Safety and Efficacy of Nivolumab Monotherapy in Recurrent or Metastatic Cervical, Vaginal, or Vulvar Carcinoma: Results From the Phase I/II CheckMate 358 Trial

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Clinical Protocol CA209358

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

Revised Protocol Number: 06

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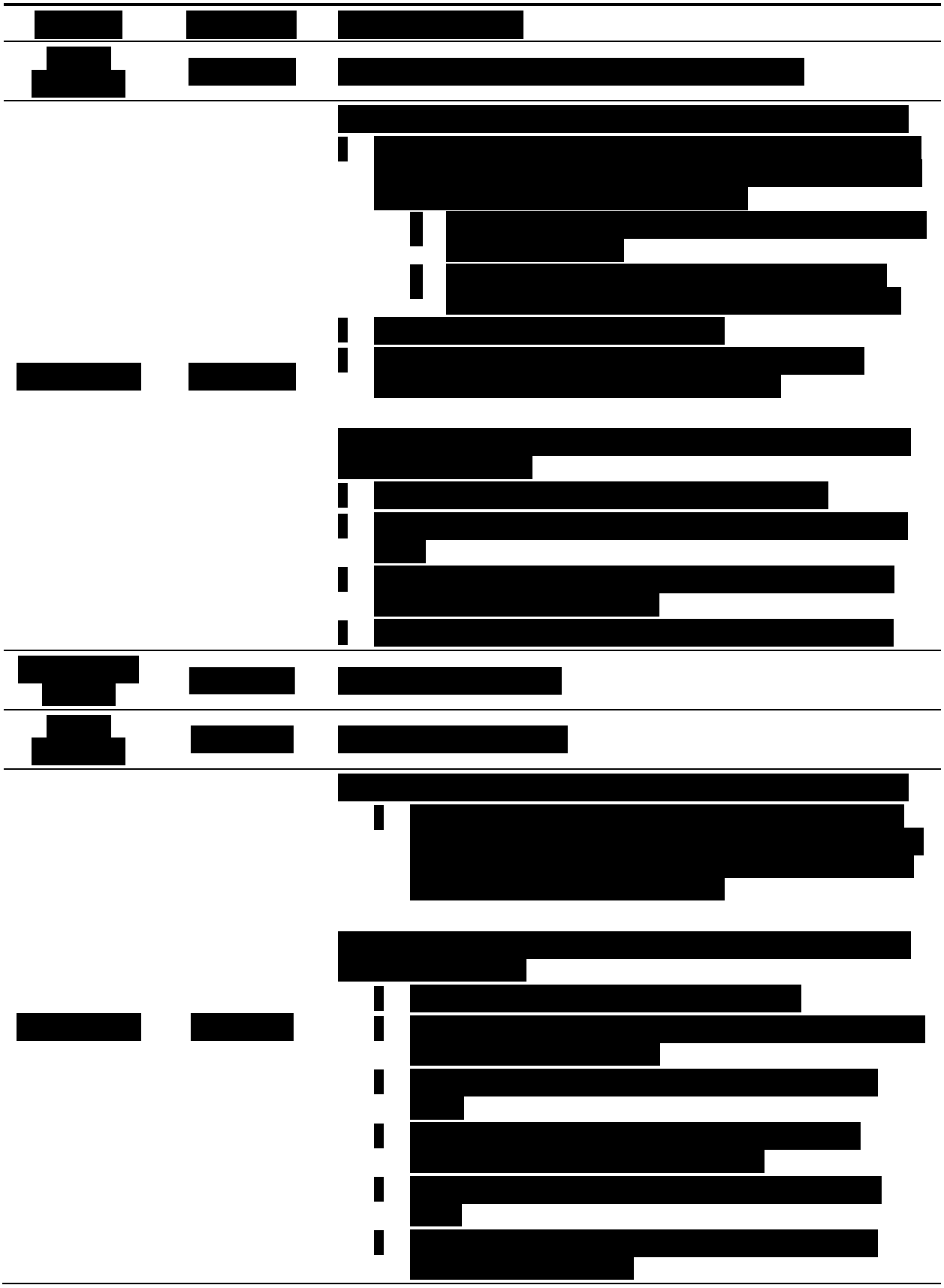
to partners to which BMS has transferred obligations, eg, a Contract Research Organization (CRO).

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



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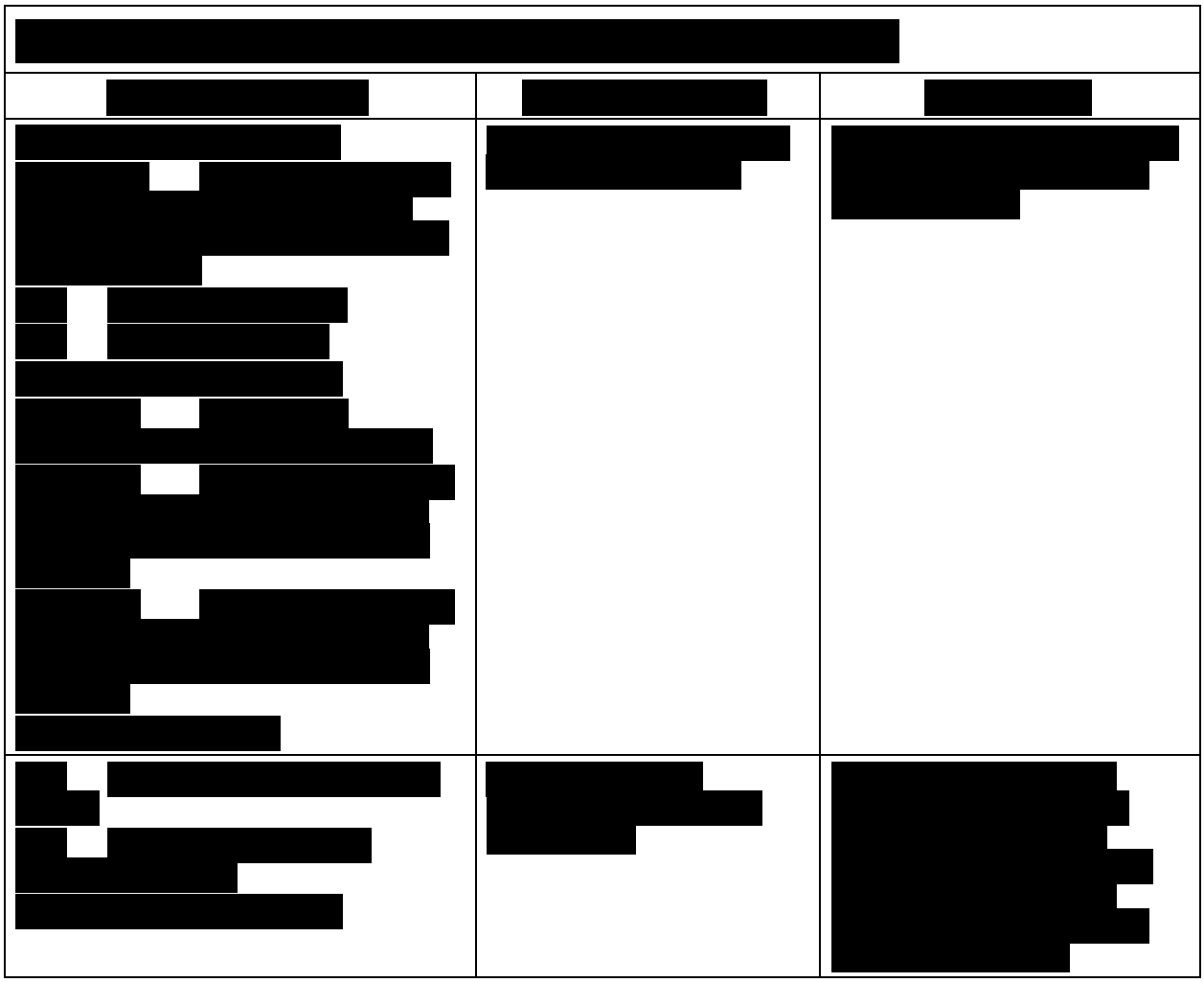


