Protocol Number: CA209358
IND Number: 129,947
EUDRACT Number 2015-000230-29
Date: 22-Apr-2015
Revised Date: 18-Jul-2018

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

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.

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 [redacted] HPV positive and negative squamous cell cancer of the head and neck [SCCHN], [redacted] the study will enroll or randomize subjects into neoadjuvant treatment [redacted]

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

[redacted]

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.

[redacted]

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
  - [redacted]
- [redacted]

Secondary Objectives

- [redacted]

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 progression-free survival up to 1 year after neoadjuvant administration of nivolumab.
- 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[redacted]
- 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 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.

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 in viral positive and viral negative tumor types of the following tumor types: HPV positive and negative SCCHN,

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).

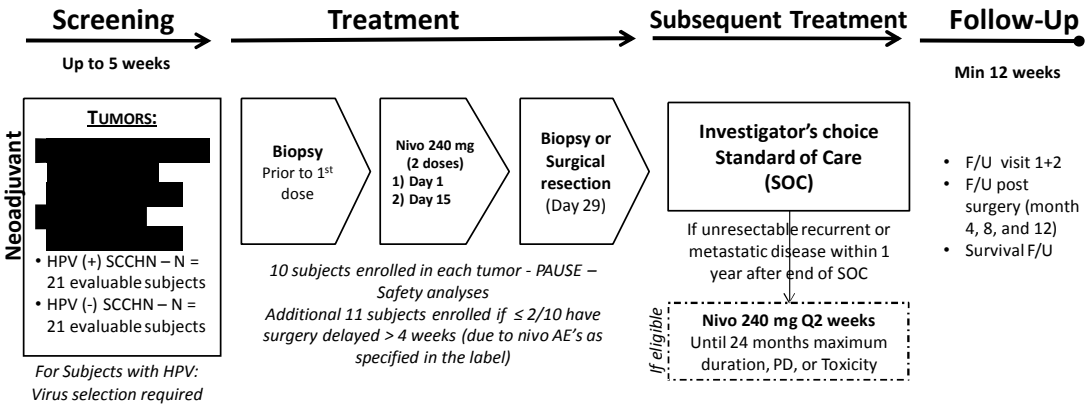
[redacted]

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

[redacted]



[redacted]

[redacted]

Study Population:

Inclusion Criteria:

[redacted]

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.

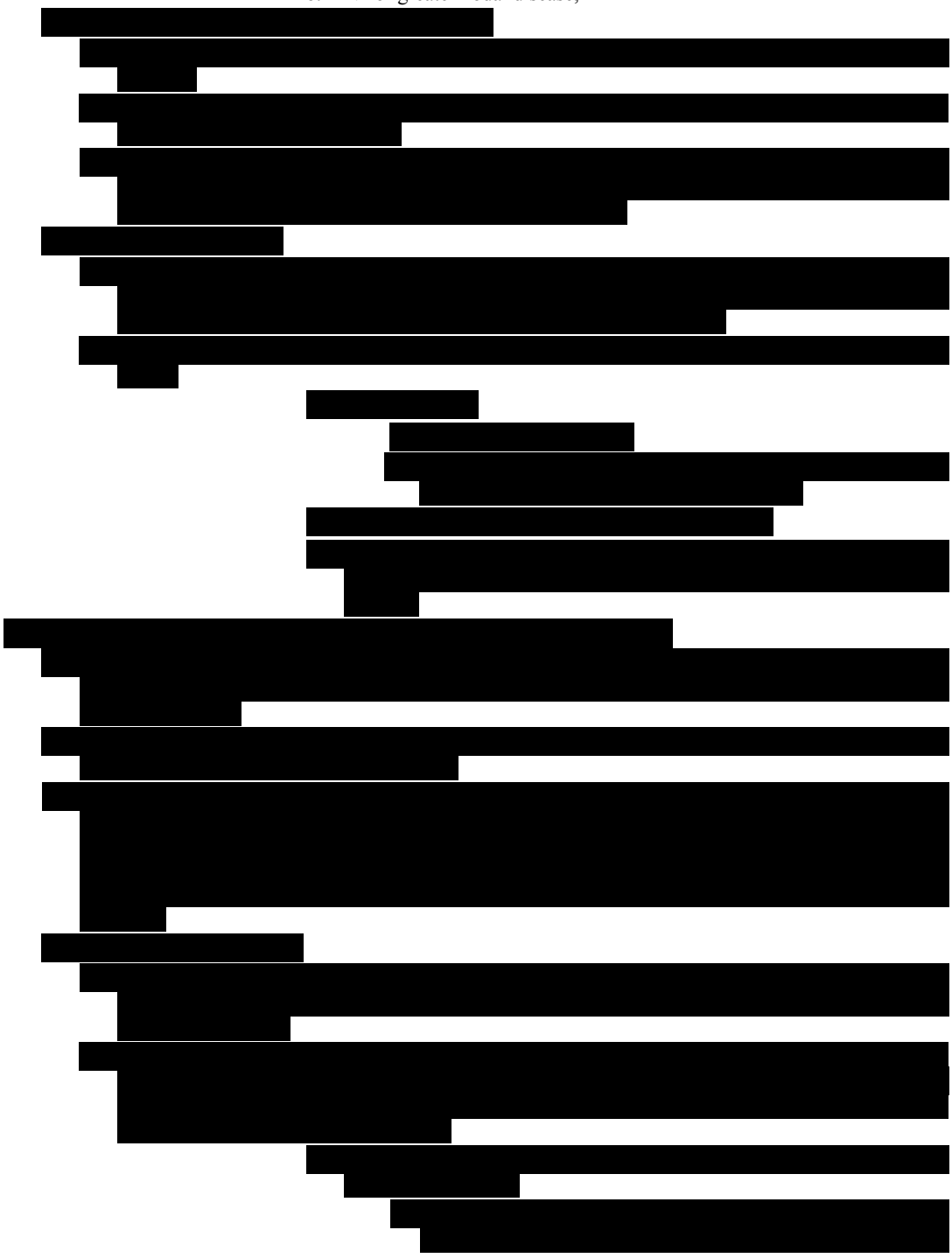
(1). Subjects must have newly diagnosed, histologically or cytologically confirmed squamous cell carcinoma or undifferentiated carcinoma of the oral cavity, pharynx and larynx. Subjects must have been determined to have resectable disease.

