti-ipilimumab, anti-BMS-986016

(relatlimab), or anti-daratumumab antibodies for technology exploration purposes; exploratory results will not be reported.

In addition, serum samples designated for PK or biomarker assessments may also be used for immunogenicity analysis if required (eg, if there is insufficient volume for complete immunogenicity assessment or to follow up on suspected immunogenicity related AE).

6 ADVERSE EVENTS

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

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

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

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

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

6.1 Serious Adverse Events

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

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

hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

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

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

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

NOTE:

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

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 100 days of the last dose of study drug. For participants assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of treatment assignment. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

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

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

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

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

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

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

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

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

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

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

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

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

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

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

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

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

6.4 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least approximately 5 half-lives after product administration plus 30 days, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug after a thorough discussion of benefits and risk with the subject

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours

of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

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

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

All occurrences of overdose must be reported as SAEs (see Section 6.1.1 for reporting details).

6.6 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

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

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

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

6.7 Other Safety Considerations

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

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Not applicable

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

- 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 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.

2) Recurrent/metastatic monotherapy cohort:

HPV+ SCCHN, GYN, MCC and NPC tumor types in the recurrent/metastatic cohort will contain approximately 23 subjects. Table 8.1-1 shows the probabilities of observing 0, 1 or 2 responders and ≥ 3 responders assuming 5%, 20% and 30% true response rate of ORR. Table 8.1-2 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 8.1-5 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.

Table 8.1-1: 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 8.1-2: 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%)

3) 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 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. 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 8.1-3.

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 2-sided alpha of 5%. In addition Table 8.1-4 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, ie, ORR ≥ 22.5%, the lower bound of the 95% CI excludes 10%.

Table 8.1-5 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 8.1-6 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, ie, ORR ≥ 44%, the lower bound of the 95% CI excludes 30%; at observed more than or equal to 26 responders, ie, ORR ≥ 52%, the lower bound of the 95% CI excludes 37%.

Table 8.1-7 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, ie, 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 8.1-3: 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 Nivo 240mg q2w	Combo C Nivo+Anti-Lag-3	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.

Table 8.1-4: 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 8.1-5: 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)

Table 8.1-6: 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 8.1-7: 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%)
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)

8.2 Populations for Analyses

The analysis populations will be by cohort (neoadjuvant and metastatic), tumor type, and combination regimen. The following populations will be defined, and their specific applications will be documented in detail in the statistical analysis plan:

- All Enrolled Subjects: All subjects who signed an informed consent form and were registered into the IRT.
- All Treated Subjects: All enrolled subjects who received at least one dose of study drug.
  - All Response Evaluable Subjects: All treated subjects in recurrent/metastatic cohorts (monotherapy and combination therapy) 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 time point (before sub-sequent therapy) with all baseline target lesion(s) assessed; ii) clinical progression or death before any on-study tumor assessment.
  - All Evaluable Neoadjuvant Subjects: All treated subjects in neoadjuvant cohorts who have available paired tissue samples at Screening and Day 29.
- Outcomes Research Subjects: All treated subjects who have an assessment at baseline and at least one post-baseline assessment.
- Pharmacokinetic Subjects: All subjects who receive at least one dose of study drug and have available serum concentration data.

- Immunogenicity Subjects: All treated subjects with baseline and at least 1 post-baseline immunogenicity assessment for nivolumab, ipilimumab and BMS-986016 (relatlimab); All treated subjects with at least 1 post-baseline immunogenicity assessment for daratumumab.
- Biomarker Subjects: All treated subjects who have available biomarker data.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

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.

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. BOR is defined as the best response designation recorded between the date of first dose and the date of the initial objectively documented tumor progression per investigator assessment using RECIST 1.1 criteria or the date of the last tumor assessment date prior to subsequent therapy. In this study, an ORR in excess of 10% will be considered of clinical interest, and an ORR of 25% or greater will be considered of strong clinical interest.

8.3.2 Secondary Endpoint(s)

Metastatic cohorts (monotherapy and combination therapies):

- Duration of response (DOR) is defined as the time from first confirmed response (CR or PR) to the date of the initial objectively documented tumor progression as determined per investigator assessment using RECIST 1.1 criteria or death due to any cause, whichever occurs first. 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 prior to death and 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. DOR will only be evaluated in subjects with objective response of CR or PR.
- 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 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 prior to death and 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.

8.3.3 Exploratory Endpoint(s)

Neoadjuvant cohort:

- The percent change from baseline of select 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.
- 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.) For subjects who remain alive and whose disease has not recurred, RFS will be censored on the date of last evaluable disease assessment. Participants who did not have any post-surgery disease assessments and did not die will be censored on the surgery date. Further details on the censoring rules for consideration of subsequent therapies, will be described in the Statistical Analysis Plan (SAP).
- 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 cervical, vaginal, or vulvar cancer. Pathological complete response (pCR) is defined as the absence of residual viable 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.

Metastatic cohorts (monotherapy and combination therapies):

- 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 and nasopharyngeal carcinoma. The change in EBV DNA levels will be used to determine the effect of BMS-936558 (nivolumab). (Monotherapy cohort only)

Neoadjuvant and Metastatic cohorts (monotherapy and combination therapies):

- The PK samples collected will be used to determine summary measures of nivolumab, ipilimumab, BMS-986016 (relatlimab), and daratumumab exposures (see Section 8.4.4)
- Exploratory endpoints for pharmacodynamics, outcomes research and immunogenicity are discussed in detail in Sections 5.6, 5.7 and 5.8.

Other exploratory endpoints will be discussed in detail in the statistical analysis plan.

8.4 Analyses

All analyses for neoadjuvant cohort will be performed as it completes safety follow-up. All analyses for each metastatic cohort (nivolumab monotherapy or combo A, B, C, or D) will be performed as it completes efficacy follow-up. All analyses will be performed independently by cohort, by tumor type, and regimen.

The randomization of the patients with metastatic cervical cancer and anogenital HPV associated (vulvar/vaginal/anal canal/penile) tumor types to combo A, B, or D is for administration purposes, not for comparison. Analyses will be done for each dosing schema separately.

8.4.1 Demographics and Baseline Characteristics

Demographic and baseline laboratory results will be summarized using descriptive statistics for all treated subjects.

8.4.2 Efficacy Analyses

8.4.2.1 Primary Endpoint Methods

Neoadjuvant cohort:

- Analyses of drug-related select AEs and drug-related SAEs are discussed in Section 8.4.3
- Rate of surgery delay will be summarized by binomial response rates and their corresponding two-sided 95% exact CIs using Clopper-Pearson method.

Metastatic cohort (monotherapy and combination therapies):

- The investigator assessed ORR in the metastatic cohort will be summarized by binomial response rates and their corresponding two-sided 95% exact CIs using Clopper-Pearson method.