SYNOPSIS

Clinical Protocol CA209358

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

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

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

Treatments for each cohort are as follows:

[redacted]

Study Phase: 1/2

[redacted]

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

Primary Objectives

- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- In the metastatic cohort (nivolumab monotherapy), to evaluate the investigator-assessed objective response rate (ORR) in subjects with the following diseases:
  - [redacted]
  - [redacted]
  - [redacted]
  - Metastatic or Recurrent cervical, vaginal, or vulvar cancers
  - [redacted]

[redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]
- [redacted]

Secondary Objectives

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

Exploratory Objectives

[redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

Metastatic Cohort (Monotherapy and Combination Therapies)

- To determine the safety and tolerability [defined as toxicity rates (worst CTC grade per subject) of adverse events and specific laboratory tests] of nivolumab monotherapy and combination therapy (ipilimumab, BMS-986016, or daratumumab) in subjects with metastatic or recurrent viral-mediated tumors.

[redacted]

- To investigate the potential association between selected biomarker measures in peripheral blood and tumor tissue, including PD-L1, with safety and clinical efficacy measures.
- To investigate the pharmacodynamic activity of nivolumab monotherapy and combination therapy (ipilimumab, BMS-986016, or daratumumab) in the peripheral blood and tumor tissue as measured by gene expression, flow cytometry, immunohistochemistry and soluble factor assays.
- To study the effect of nivolumab monotherapy and combination therapy (ipilimumab, BMS-986016, or daratumumab) on the viral antigen specific T cell responsiveness in the peripheral blood.
- To evaluate the potential association between the number of tumor mutations and neoantigens with clinical efficacy measures and determine if tumor antigen-specific T cells are present in the periphery.
- To assess the subject's overall health status as assessed by the EQ-5D.
- To evaluate cancer specific health related quality of life as assessed by EORTC QLQ-C30.
- To characterize pharmacokinetics of nivolumab monotherapy and combination therapy (ipilimumab, BMS-986016, or daratumumab) and explore exposure-response relationships.
- To characterize the immunogenicity of nivolumab monotherapy and combination therapy (ipilimumab, BMS-986016, or daratumumab).

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

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

[redacted]

[redacted]

Treatments for each cohort are as presented above.

[redacted]

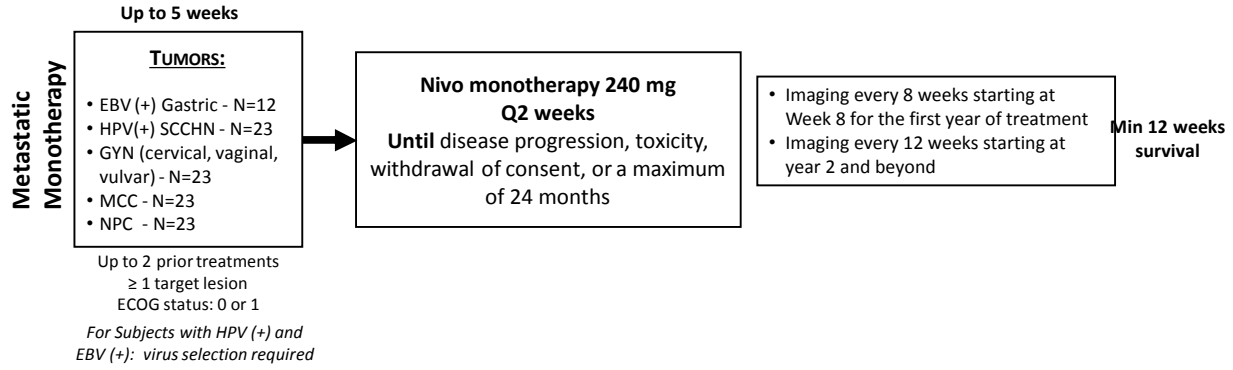
[redacted]

[redacted]

[redacted]

[redacted]

Study Design Schematic for the Metastatic Monotherapy Cohort



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[redacted]

[redacted]

[redacted]

Study Population:

Inclusion Criteria:

a) Histopathologic confirmation of the following tumor types

[redacted]

iv) Squamous cell carcinoma of the cervix, vagina, vulva, anal canal, and penile **(Note: anal canal and penile for metastatic combination cohorts only)**

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

[redacted]

[redacted]

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

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

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

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

[redacted]

[redacted]

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

[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. Exception: Combo C SCCHN prior exposure to anti PD-1/PD-L1/CTLA-4 therapy

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

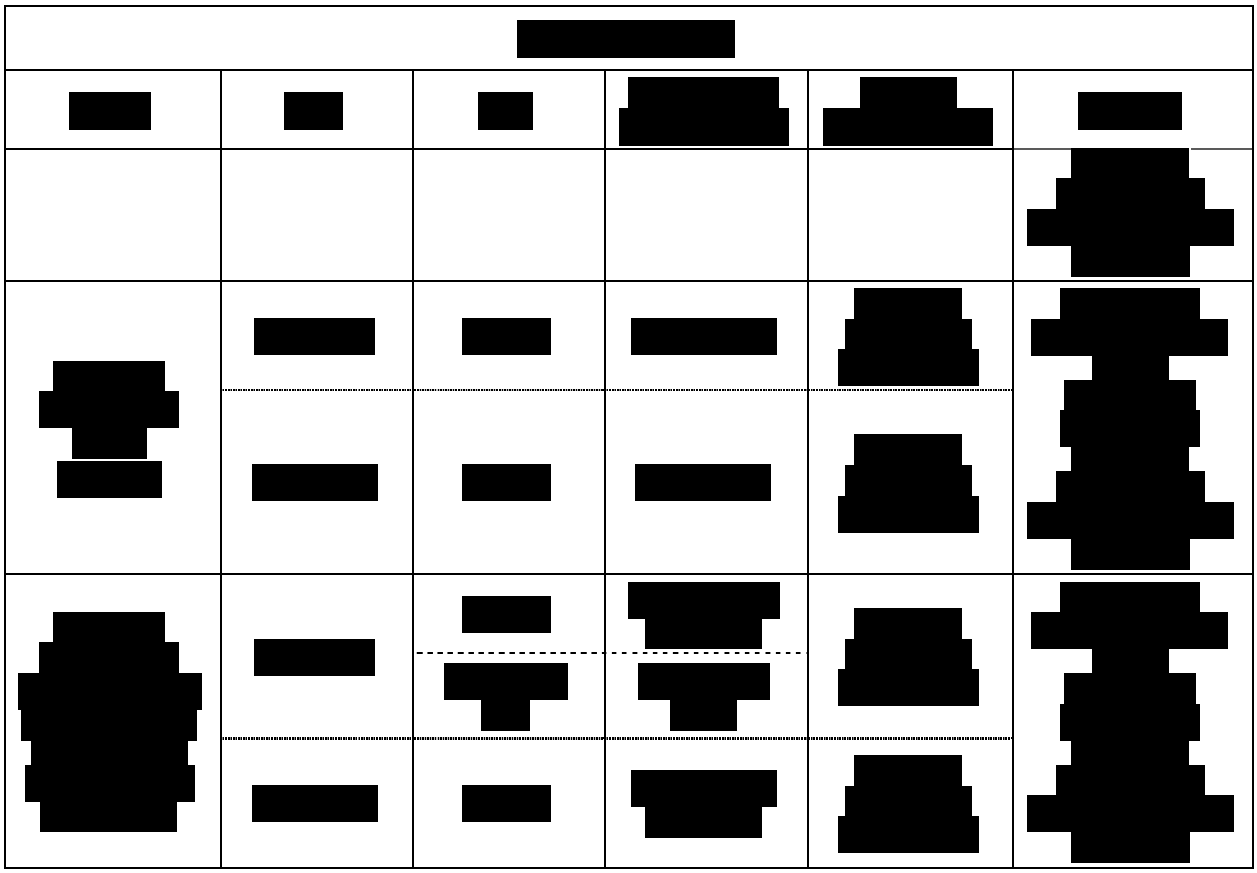
h) Treatment with any chemotherapy, radiation therapy, biologics for cancer, or investigational therapy within 28 days of first administration of study treatment (subjects with prior cytotoxic or investigational products < 4 weeks prior to treatment might be eligible after discussion between investigator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