(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,



[redacted]

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. [redacted]

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).

[redacted]

[redacted]

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.

[redacted]

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
[redacted]					
[redacted]					

[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. [redacted]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.

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.

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.
- Investigator-assessed progression free survival (PFS) after surgery/biopsy, 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, [redacted]. 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.

[redacted]

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.

[redacted]

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.

[redacted]

Biomarker Analyses

The pharmacodynamic effects of nivolumab as monotherapy [redacted] 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.

[redacted]

[redacted]

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 [redacted] in viral positive and viral negative tumor types of the following tumor types: [redacted] HPV positive and negative squamous cell cancer of the head and neck (SCCHN), [redacted].

On the basis of eligibility and tumor type, patients will be enrolled into the neoadjuvant or recurrent/metastatic monotherapy [redacted] cohorts [redacted]

[redacted]

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

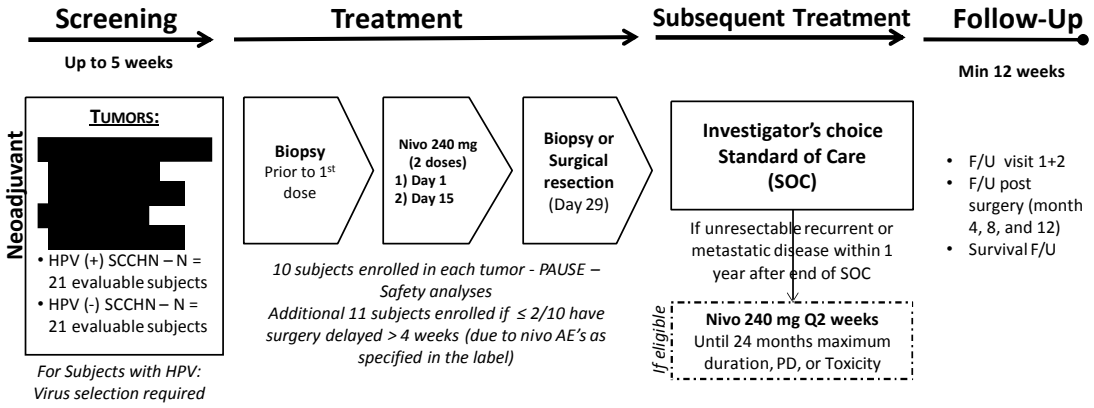
[redacted]

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

[redacted]