8.4.2.2 Secondary Endpoints Methods

Metastatic cohort (monotherapy and combination therapies):

- Time to event distribution will be estimated using Kaplan Meier techniques. This will be done for PFS (based on investigator assessments) and OS. Median PFS or OS along with 95% CI will be constructed based on a log-log transformed CI for the survivor function. Rates at some fixed time points will be derived from the Kaplan Meier estimate and corresponding

confidence interval will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function.

- The DOR will be summarized for all treated subjects who achieve confirmed PR or CR using the Kaplan-Meier (KM) product-limit method. Median values of DOR, along with two-sided 95% CI using Brookmeyer and Crowley method, will also be calculated.

8.4.2.3 Exploratory Endpoints Methods

Methods for exploratory endpoints will be discussed in detail in the statistical analysis plan.

8.4.3 Safety Analyses

Safety analyses will be performed in all treated subjects. Descriptive statistics of safety will be presented using NCI CTCAE version 4. All on-study AEs, drug-related, AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE version 4 criteria by system organ class and MedDRA preferred term. On-study lab parameters including hematology, chemistry, liver function, thyroid function, and renal function will be summarized using worst grade per NCI CTCAE version 4 criteria.

The proportion of subjects in the neoadjuvant cohort with surgery delayed > 4 weeks due to a drug-related AE will be reported for each tumor type and the Clopper-Pearson method will be used to estimate the two-sided 95% confidence interval.

8.4.4 Pharmacokinetic Analyses

The nivolumab, ipilimumab, BMS-986016 (relatlimab), and daratumumab concentration data obtained in this study may be combined with data from other studies in any of the clinical development programs (nivolumab, ipilimumab, BMS-986016, and daratumumab) to develop or refine a population PK model. The models may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of nivolumab or other compounds and to determine measures of individual exposure (such as steady-state peak, trough, and time-averaged concentration). In addition, model determined exposures may be used for exposure-response analyses. If performed, results of population PK and exposure response-analyses will be reported separately.

8.4.5 Biomarker Analyses

The pharmacodynamic effects of nivolumab as monotherapy or in combination with ipilimumab, BMS-986016 (relatlimab), or daratumumab on selected biomarkers will be assessed by summary statistics and corresponding changes (or percent changes) from baseline tabulated by time and cohort. In addition, the time course of biomarker outcomes will be investigated graphically, by summary plots or individual subject plots. If there is an indication of a meaningful pharmacodynamic trend, methods such as linear mixed models may be used to characterize the pattern of change over time. The potential association between PD-L1 expression level (IHC) and clinical efficacy measures will be assessed using Fisher's exact test or other methodology as appropriate.

Potential associations of various biomarker measures with pharmacokinetic exposure, safety and clinical efficacy measures will be investigated based on data availability. Methods such as, but not limited to, logistic regression and graphical summaries may be used to assess these associations.

The methodology for additional exploratory biomarker analyses will be described in the statistical analysis plan.

8.4.6 Outcomes Research Analyses

8.4.6.1 EQ-5D

Outcomes Research Subject's overall health on the EQ-5D VAS at each assessment time point will be summarized using descriptive statistics (N, mean, standard deviation, median, first and third quartiles, 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 the number subjects with EQ-5D data at each assessment time point.

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) and EQ-5D VAS will be provided.

8.4.6.2 EORTC QLQ-C30

The analysis of EORTC QLQ-C30 data will be performed in all Outcomes Research Subjects.

For each cohort, baseline scores and post-baseline score changes for all EORTC QLQ-C30 scales will be summarized using descriptive statistics (N, mean, standard deviation, median, first and third quartiles, minimum, maximum). Baseline and change from baseline in EORTC QLQ-C30 global health status/QoL composite scale data and the remaining EORTC QLQ-C30 scale data will be summarized by time point using descriptive statistics for each cohort (N, mean, standard deviation, median, first and third quartiles, minimum, maximum). 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 time point. Percentages will be based on the number of subjects with EORTC QLQ-C30 data at each assessment time point.

8.4.7 Other Analyses

8.4.7.1 Immunogenicity Analyses

Immunogenicity may be reported for 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. Effect of immunogenicity on safety, efficacy, biomarkers and PK may be explored. Additional details will be described in the SAP.

8.5 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.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

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

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

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

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

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

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

9.1.2 Monitoring

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

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

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

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

9.1.2.1 Source Documentation

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

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

9.1.3 Investigational Site Training

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

9.2 Records

9.2.1 Records Retention

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

BMS will notify the investigator when the study records are no longer needed.

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

9.2.2 Study Drug Records

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

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (eg, lost, wasted)

- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

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

9.2.3 Case Report Forms

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

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

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

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

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

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

9.3 Clinical Study Report and Publications

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

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

- External Principal Investigator designated at protocol development
- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design

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

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	If one form of contraception is required, Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. If two forms of contraception is required, Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. **Expanded definition** Complete abstinence as defined as complete avoidance of heterosexual intercourse is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence

11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
ACLS	advanced cardiac life support
AI	accumulation index
AI_AUC	AUC Accumulation Index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose
AI_Cmax	Cmax Accumulation Index; ratio of Cmax at steady state to Cmax after the first dose
AI_Ctau	Ctau Accumulation Index; ratio of Ctau at steady state to Ctau after the first dose
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
A-V	atrioventricular
β-HCG	beta-human chorionic gonadotrophin
BA/BE	bioavailability/bioequivalence
%BE	percent biliary excretion
BID, bid	bis in die, twice daily
BLQ	below limit of quantification
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
BRt	Total amount recovered in bile

Term	Definition
%BRt	Total percent of administered dose recovered in bile
BUN	blood urea nitrogen
C	Celsius
C12	concentration at 12 hours
C24	concentration at 24 hours
Ca++	calcium
Cavg	average concentration
CBC	complete blood count
Cexpected-tau	expected concentration in a dosing interval
CFR	Code of Federal Regulations
cHL	classical Hodgkin's lymphoma
CI	confidence interval
C1-	chloride
CLcr	creatinine clearance
CLD	Dialysate clearance of drug from plasma/serum
CLNR	nonrenal clearance
CLR	renal clearance
CLT	total body clearance
CLT/F (or CLT)	apparent total body clearance
CLT/F/fu or CLT/fu	Apparent clearance of free drug or clearance of free if (if IV)
cm	centimeter
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	trough observed concentration
CNS	Central nervous system
CRC	Clinical Research Center
CRF	Case Report Form, paper or electronic
Ct	Expected concentration at a certain time, usually at the end of an expected future dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
Ctau	Concentration in a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)