[redacted]

[redacted]

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**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic Monotherapy	Nivolumab	240 mg flat dose	every 2 weeks	30 minute Intravenous (IV) infusion	Maximum of 24 months or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever comes first
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]



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.

[redacted]

2) Recurrent/metastatic monotherapy cohort:

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

[redacted] Table 3 shows the precision of the estimation of ORR based on the two sided 95% exact CI using Clopper-Pearson methods based on 1, 2, 3, 4, and 5 responders out of 12 subjects.

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

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

Table 2 Two-sided 95% exact CI Using Clopper-Pearson Method Based on Number of Observed Responses out of 23 Subjects

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

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

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

[redacted]

[redacted]

Endpoints:

Primary Endpoints:

[redacted]

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

Secondary Endpoints:

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

- Duration of response (DOR) is defined as the time from first confirmed response (CR or PR) to the date of the initial objectively documented tumor progression as determined per investigator assessment using RECIST 1.1 criteria or death due to any cause, whichever occurs first. Subjects who did not start subsequent anti-cancer therapy and die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on the date they were treated. Subjects who started any subsequent anti-cancer therapy prior to death and without a prior reported progression will be censored at the last tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy. DOR will only be evaluated in subjects with objective response of CR or PR
- Overall survival (OS) is defined as the time from first dosing date to the date of death. A subject who has not died will be censored at last known date alive.
- Investigator-assessed progression free survival (PFS) is defined as the time from first dosing date to the date of the first documented tumor progression, as determined by investigators (per RECIST 1.1), or death due to any cause. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on the date they were treated. Subjects who started any subsequent anti-cancer therapy prior to death and without a prior reported progression will be censored at the last tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy.

Exploratory Endpoints:

[redacted]

[redacted]

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

- The safety and tolerability objective will be measured by the incidence of adverse events, serious adverse events, deaths and laboratory abnormalities.

[redacted]

[redacted] Metastatic cohort **(monotherapy and combination therapies)**:

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

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

Analyses:

Analyses for primary endpoints:

[redacted]

Metastatic cohort (monotherapy and combination therapies):

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

Analyses for secondary endpoints:

Metastatic cohort (monotherapy and combination therapies):

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

Analyses for exploratory endpoints:

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

Safety Analyses

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

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

Pharmacokinetic Analyses

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

Biomarker Analyses

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

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

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

Outcomes Research Analyses

EQ-5D

Subject's overall health state on a visual analog scale (EQ-VAS) at each assessment time point will be summarized using descriptive statistics (N, mean, standard deviation, median, first and third quartiles, minimum, maximum). Proportion of subjects reporting problems for the 5 EQ-5D dimensions at each assessment time point will be summarized by level of problem. Percentages will be based on number subjects assessed at assessment time point.

A by-subject listing of EQ-5D with the problem levels for each of the 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), health state (5 dimensions digits combined in a 5-digit number) and EQ-VAS will be provided. Each dimension has three levels: no problems, some problems, and severe problems.

EORTC QLQ-C30

The analysis of EORTC QLQ-C30 will be performed in all treated subjects who have an assessment at baseline and at least one subsequent assessment.

All scales and single items are scored on a categorical scale and linearly transformed to 0-to-100 scales with higher scores for a functional scale representing higher levels of functioning, higher scores for the global health status/quality of life representing higher levels of global health status/quality of life, and higher scores for a symptom scale representing higher level of symptoms.

Baseline and change from baseline in EORTC QLQ-C30 global health status/QoL composite scale data and the remaining EORTC QLQ-C30 scale data will be summarized by time point using descriptive statistics for each cohort

(N, mean, standard deviation, median, first and third quartiles, minimum, maximum). In addition, the percentage of subjects demonstrating a clinically meaningful deterioration (defined as a 10 point change from baseline) will be presented for each scale at each assessment time point. Percentages will be based on number subjects assessed at assessment time point.

Immunogenicity Analyses

Immunogenicity may be reported for anti-drug antibody (ADA) positive status (such as persistent positive, neutralizing positive, only last sample positive, baseline positive and other positive) and ADA negative status, relative to baseline. Effect of immunogenicity on safety, efficacy, biomarkers and PK may be explored. Additional details will be described in the statistical analysis plan.

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1 INTRODUCTION AND STUDY RATIONALE