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



[redacted]

[redacted]

3.1.1 Viral Status Determination Prior to Entry

[redacted]

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 [redacted]. 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

[redacted]

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. [redacted]

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)
[redacted]		

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 [redacted]

All subjects must have tumor amenable to pre-treatment biopsy (core needle); post-treatment biopsy will consist of the operative specimen [redacted]

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 [redacted]), [redacted] will occur on Day 29 (+/- [redacted] days). No other pre-surgical therapy is allowed.
- After neoadjuvant nivolumab treatment followed by surgical resection [redacted], 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 [redacted] 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 [redacted] surgical delays beyond 4 weeks from the planned surgery date [redacted] If ≥ 3 of the first 10 subjects for a single tumor type have delays beyond 4 weeks from the planned surgery date [redacted] 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.

[redacted]

[redacted]

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

[redacted]

- [redacted]
  - [redacted]
- Squamous cell carcinoma of the Head and Neck
  - For subjects in the neoadjuvant [redacted] 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.
  - HPV positive status can be obtained from either the primary tumor or metastatic lymph node.
  - 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.

- **For subjects in the neoadjuvant cohort**
  - Squamous cell carcinoma of the Head and Neck for whom surgical resection is planned.
    - 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.
    - 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.
    - Subjects must have:
      - T1 or greater primary lesions, AND
      - N1 or greater nodal disease,

[redacted]

[redacted]

- **For both neoadjuvant and metastatic (monotherapy and combination)cohorts**
  - Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
  - Men and women of age 18 or older.
  - 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.
- **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:**
  - WBCs ≥ 2000/µL
  - Neutrophils ≥ 1500/µL
  - Platelets ≥ 100 x 10^3/µL
  - Hemoglobin ≥ 9.0 g/dL
  - Creatinine Serum creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥ 40 mL/minute (using Cockcroft/Gault formula)
  - AST ≤ 3 x ULN
  - ALT ≤ 3 x ULN
  - Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome who can have total bilirubin < 3.0 mg/dL)
  - [redacted]

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

- **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.

- **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 [redacted]

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).

[redacted]

[redacted]

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.

[redacted]

- **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.
- **Allergies and Adverse Drug Reaction**
  a) History of allergy to study drug components.
  b) History of severe hypersensitivity reaction to any monoclonal antibody.
- **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
- **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.

[redacted]

The potential for overlapping toxicities with radiotherapy and nivolumab [redacted] 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.

[redacted]

[redacted]

[redacted]

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
- [redacted]

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.
- [redacted]

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.

[redacted]

Confirmation of viral status will also be required prior to study drug assignment for SCCHN subjects enrolled in the neoadjuvant cohort. Subjects with [redacted] 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 [redacted] 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

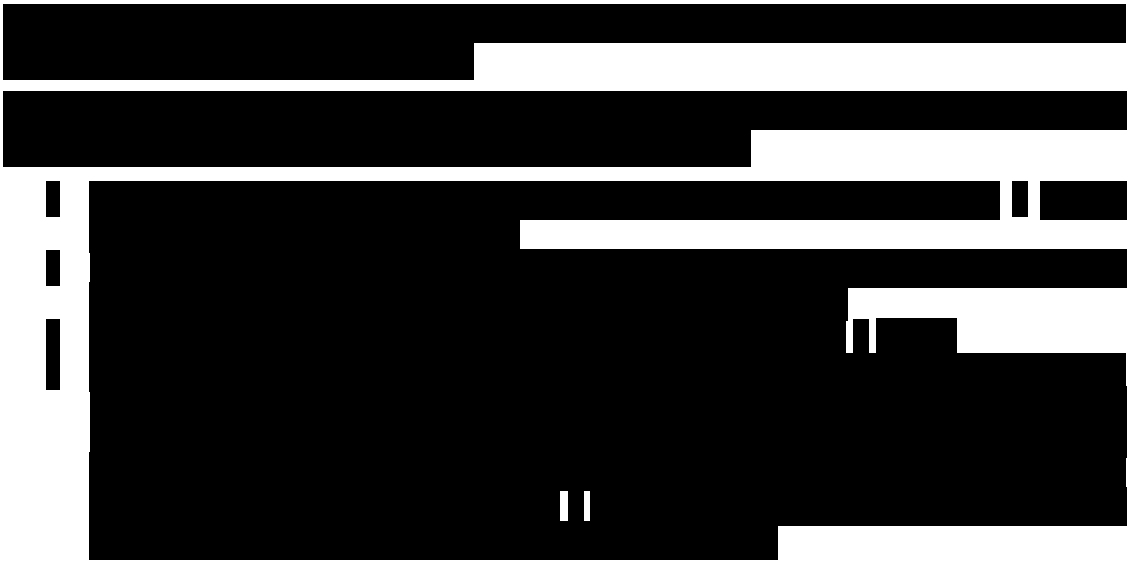
Table 4.5-1: Study Drug Dosing

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
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 4.5-1: Study Drug Dosing