Term	Definition
Ctrough	Trough observed plasma concentration
CV	coefficient of variation
CYP	cytochrome p-450
D/C	discontinue
dL	deciliter
DRt	Total amount recovered in dialysate
%DRt	Total percent of administered dose recovered in dialysate
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4th Edition)
EA	extent of absorption
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEG	electroencephalogram
eg	exempli gratia (for example)
EORTC QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire - Core 30
EQ-5D-3L	3-level EQ-5D questionnaire
eg	exempli gratia (for example)
ESR	Expedited Safety Report
F	bioavailability
Fb	fraction of bound drug
FDA	Food and Drug Administration
FI	fluctuation Index ([Cmax-Ctau)/Cavg])
FRt	total amount recovered in feces
%FRt	total percent of administered dose recovered in feces
FSH	follicle stimulating hormone
%FE	percent fecal excretion
fu	fraction of unbound drug
g	gram
GC	gas chromatography
GCP	Good Clinical Practice

Term	Definition
G criteria	adjusted R2 value of terminal elimination phase
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCO3-	bicarbonate
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
Ig	immunoglobulin
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IO	immuno-oncology
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	International Unit
IV	intravenous
K	slope of the terminal phase of the log concentration-time curve
K3EDTA	potassium ethylenediaminetetraacetic acid
K+	potassium
kg	kilogram
λz	terminal disposition rate constant
L	liter
LAG-3	lymphocyte activation gene 3

Term	Definition
LC	liquid chromatography
LDH	lactate dehydrogenase
ln	natural logarithm
Lz_Start	The time point starting the log-linear elimination phase defining the terminal half life
Lz_End	The time point ending the log-linear elimination phase defining the terminal half life
Lz_N	Number of time points in the log-linear elimination phase defining the terminal half life
LVEF	left ventricular ejection fraction
MEL	melanoma
mg	milligram
Mg++	magnesium
MIC	minimum inhibitory concentration
min	minute
mL	milliliter
mmHg	millimeters of mercury
MR_AUC(0-T)	Ratio of metabolite AUC(0-T) to parent AUC(0-T), corrected for molecular weight
MR_AUC(INF)	Ratio of metabolite AUC(INF) to parent AUC(INF), corrected for molecular weight
MR_AUC(TAU)	Ratio of metabolite AUC(TAU) to parent AUC(TAU), corrected for molecular weight
MR_Cmax	Ratio of metabolite Cmax to parent Cmax, corrected for molecular weight
MR_Ctau	Ratio of metabolite Ctau to parent Ctau, corrected for molecular weight
MRT	mean residence time
MS	mass spectrometry
MTD	maximum tolerated dose
μg	microgram
N	number of subjects or observations
Na+	sodium
N/A	not applicable

Term	Definition
ng	nanogram
NIMP	non-investigational medicinal products
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
pAUCe	Extrapolated partial AUC from last quantifiable concentration to infinity
Pb	percent of bound drug
PD	pharmacodynamics
PK	pharmacokinetics
PO	per os (by mouth route of administration)
PT	prothrombin time
PTT	partial thromboplastin time
Pu	percent of unbound drug
QC	quality control
QD, qd	quaque die, once daily
R2	coefficient of determination
RBC	red blood cell
RCC	renal cell carcinoma
SAE	serious adverse event
SCC	squamous cell cancer
SCLC	small cell lung cancer
SD	standard deviation
SEB	staphylococcal enterotoxin B
SOC	standard of care
SOP	Standard Operating Procedures
sp.	species
Subj	subject
t	temperature
T	time
TAO	Trial Access Online, the BMS implementation of an EDC capability
T-HALF	Half life

Term	Definition
T-HALFeff_AUC	Effective elimination half-life that explains the degree of AUC accumulation observed
T-HALFeff_Cmax	Effective elimination half-life that explains the degree of Cmax accumulation observed)
TID, tid	ter in die, three times a day
TIL	tumor infiltrating lymphocytes
Tmax, TMAX	time of maximum observed concentration
TR_AUC(0-T)	AUC(0-T) treatment ratio
TR_AUC(INF)	AUC(INF) treatment ratio
TR_Cmax	Cmax treatment ratio
UR	urinary recovery
%UR	percent urinary recovery
URt	total amount recovered in urine
%URt	total percent of administered dose recovered in urine
UV	ultraviolet
Vss/F (or Vss)	apparent volume of distribution at steady state
Vz	Volume of distribution of terminal phase (if IV and if multi-exponential decline)
W	washout
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
x g	times gravity

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APPENDIX 1 ECOG PERFORMANCE STATUS

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

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APPENDIX 2 MANAGEMENT ALGORITHMS