1.1 Study Rationale

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

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

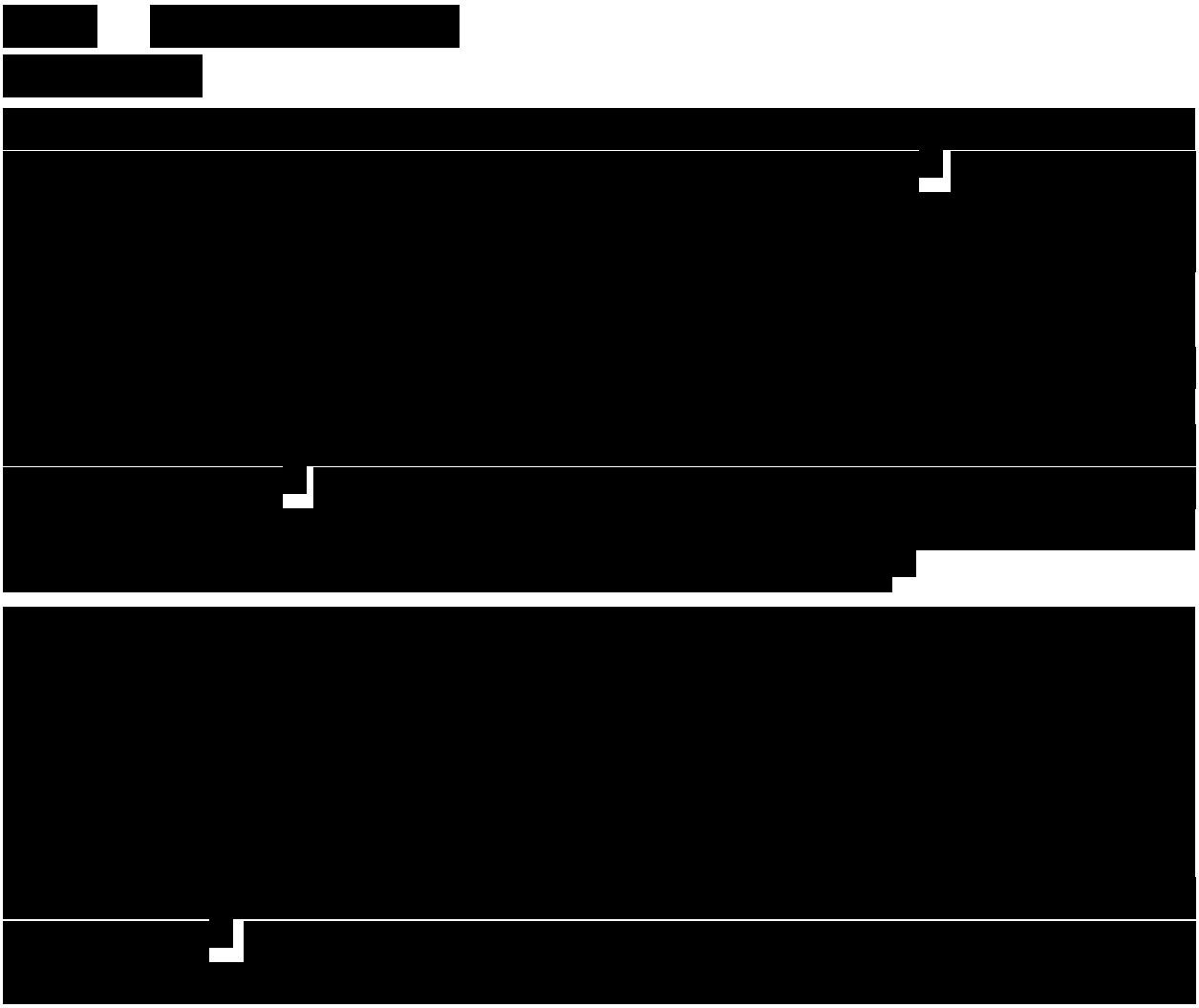
Preclinical animal models of tumors have shown that blockade of PD-1 by monoclonal antibodies (mAbs) can enhance the anti-tumor immune response and result in tumor rejection. This suggests that host mechanisms limit the antitumor response.[13,14,15,16,17,18]

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

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

1.1.1 Disease Background

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



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1.1.1.2 HPV Positive Tumors

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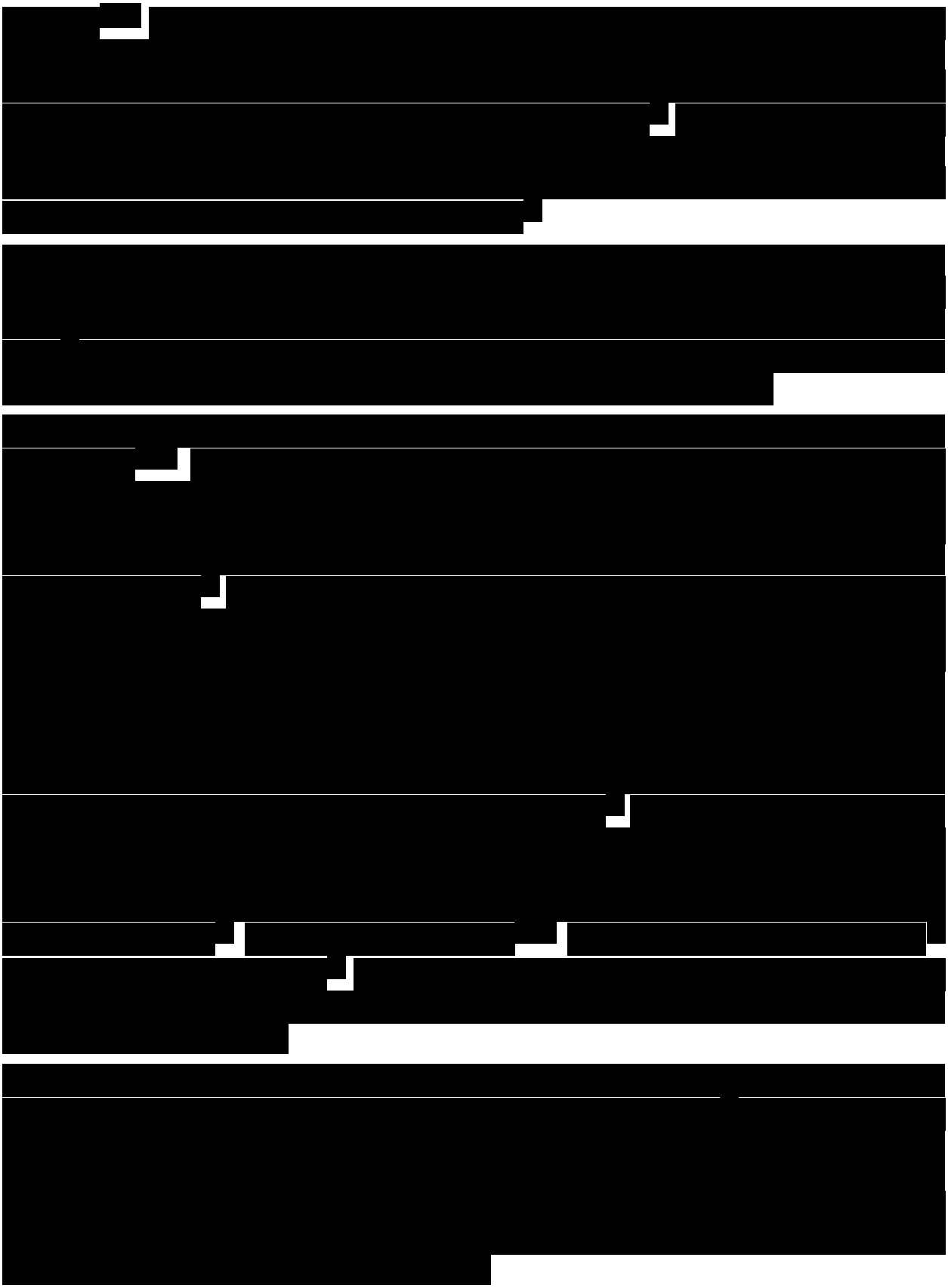
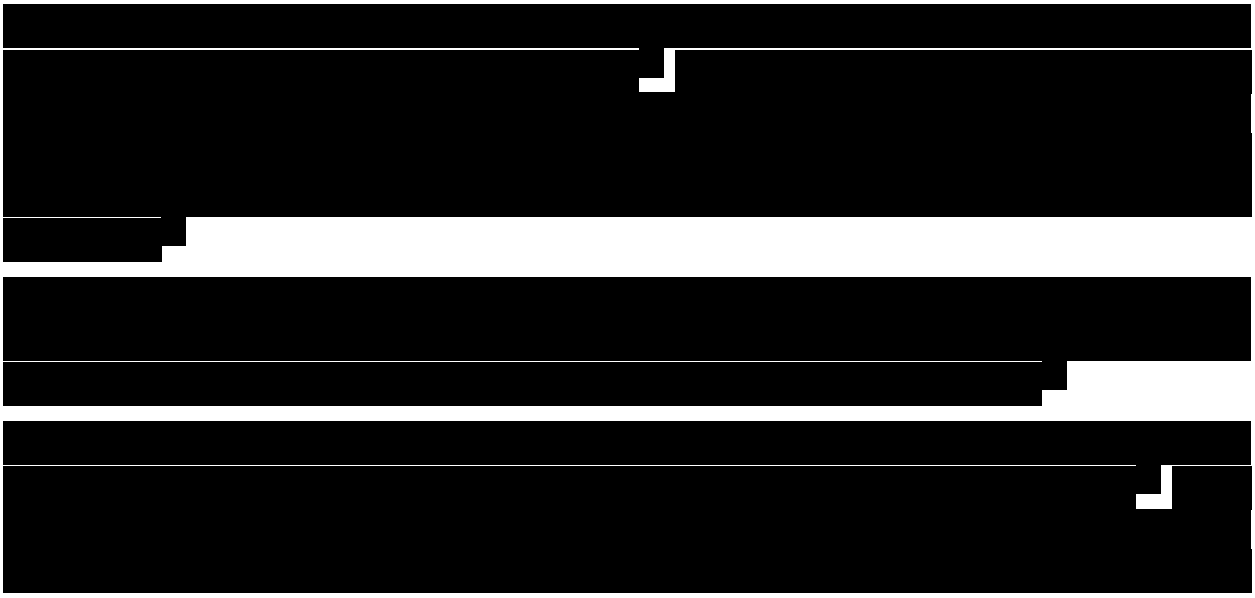