Cohort	Drug	Dose	Frequency of administration	Route of administration	Duration
[redacted]					
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
[redacted]					

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.



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.

[redacted]

Dosing modifications:

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

[redacted]

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 [redacted] See Section 4.7.7 for subsequent premedication recommendations following a study drug-related infusion reaction.

[redacted]

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. [redacted] 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

[redacted]

4.7.3 Dose Delay Criteria

Study drug administration (nivolumab [redacted]) 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
- [redacted]
- 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)
- [redacted]
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study drug.
- [redacted]
- 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.

[redacted]

[redacted]

4.7.4 Dose Reductions

There will be no dose reductions for nivolumab[redacted].

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.
- [redacted]

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.
- [redacted]
- 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.
- [redacted]

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.

[redacted]

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. [redacted]

[redacted]

[redacted]

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).

[redacted]

[redacted]

5.6.1 Determination of Tumor's Viral Positivity

Confirmation of viral status will be required prior to study drug assignment for [redacted] SCCHN subjects enrolled in the neoadjuvant cohort [redacted] Viral status will be determined using an appropriately validated test as described below for each of the tumor types.

[redacted]

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.

[redacted]

[redacted]

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.

[redacted]

[redacted]

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.

[redacted]

[redacted]

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

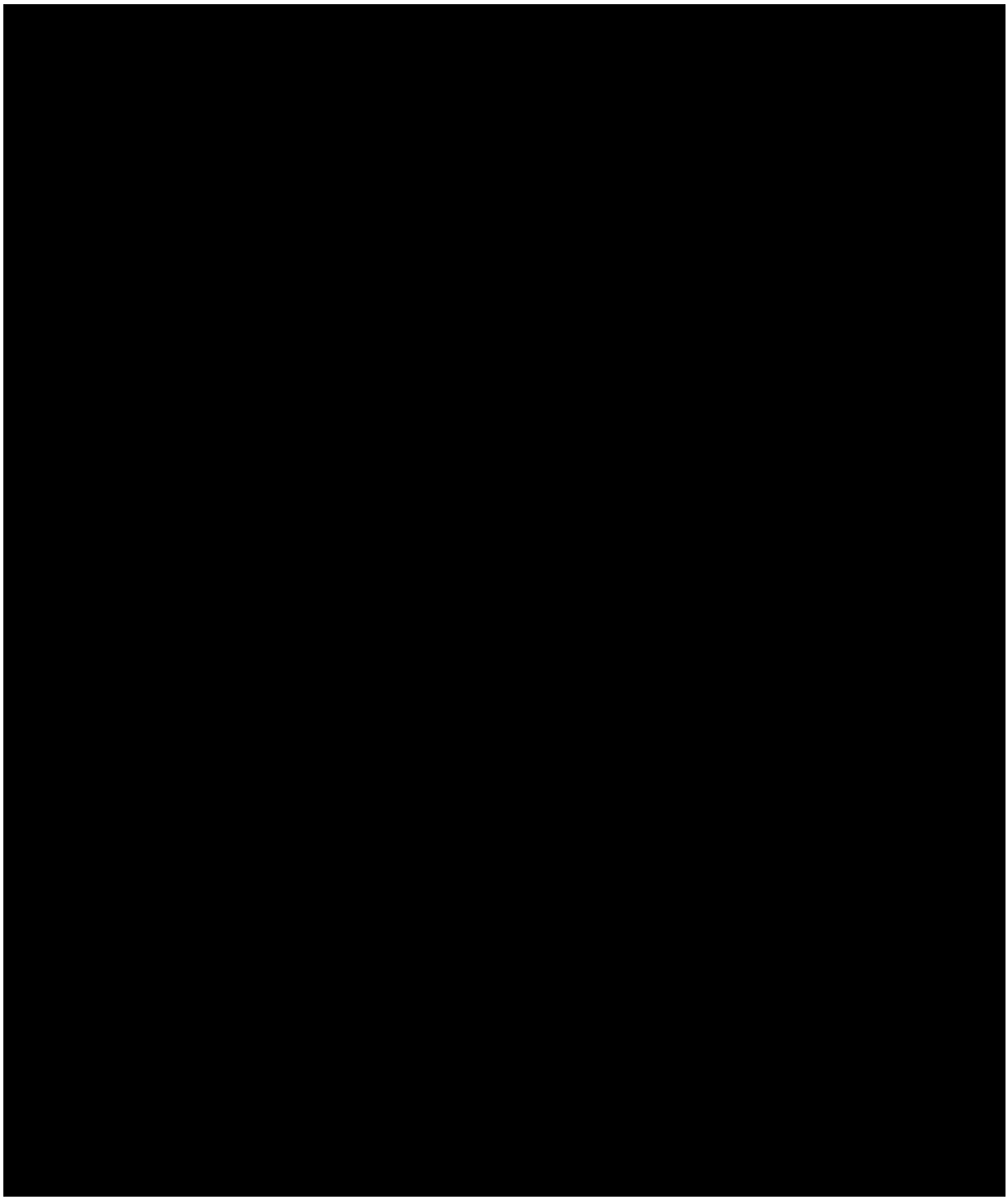
- Sample size determination is not based on statistical power calculation.