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

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

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

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

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

GI Adverse Event Management Algorithm

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

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

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

Updated 05-Jul-2016

Renal Adverse Event Management Algorithm

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

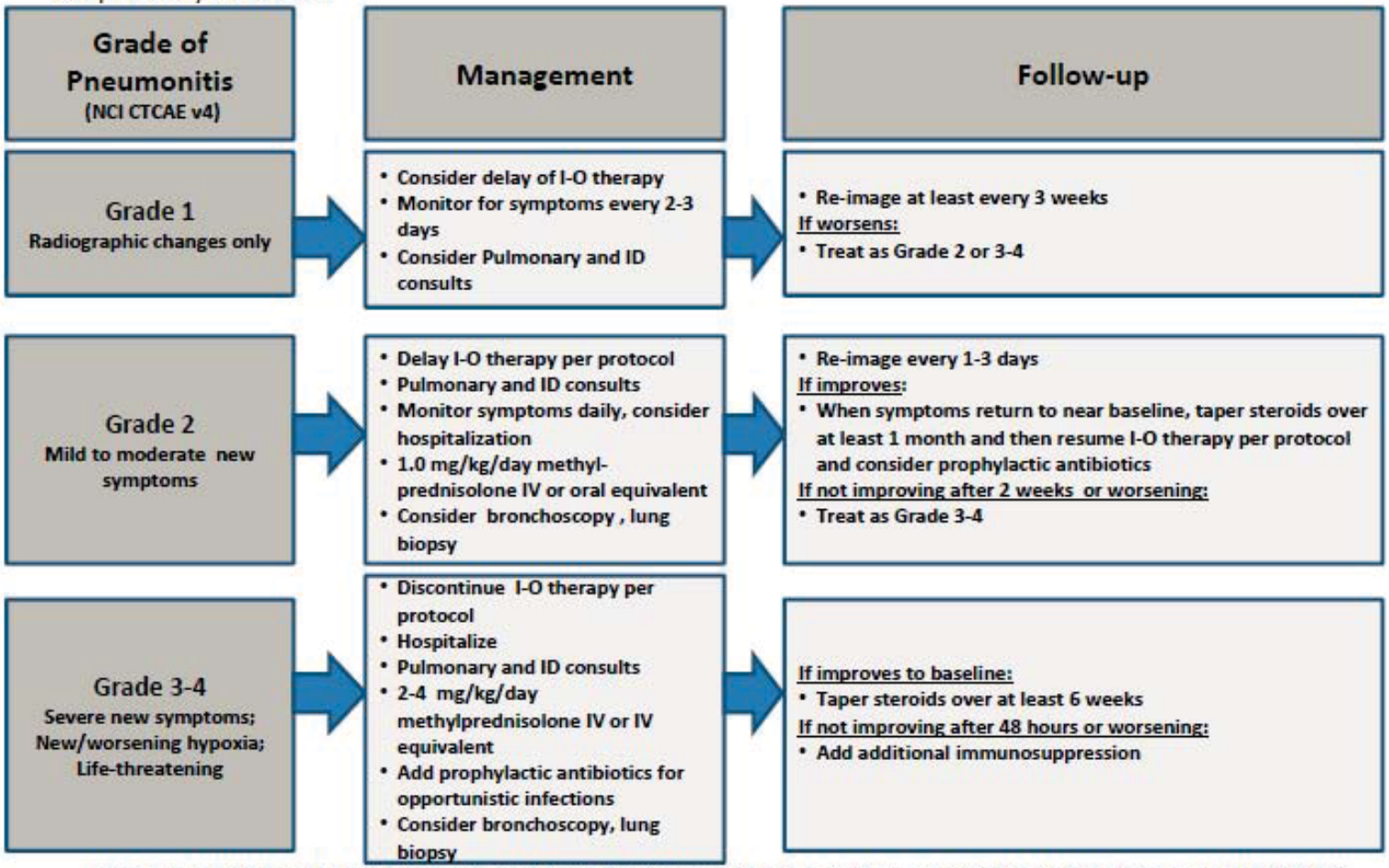
Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > ULN and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	<u>If returns to baseline</u>: •Resume routine creatinine monitoring per protocol <u>If worsens:</u> •Treat as Grade 2 or 3/4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy with nephrology consult	<u>If returns to Grade 1:</u> •Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol <u>If elevations persist > 7 days or worsen:</u> •Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	<u>If returns to Grade 1</u> : Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

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

Updated 05-Jul-2016

Pulmonary Adverse Event Management Algorithm

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

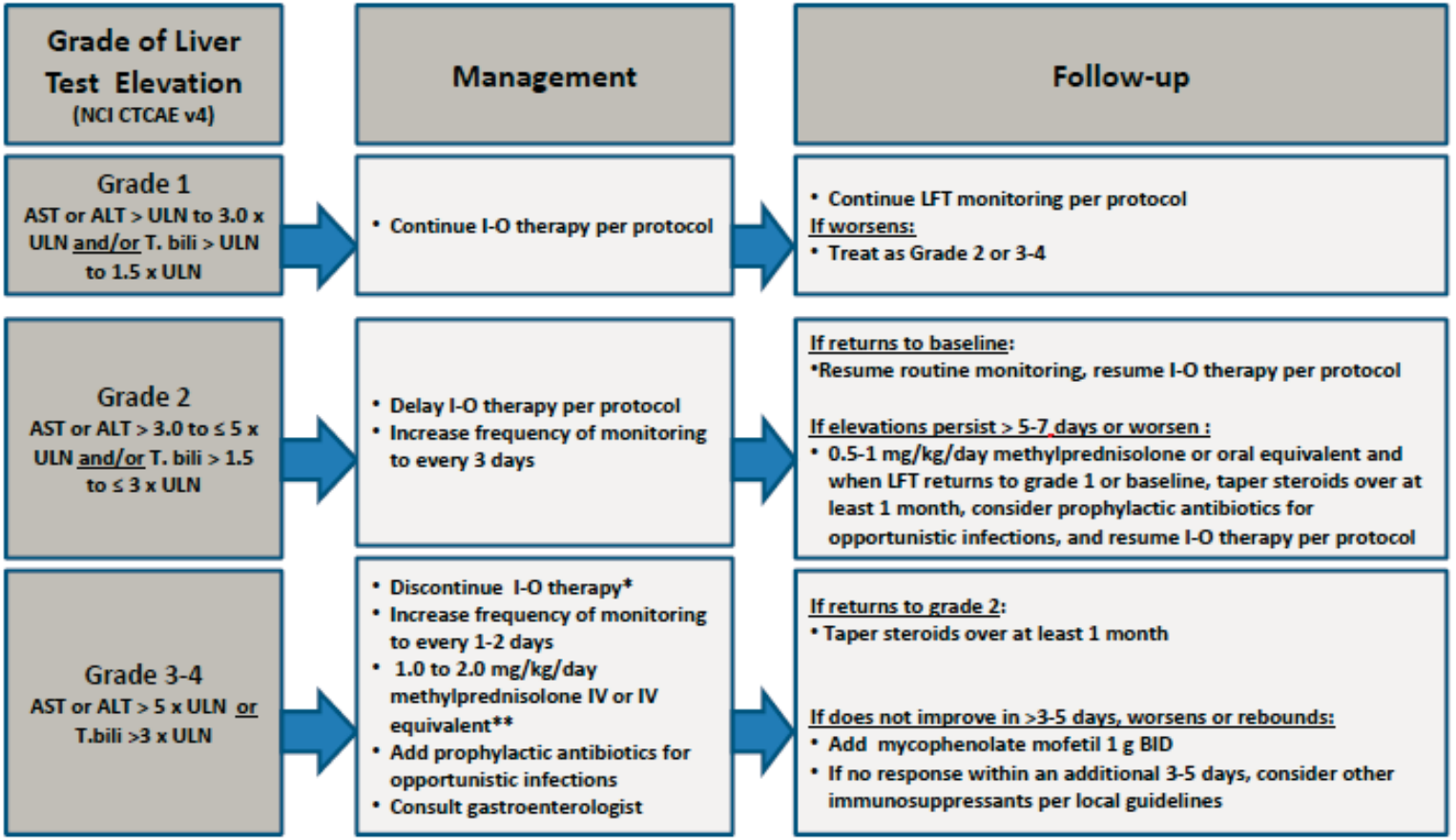


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Hepatic Adverse Event Management Algorithm