Cervical, Vaginal, Vulvar, Anal Canal, and Penile Cancers

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

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

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



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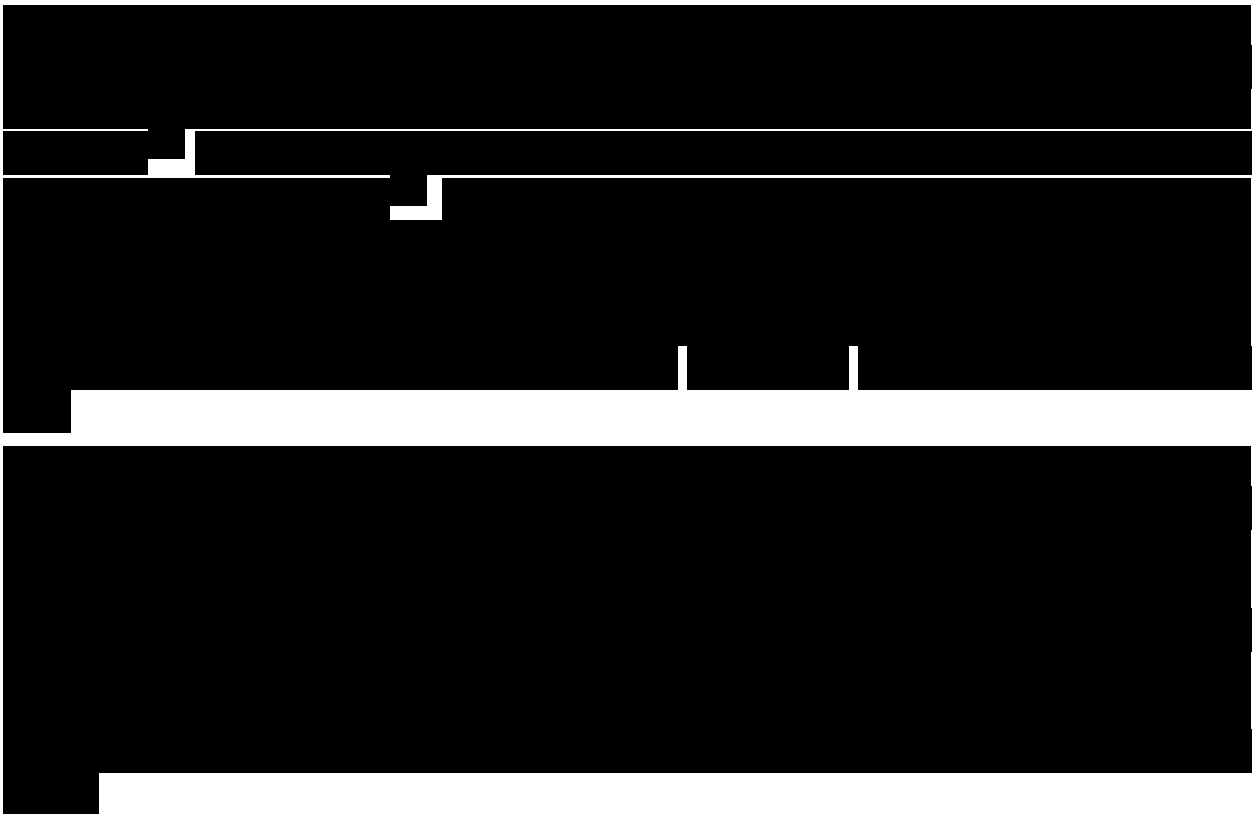