1) Neoadjuvant cohort:

The SCCHN tumor types will contain 21 HPV-positive and 21 HPV-negative evaluable subjects. [redacted]

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.



[redacted]

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.
  - [redacted]
  - All Evaluable Neoadjuvant Subjects: All treated subjects in neoadjuvant cohorts who have available paired tissue samples at Screening and Day 29.

[redacted]

- [redacted]
- 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.

[redacted]

[redacted]

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.
- Investigator-assessed progression free survival (PFS) after surgery/biopsy, which is defined as the time from surgery or biopsy to the date or recurrence, as determined by investigators or death due to any cause 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 [redacted]. 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.

[redacted]

8.4 Analyses

All analyses for neoadjuvant cohort will be performed as it completes safety follow-up. [redacted]

[redacted]

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.

[redacted]

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.

[redacted]

[redacted]

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.

APPENDIX 1 ECOG PERFORMANCE STATUS

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

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

APPENDIX 2 MANAGEMENT ALGORITHMS

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

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

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

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

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

GI Adverse Event Management Algorithm

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

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

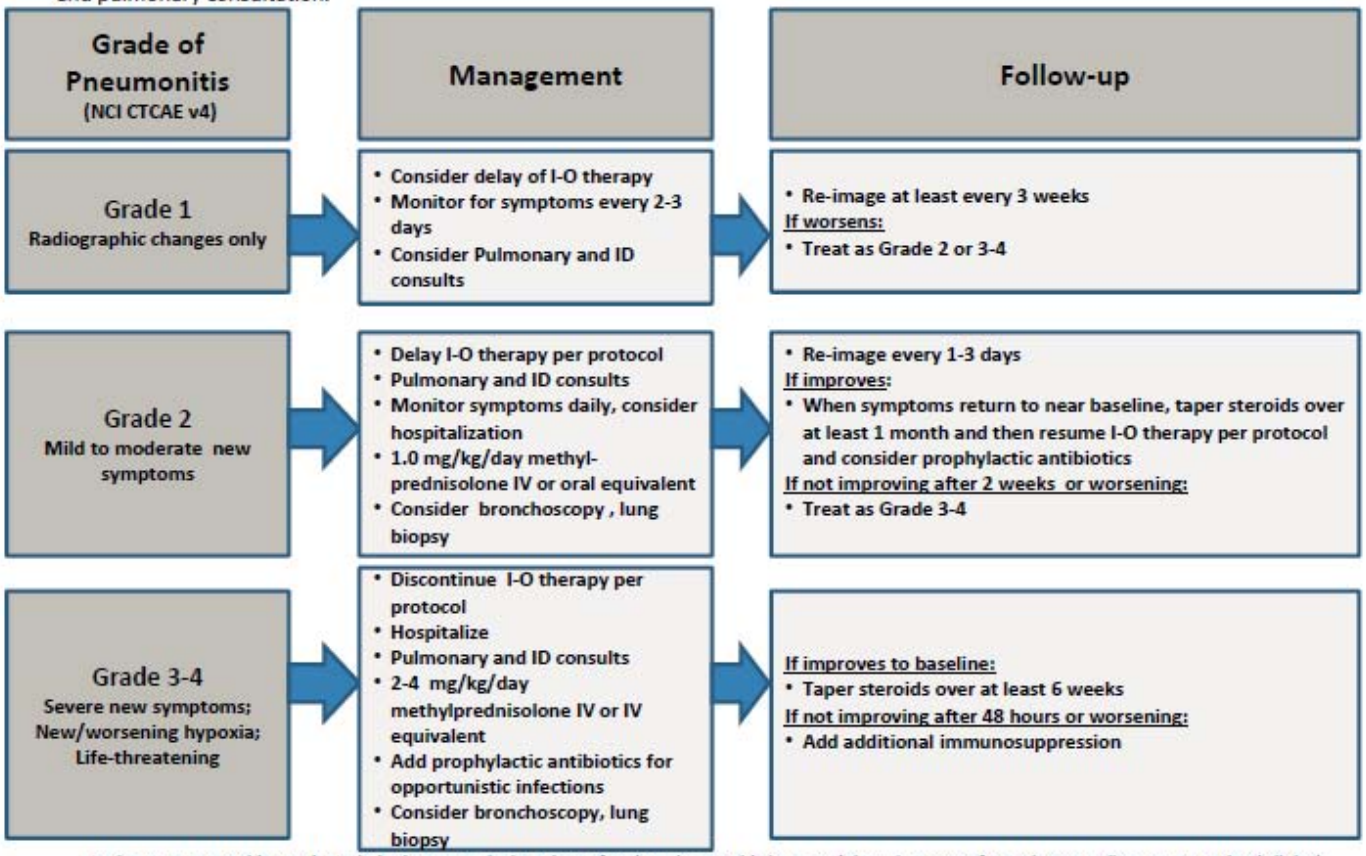
Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > ULN and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	<u>If returns to baseline</u>: •Resume routine creatinine monitoring per protocol <u>If worsens:</u> •Treat 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.

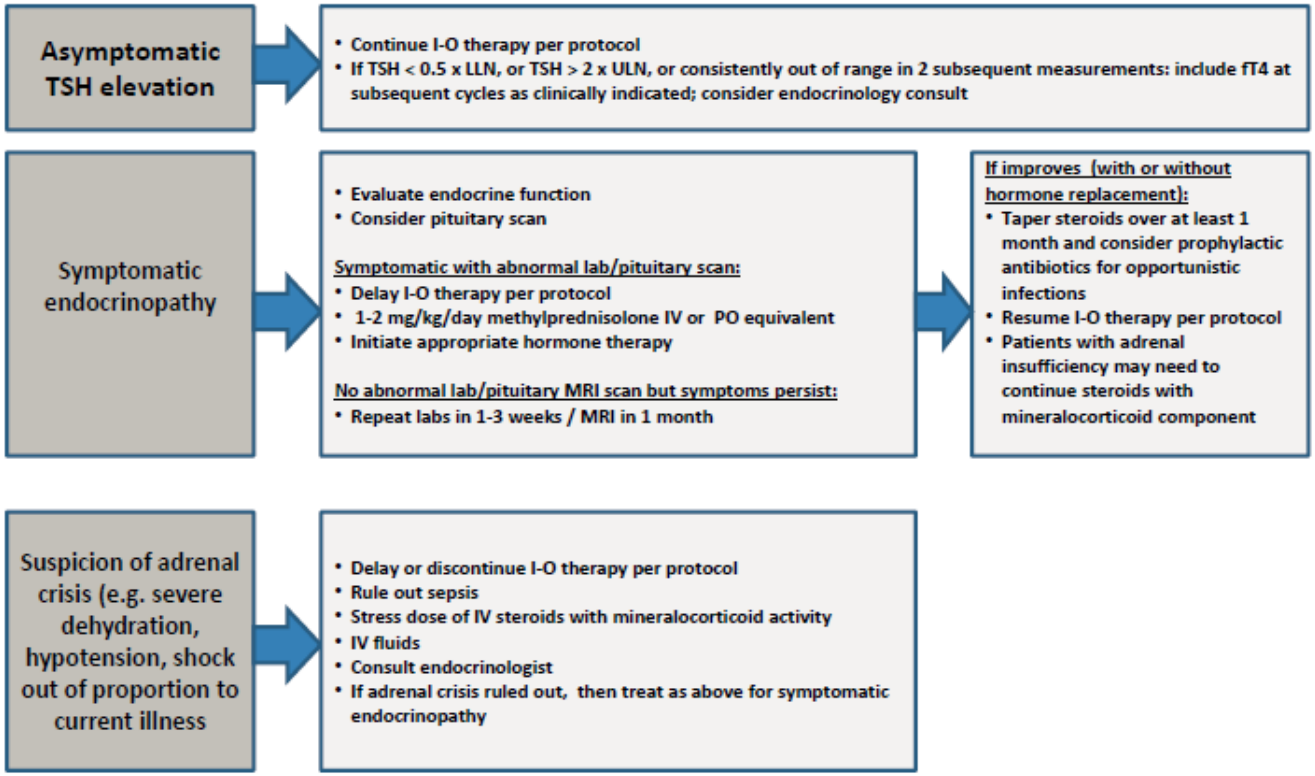
Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or T. bili > ULN to 1.5 x ULN	• Continue I-O therapy per protocol	• Continue LFT monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili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