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



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

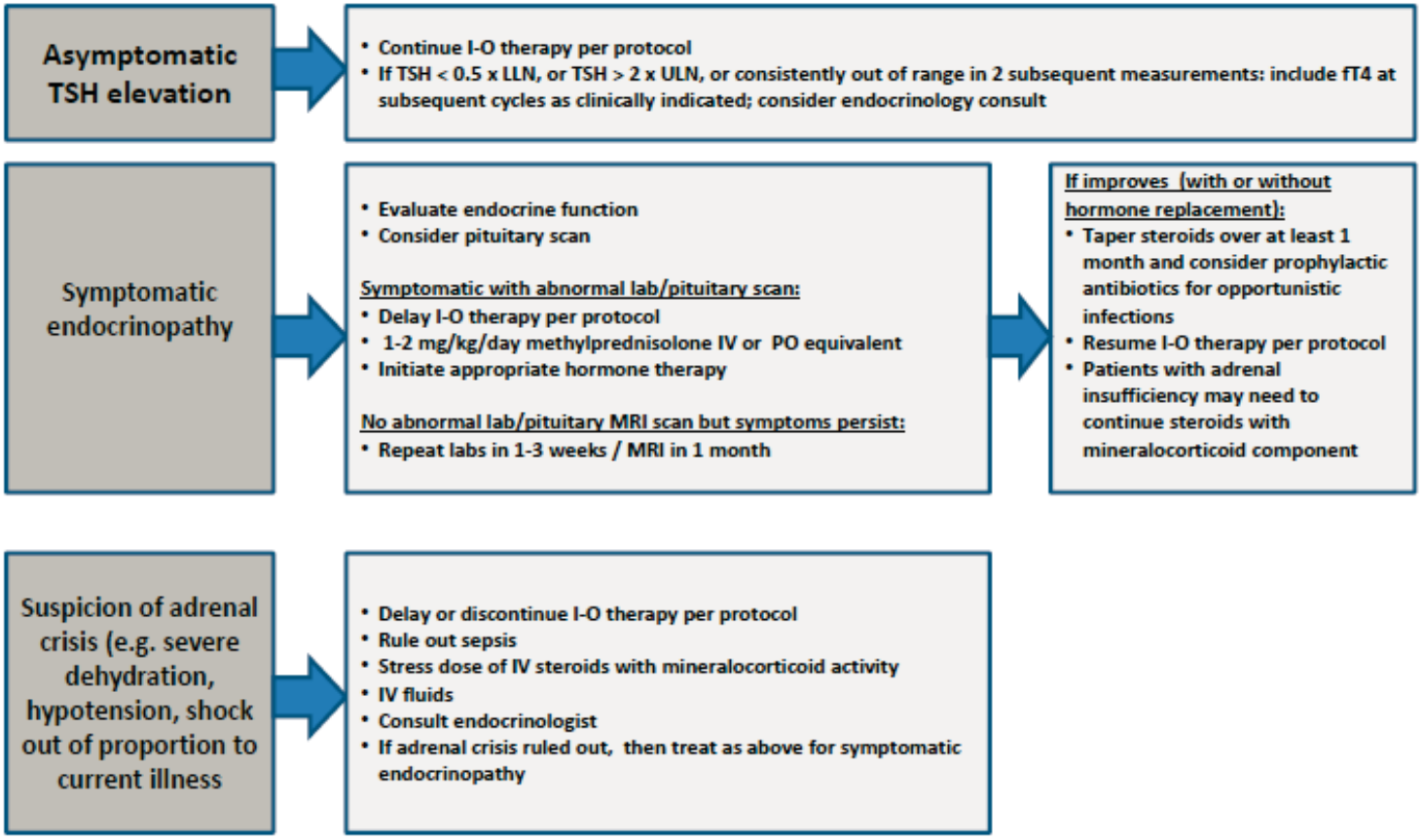
*I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.

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

Updated 05-Jul-2016

Endocrinopathy Management Algorithm

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

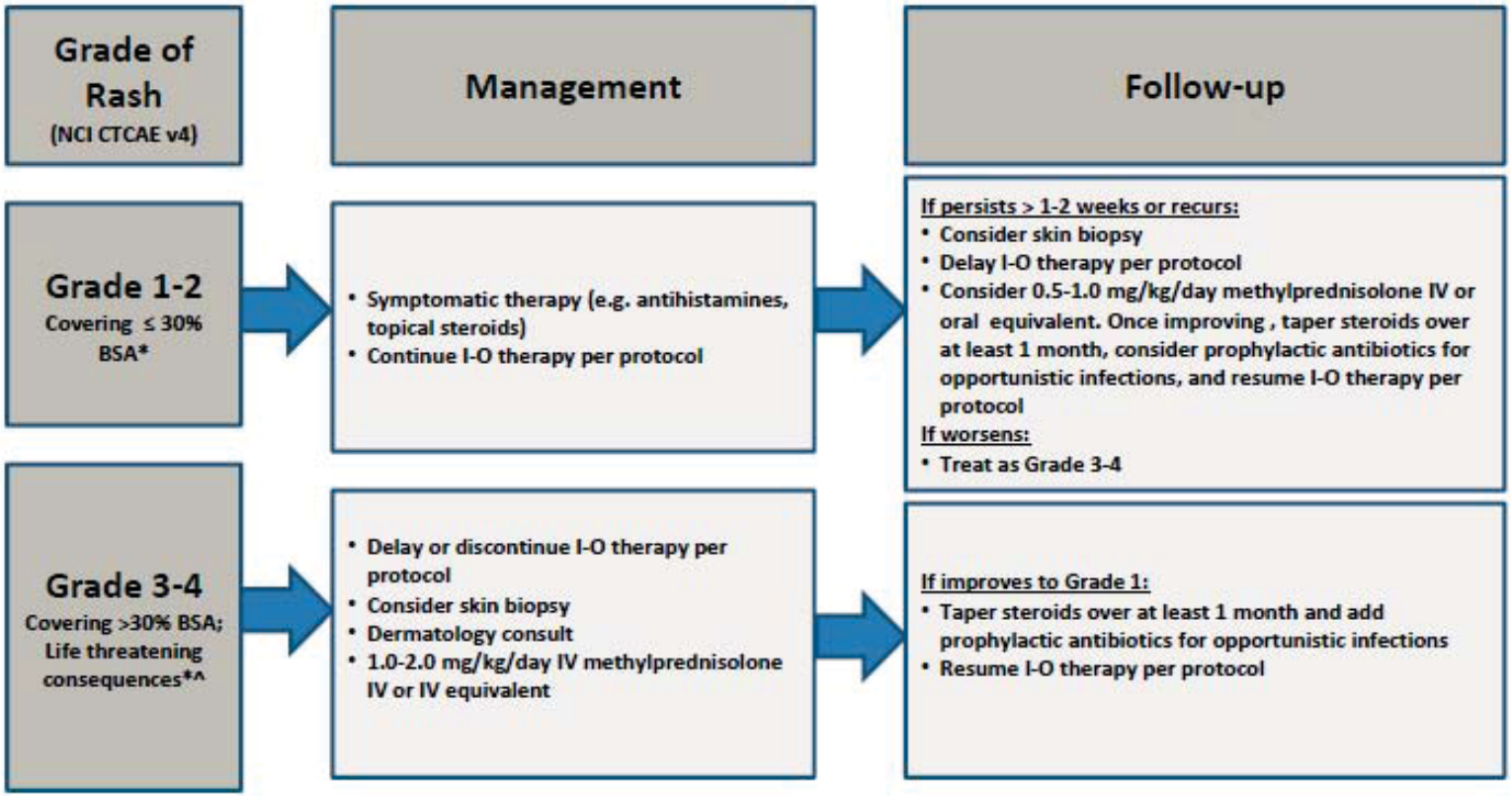


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Skin Adverse Event Management Algorithm