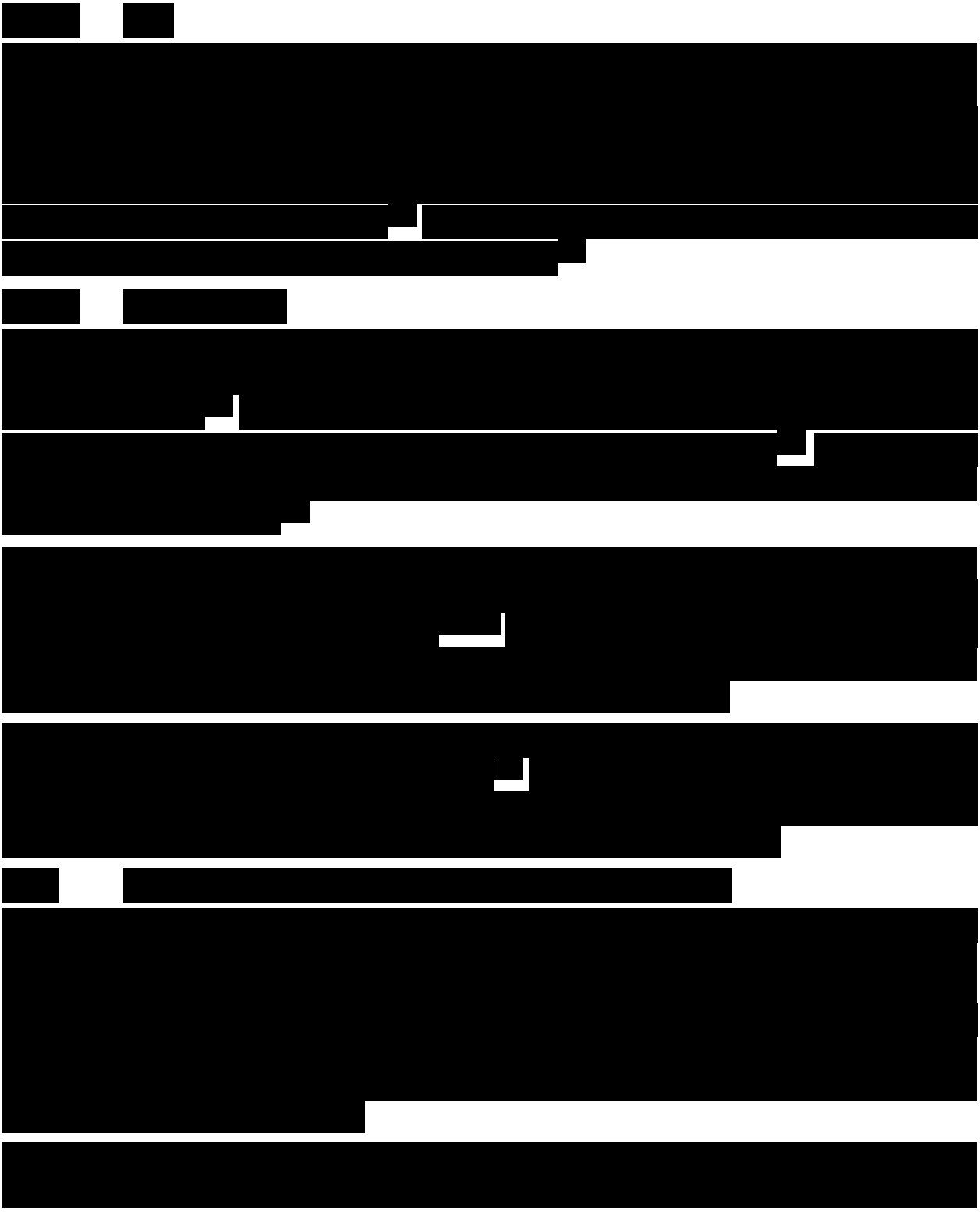
1.1.2 Infection and Tumorigenesis

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

1.1.2.1 HPV

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

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



1.1.4 Rationale for Immunotherapy in Virus-Associated Tumors

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

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

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

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

1.1.5 Rationale and Aims for Biomarker Assessments

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

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

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

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

1.1.6 Rationale for Dose Selection for Nivolumab

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

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

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

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

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

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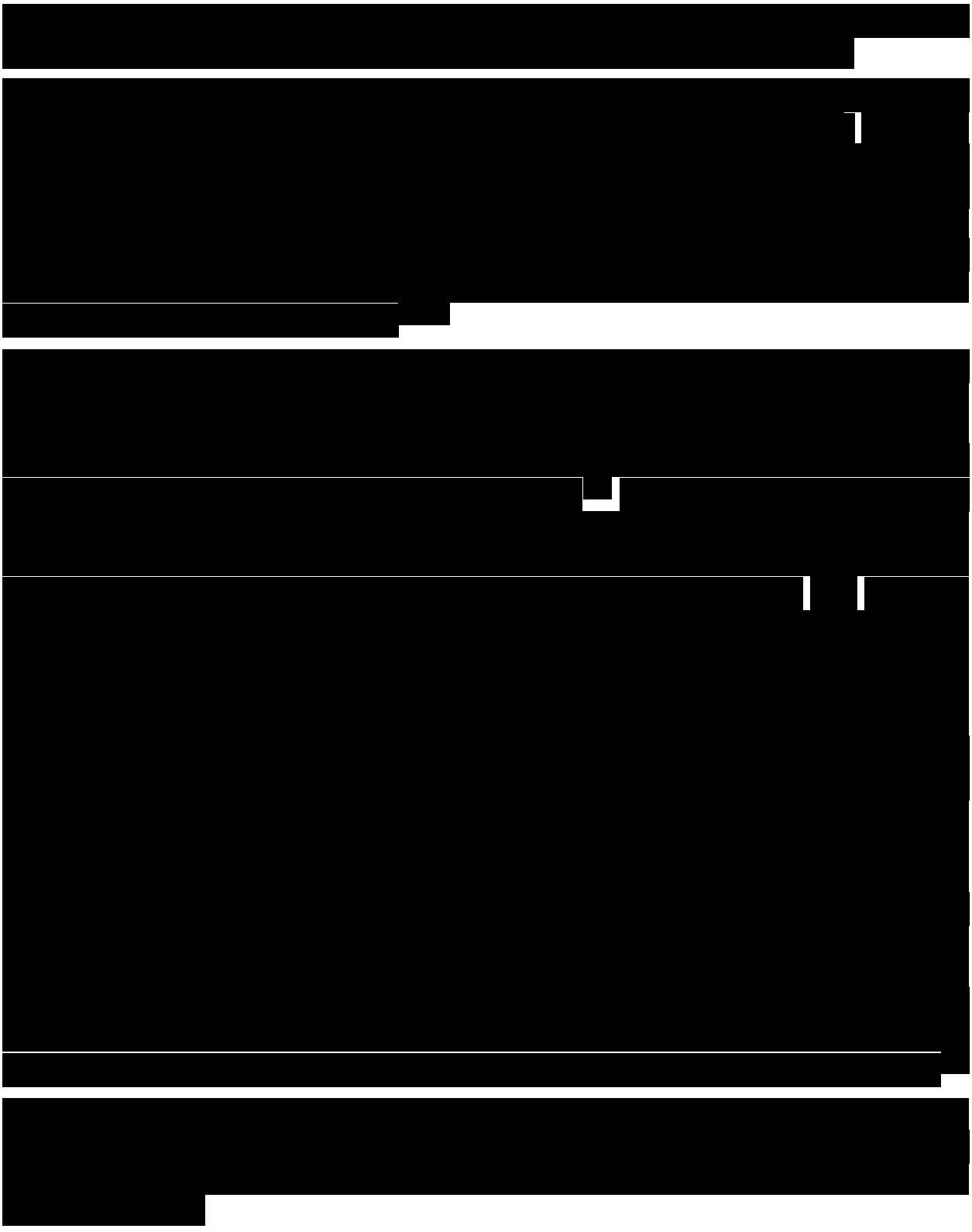

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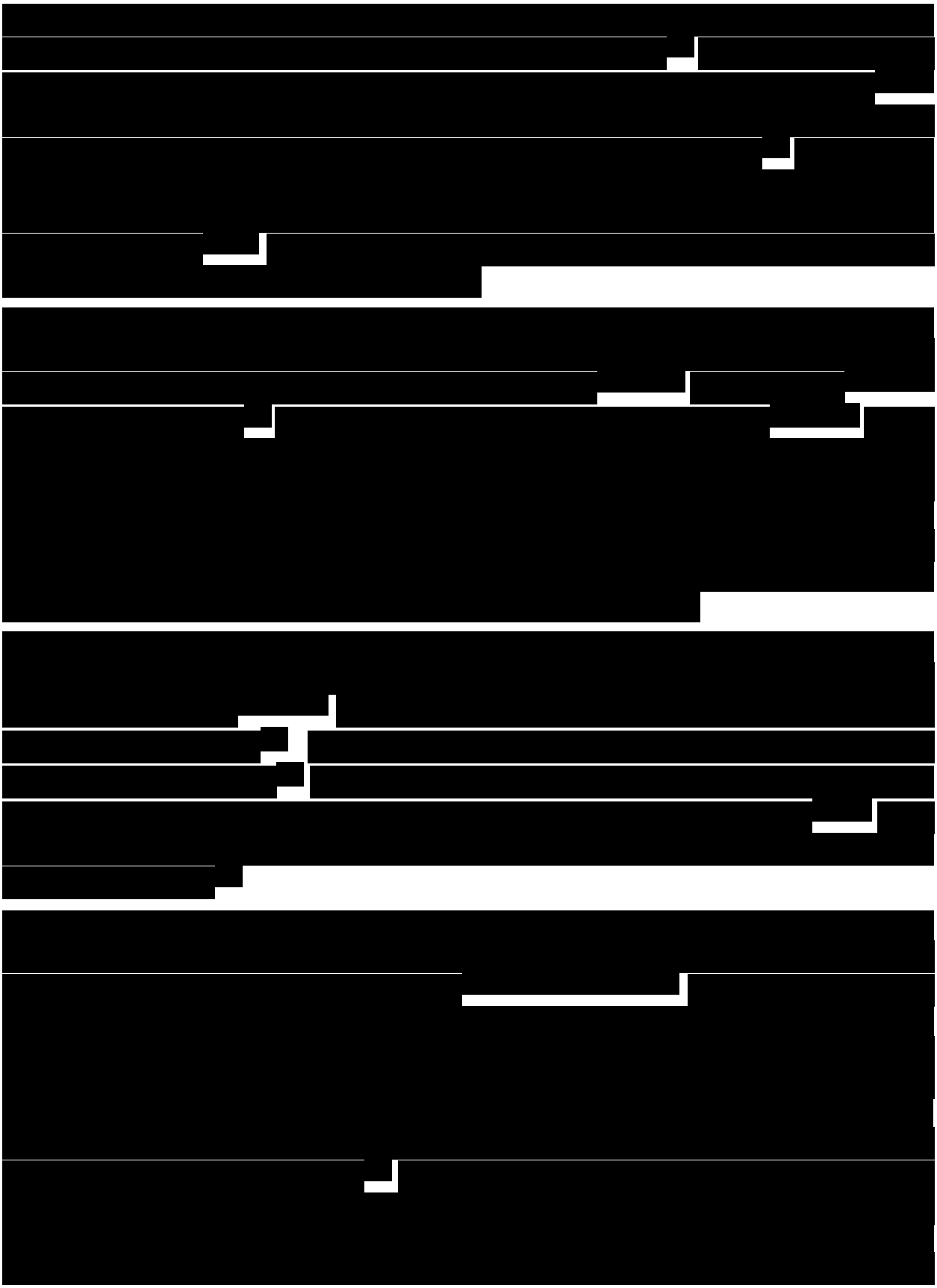