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

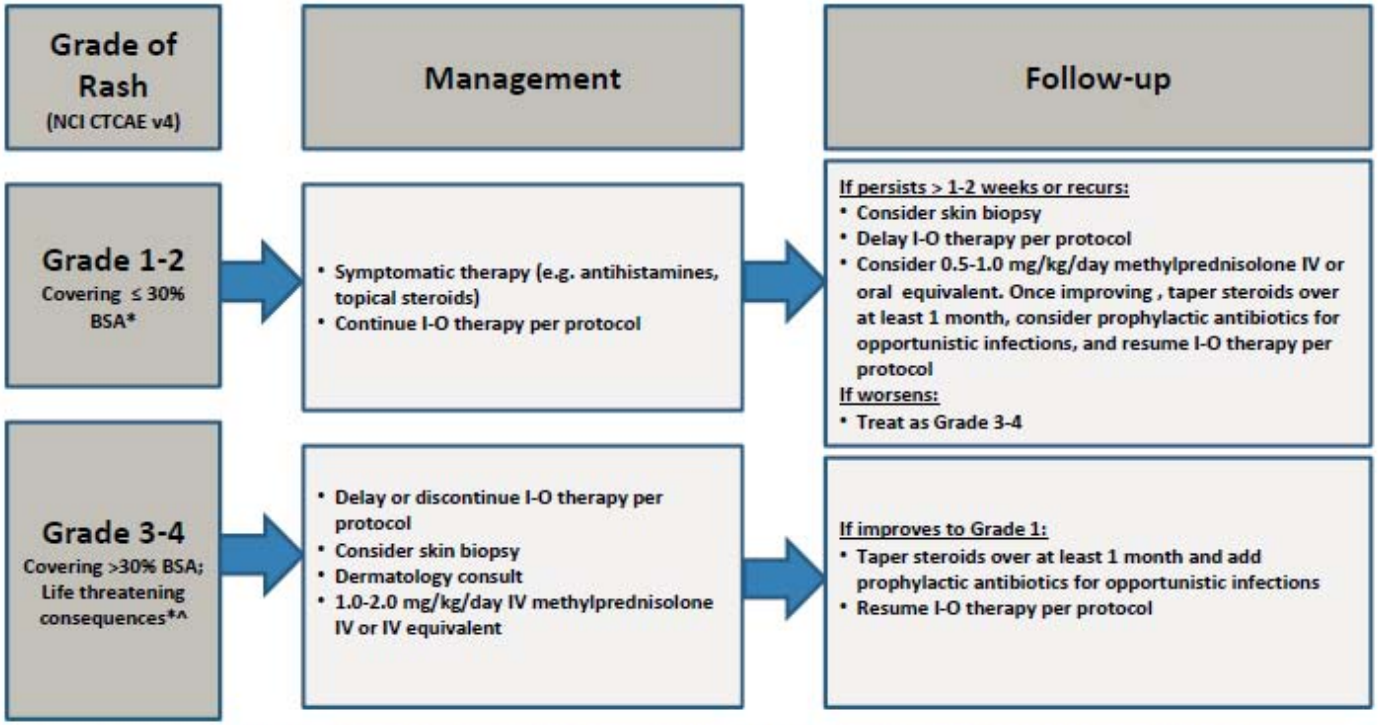


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. If worsens: • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: •Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

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

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.