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



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

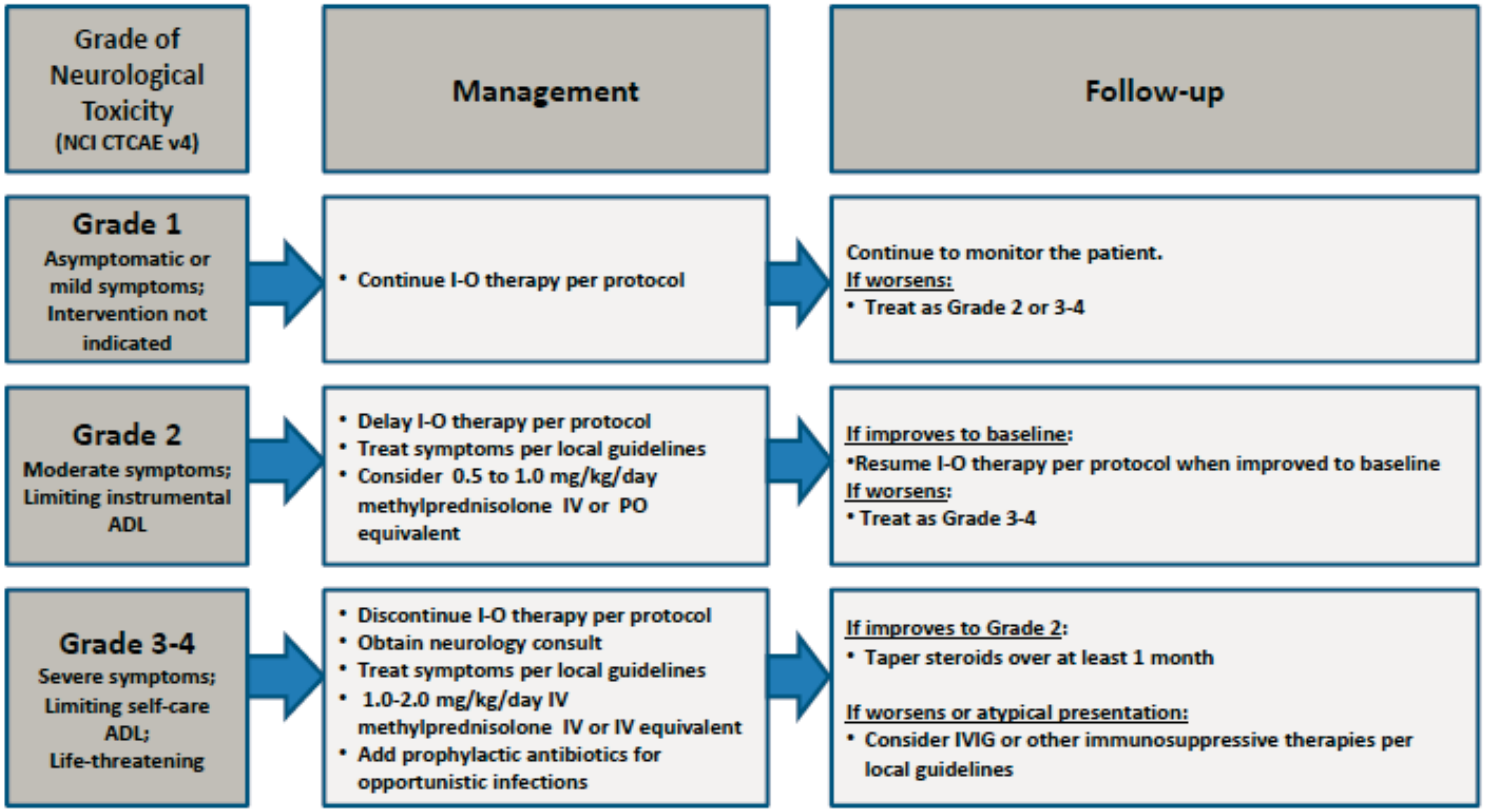
*Refer to NCI CTCAE v4 for term-specific grading criteria.

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

Updated 05-Jul-2016

Neurological Adverse Event Management Algorithm

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



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

Updated 05-Jul-2016

APPENDIX 3 RECIST 1.1 GUIDELINES

1 EVALUATION OF LESIONS

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

1.1 Measurable

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

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

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

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

1.2 Non-Measurable

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

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

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

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

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

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

3 RESPONSE CRITERIA

3.1 Evaluation of Target Lesions

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

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

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

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

3.1.1 Special Notes on the Assessment of Target Lesions

3.1.1.1 Lymph nodes

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

3.1.1.2 Target lesions that become 'too small to measure'

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

3.1.1.3 Lesions that split or coalesce on treatment

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

3.2 Evaluation of Non-Target Lesions

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

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

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

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

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

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

3.2.1.1 When the patient also has measurable disease

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

3.2.1.2 When the patient has only non-measurable disease

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

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

3.2.2 New Lesions

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

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

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

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

3.3 Response Assessment

3.3.1 Evaluation of Best Overall Response

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

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

3.3.2 Time Point Response

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

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

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

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

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

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

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

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

3.3.3 Best Overall Response

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

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

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

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

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

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

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

3.3.4 Confirmation Scans

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

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

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

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

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal

• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)[c] • Intrauterine device (IUD)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* – It is not necessary to use any other method of contraception when complete abstinence is elected. – WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. – Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence

NOTES:

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Unacceptable Methods of Contraception
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action • Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

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

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

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

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 6.1.1 and Section 6.4.

APPENDIX 5 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for the Revised Protocol 06, 18-Jul-2018

Rationale for Discontinuation of Nivolumab plus Daratumumab Combination Therapy

A decision to temporary hold on further enrollment was made on 26-May-2018 based on a communication that the Data Monitoring Committee (DMC) of a Phase Ib/II study in non-small cell lung cancer of daratumumab in combination with atezolizumab (an anti PD-L1 antibody from Roche) had recommended that study be terminated. The DMC of that study determined that there was no observed benefit within the combination arm of daratumumab plus atezolizumab over atezoluzimab monotherapy and in addition to the lack of benefit, the DMC noted a numerical increase in mortality-related events in the combination arm.