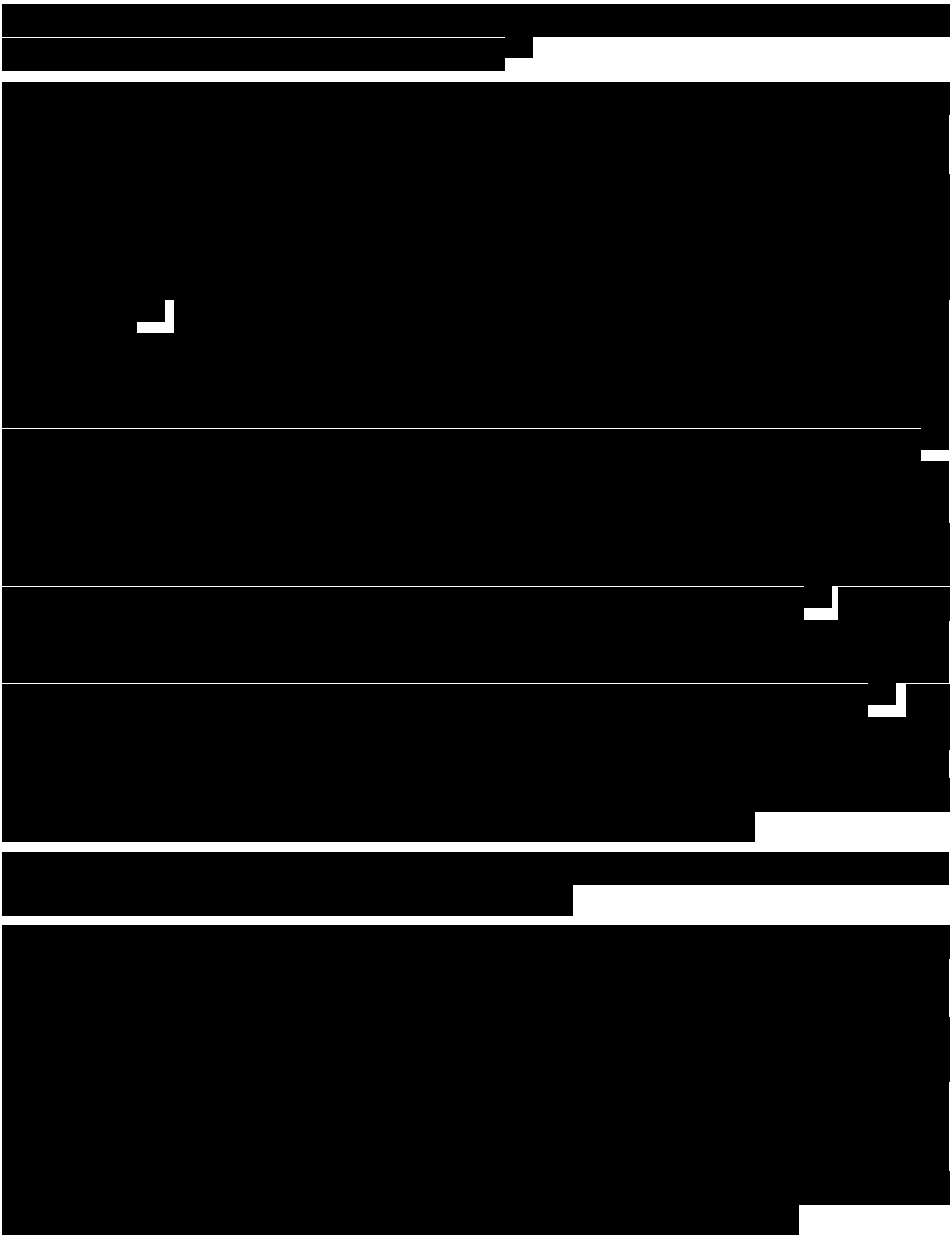

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1.1.15 Duration of Treatment with Nivolumab Monotherapy or Combination Therapy

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

treatment.[166] Furthermore, a limited duration of ipilimumab, including only 4 induction doses, resulted in long term survival in patients with metastatic melanoma, with a sustained plateau in survival starting around 2 years after the start of treatment.[167]

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

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

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

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

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

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

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

1.2 Research Hypothesis

[redacted]

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

1.3 Objectives(s)

1.3.1 Primary Objectives

[redacted]

- In the metastatic cohort (nivolumab monotherapy), to evaluate the investigator-assessed objective response rate (ORR) in subjects with the following diseases:

[redacted]

  - Metastatic or recurrent cervical, vaginal, or vulvar cancers

[redacted]

[redacted]

1.3.2 Secondary Objectives

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

1.3.3 Exploratory Objective(s)

[redacted]