As such, BMS has decided to terminate the daratumumab arms in this study.

Rationale for Adding Cervical Cancer Cohort Expansion

The cervical cancer expansion cohort was added to further confirm the preliminary efficacy and safety signals of the combination B as first- or second-line treatment for recurrent or metastatic SCC of the cervix.

Rationale for Moving Neoadjuvant Cohort from Secondary to Exploratory Objective

This endpoint is primarily to explore the effect of treatment on immune cells and immune regulatory markers and generate hypothesis for further validation. Because it is measured to generate a hypothesis, is has been changed to an exploratory endpoint.

Summary of key changes for Revised Protocol 06

Section Number & Title	Description of Change	Brief Rationale
1.1.12 Rationale for Nivolumab plus Daratumumab Combination Therapy 1.1.13 Rationale for Nivolumab Combined with Daratumumab in Patients with HPV Positive and Negative or Unknown SCCHN 1.1.14 Rationale to Support Dose/Schedule of Nivolumab Combined with Daratumumab 1.5 Overall Risk/Benefit Assessment 3.1.1 Viral Status Determination Prior to Entry 4.7.7 Treatment of Study Drug-related Infusion Reactions 8.1 Sample Size Determination	Added rationale for discontinuing nivolumab plus daratumumab combination therapy.	Terminating the daratumumab combination arms.
1.3.2 Secondary Objectives 1.3.3 Exploratory Objective(s) 8.3.2 Secondary Endpoint(s) 8.3.3 Exploratory Endpoint(s) 8.4.2.2 Secondary Endpoints Methods	Moved neoadjuvant cohort from secondary to exploratory objective.	Reclassified endpoint from secondary to exploratory.

Summary of key changes for Revised Protocol 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
3.1 Study Design and Duration Figure 3.1-3: Study Design Schematic for the Metastatic Cohort Combination Therapies A and B and Combo B Cervical Cancer Expansion 3.3.1 Inclusion Criteria 2), a) 3.3.2 Exclusion Criteria m) 8.1 Sample Size Determination Table 8.1-3: Sample size in Recurrent/metastatic combination cohort Table 8.1-6: Two-sided 95% exact CI using Clopper-Pearson method based on the number of observed responses out of 55 subjects Table 8.1-7: Two-sided 95% exact CI using Clopper-Pearson method based on the number of observed responses out of 35 subjects 11 List of Abbreviations	Added description of cervical cancer expansion cohort.	Adding cervical cancer expansion arm to further confirm efficacy and safety signals.
3.1.1 Viral Status Determination Prior to Entry 3.1.4 Subjects in the Metastatic Combination Cohorts 8.1 Sample Size Determination	Noting closure of the anogenital HPV associated tumor cohorts.	Due to slow accrual and the current investigation of these tumor types in other BMS-sponsored studies, combination cohorts in this study will no longer include anogenital HPV associated tumor types.

Overall Rationale for the Revised Protocol 05, 18-Apr-2018

The revisions incorporated in Revised Protocol 05 allow for the concurrent enrollment of subjects with eligible tumor types in all metastatic Combination Cohorts A, B, and D.

Combination cohorts in this study will no longer include the Epstein Barr Virus (EBV) positive gastric tumor type; however, subjects with this tumor type already enrolled may continue to receive study treatment as per protocol.

In addition, enrollment for Combination Cohort C will be closed. Enrollment for this cohort has been low, and this combination is being evaluated in other studies. Subjects who have already enrolled in this cohort will continue in the study as planned. In addition, crossover from other cohorts into Combo C will not be allowed.

Current clinical and safety data for both BMS-986016 (Anti-LAG3) and daratumumab now available are included.

A 24-month maximum duration of nivolumab treatment has also been implemented in this Revised Protocol. The optimal duration of immunotherapy is an important question and continues to be investigated. Clinical trials across different tumors types in the nivolumab and ipilimumab development program indicate that most of the responses occur early, with a median time to response of 2-4 months, and emerging data suggests that benefit can be maintained in the absence of continued treatment. A recent analysis in a melanoma study suggests the majority of patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment. Furthermore, a limited duration of ipilimumab, including only four induction doses, resulted in long-term survival in patients with metastatic melanoma, with a sustained plateau in survival starting around 2 years after the start of treatment.

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

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

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

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

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

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

Summary of key changes for Revised Protocol 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
• Synopsis, Investigational Product; • Synopsis, Study Design • Section 3.1, Study Design and Duration • Section 3.1.1, Viral Status Determination Prior to Entry	Condensed text to better clarify the various populations in this study.	To provide clarity for the sites.

Summary of key changes for Revised Protocol 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
• Synopsis, Investigational Product, Study Design, Schematics, Study Dosing Table • Section 1.1.15, Rationale for Nivolumab Combination Therapy: 2-Year Duration • Section 3.1, Study Design and Duration • Section 3.1.3, Subjects in the Metastatic Monotherapy Cohort • Section 3.1.4, Subjects in the Metastatic Combination Cohorts • Section 4.5, Selection and Timing of Dose for Each Subject	Nivolumab program level revision limiting treatment to 24 months	Instituted this maximum duration based on the data described above.
• Synopsis, Investigational Product, Objectives, Inclusion Criteria a)ii)(1); c)iv)(1) Study Design, Schematics; Statistical Considerations; • Section 1.3.1, Primary Objectives • Section 1.3.3, Exploratory Objective(s) • Section 3.1, Study Design and Duration • Section 3.1.4, Subjects in the Metastatic Combination Cohorts • Section 3.3.1, Inclusion Criteria Inclusion Criteria 2 a)ii)(1); 2 c)iv)(1) • Section 8.1, Sample Size • Table 8.1-3, Sample size in Recurrent/metastatic combination cohort • Section 8.3, Exploratory Endpoint(s)	Enrollment of Epstein Barr Virus (EBV) gastric cancer into the metastatic combination therapies A and C has been closed. Accrual of EBV positive gastric cancer in the metastatic monotherapy cohort has been attained and is closed to enrollment.	Due to the low prevalence of EBV positive 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.

Summary of key changes for Revised Protocol 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
• Synopsis Study Design; Statistical Considerations Table 4 • Section 3.1, Study Design and Duration • Section 3.1.4, Subjects in the Metastatic Combination Cohorts • Section 4.4, Method of Assigning Subject Identification • Section 8.1, Sample Size	All Metastatic Combination Cohorts A B and D to enroll patients concurrently in eligible tumor types. All references to staggered enrollment or enrollment cap on any cohort has been removed. In addition, enrollment in Metastatic Combination Cohort C (all tumor types) is closed, including crossovers.	Concurrent enrollment in the metastatic combination cohorts enables accrual across all cohorts, allows for the generation of clinical data, and provides an opportunity to bring effective treatments faster to patients with high unmet medical need.
• Synopsis Sections: Investigational Product, Study Design, Schematics, Study Dosing Table • Section 1.5, Overall Risk/Benefit Assessment • Figure 3.1-5, Study Design Schematic for the Metastatic Cohort Combination Therapy CD: Tumor Type SCHHN HPV positive, negative or unknown I-O naive • Section 3.1.4, Subjects in the Metastatic Combination Cohorts • Section 4.3, Storage and Dispensing • Section 4.5, Selection and Timing of Dose for Each Subject and Table 4.5-1 Study Drug Dosing • Table 5.1-3, On-Treatment Assessments Metastatic Combination Therapy Cohorts (CA209358) • Table 5.5-7: Pharmacokinetic and Immunogenicity Sampling Schedule for Nivolumab (Nivolumab and Daratumumab Combination-Combo D).	Nivolumab will be administered before daratumumab when both study drugs are administered on the same study day (Combo D arm). Administration of daratumumab should follow instructions in the USPI/pharmacy manual. Specifications for administration of daratumumab previously presented have been deleted.	Daratumumab infusion requires longer infusion time and pre and post infusion medications to reduce the risk of infusion reactions. Nivolumab will be administered before daratumumab across studies that are evaluating the safety and efficacy of daratumumab in combination with nivolumab, in order enable management of daratumumab post infusion reactions.
• Section 1.1.11, Rationale to Support Dose/Schedule of Nivolumab Combined with BMS -986016	Added a section on Relatlimab Adverse Event Guidelines	To clarify for the sites that they should follow the Nivolumab Adverse Event Algorithms.
• Section 1.1.6, Rationale For Dose Selection for Nivolumab	Added the rationale for the use of 480 mg dose of nivolumab and updated the rationale for the 240 mg dose.	To provide updated data and recent HA approvals of the dose rationales.
• Section 1.1.14, Rationale to Support Dose/Schedule of Nivolumab	Update of safety and clinical data for daratumumab	Protocol now reflects current safety and clinical data for BMS-

Summary of key changes for Revised Protocol 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Combined with Daratumumab		986016.
• Section 1.4.3.1, Non-clinical Pharmacology Studies Utilizing Murine Anti-PD-1 and Anti-Lag-3 Antibodies	Added additional data.	To provide the most updated and complete non-clinical information available.
• Section 1.4.3.5, Clinical Safety Combination Therapy (Nivolumab plus Relatlimab)	Deleted repeated information and added a reference to Section 1.1.11 and the Investigator's Brochure	To avoid repeated data in multiple places in the protocol.
• Section 1.5, Overall Risk/Benefit Assessment	Provided updated language regarding the nivolumab plus relatlimab combination.	To provide the most updated information in the overall risk benefit section.
• Section 3.3.2, Exclusion Criteria	Added a criterion excluding treatment with botanical preparations	To prevent drug-drug interactions.
• Section 3.4.1, Prohibited and/Restricted Treatments	Added botanical preparations as a prohibited medication.	To prevent drug-drug interactions
• Table 4.-1, Product Description: Treatment Period	Updated the potency for daratumumab (added 400-mg vials) and added a footnote to allow commercial product where allowed by local regulations.	To provide flexibility in providing daratumumab.
• Section 4.7.3, Dose Delay Criteria	The nivolumab Dose Delay Criteria were updated.	To align with the Summary of Product Characteristics.
	The daratumumab Dose Delay Criteria were updated.	To eliminate repetition and contradicting information.
• Section 4.7.5, Criteria to Resume Dosing	Removed one nivolumab criterion	To remove redundancies in other sections.
	Revised the criterion for participants in Combo C regarding troponin elevations	
• Section 4.7.6, Discontinuation Criteria	Revised the second bullet and first sub-bullet	To align with the Summary of Product Characteristics.
• Table 5.1-1:Screening Procedural Outline for All Subjects (CA209358)	Added to note section for collection of tumor tissue that fresh Biopsies are mandatory for neoadjuvant cohort patients.	Clarification
• Table 5.1-2: On-Treatment Assessments Metastatic Monotherapy Cohort (CA209358)	Oxygen saturation testing removed from vital signs	This protocol now reflects the nivolumab program-wide removal of oxygen saturation testing.
• Table 5.1-3: On-Treatment Assessments Metastatic Combination	Oxygen saturation testing removed from vital signs and	This protocol now reflects the nivolumab program-wide removal

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Therapy Cohorts (CA209358)	provides the dosing windows for daratumumab.	of oxygen saturation testing.
• Table 5.1-4: On Treatment Assessments Neoadjuvant Cohort (CA209358) • Table 5.1-5: Eligibility Assessments and On-Treatment Assessments - Subjects Receiving Study Drug Post-Standard of Care (CA209358)	Oxygen saturation testing removed from vital signs	This protocol now reflects the nivolumab program-wide removal of oxygen saturation testing.
• Table 5.1-6: Follow-Up Assessments - All Subjects (CA209358)	Clarification to timing of follow up visits for neoadjuvant cohort and correlation with case report form added to table footnote	Clarification.
• Table 5.6.9-1: CA209358 Biomarker Sampling Schedule (Neo-Adjuvant Cohort) • Table 5.6.9-2: CA209358 Biomarker Sampling Schedule (Metastatic Monotherapy Cohorts and Metastatic Cohort Combo A and B) • Table 5.6.9-3: CA209358 Biomarker Sampling Schedule (Metastatic Combination Cohort Combo C and Combo D)	Plasma samples (one sample at Cycle 1 Day 1) have been added for tumor and/or immune-related genomic analysis.	The plasma samples will be collected for ctDNA analysis to assess tumor mutations, tumor mutation burden, and other biomarkers.
• Table 5.4.1-1: Schedule of Spiral CT/MRI Tumor Assessments for Metastatic Cohorts (Monotherapy and Combination Therapy), and Subjects Treated with Study Drug Post-Standard of Care Adjuvant Treatment	Adjusted week numbers for assessments dates.	Original week numbers started at week 9 instead of week 8.
• Section 8.2, Populations for Analysis	Definitions for all response evaluable subjects, all evaluable neoadjuvant subjects, and biomarker subjects have been added.	

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All	The name of BMS-986016 (relatlimab) has been added.	Provide familiarity with the name of BMS-986016 to investigators.
All	All references to the metastatic or recurrent HPV positive tumors have been replaced with anogenital metastatic or recurrent HPV associated tumors (vulvar, vaginal, anal canal, penile).	Clarification to align with therapeutic area standard.
All	Additional editorial and format changes for clarification and consistency.	Minor, therefore have not been summarized.