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

1.4 Product Development Background

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

1.4.1 Nivolumab

1.4.1.1 Summary of Nivolumab Clinical Activity in the Metastatic Setting

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

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

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

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

1.4.1.2 Summary of Nivolumab Safety in the Metastatic Setting

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

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

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

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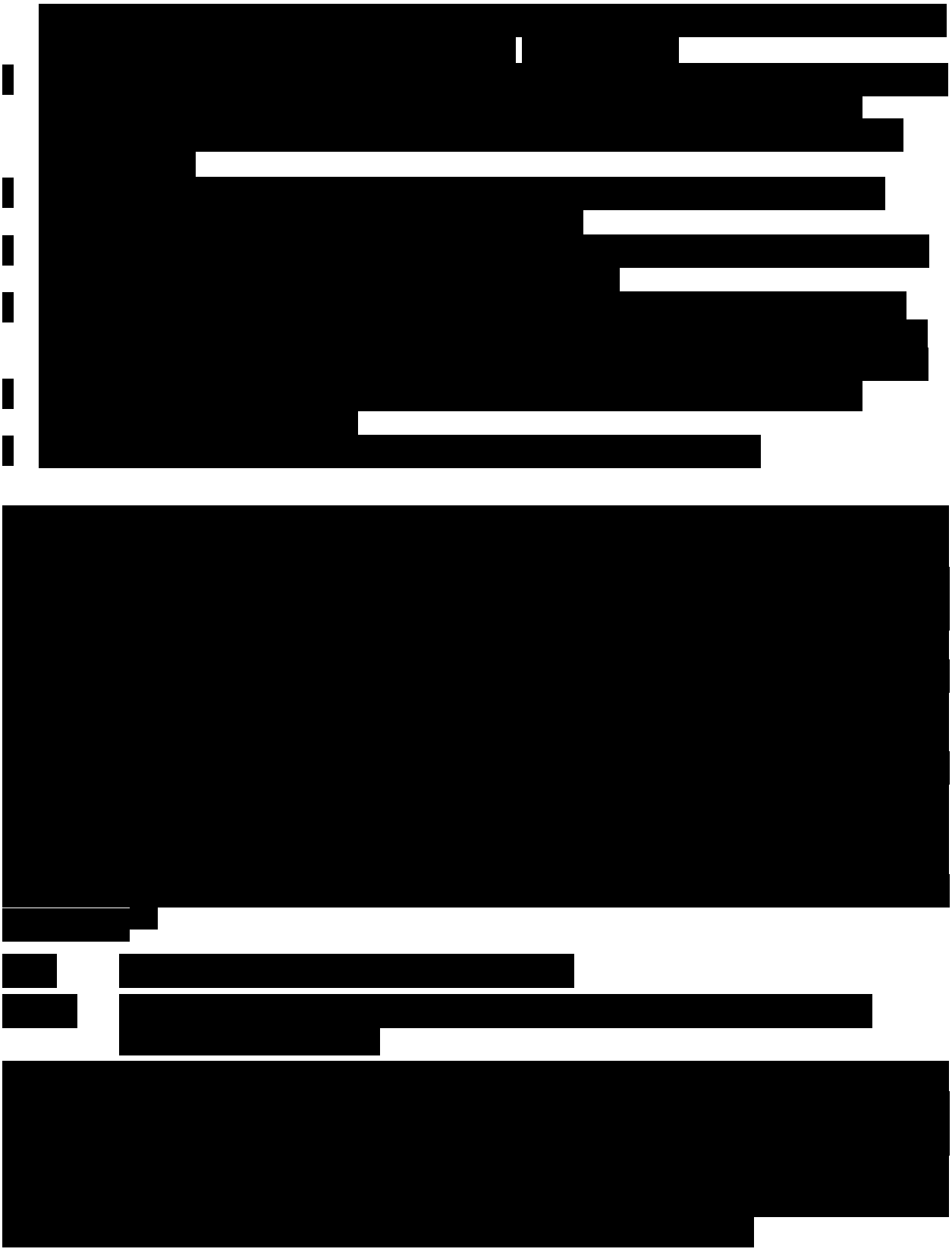

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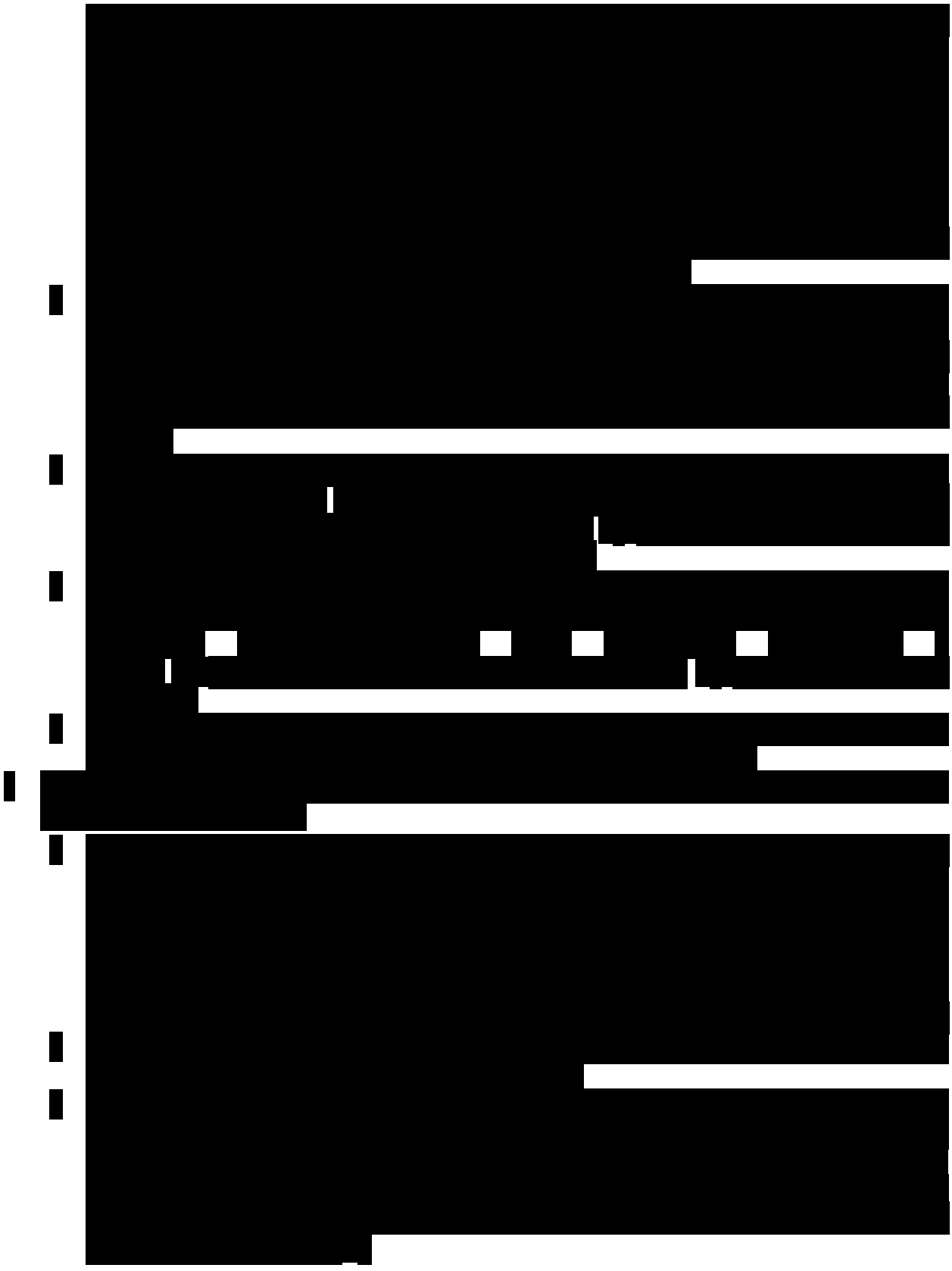

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[redacted]

1.5 Overall Risk/Benefit Assessment

There is a significant unmet medical need for subjects with virus positive tumors including [redacted] cervical/vulvar/vaginal/[redacted] as outlined in Section 1.1. Virus positive tumors may have distinct patterns of immune responses and tumor immune microenvironments (Section 1.1.4); therefore, a strong rationale exists to support blocking the PD-1 signaling pathway with the goal of improving patient outcomes in the metastatic/recurrent settings. In the metastatic setting, subjects with virus-positive tumors generally have limited treatment options with high mortality rates, and NCCN guidelines recommend clinical trials as an option for each of the tumor types in this trial.

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

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

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

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

[redacted]

[redacted]

[redacted]

[redacted]

A pattern of immune-related adverse events has been defined for treatment with nivolumab monotherapy [redacted]

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

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

[redacted]

[redacted]

[redacted]

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

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

[redacted]

[redacted]

In summary, based on the manageable safety profile of nivolumab [redacted] the observed clinical activity of nivolumab [redacted] and the rationale for immune checkpoint inhibition for patients with virus-associated tumors, it is felt that the overall benefits to subjects outweigh the potential risks in the neoadjuvant or metastatic/recurrent settings. [redacted]

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

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

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

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

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

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

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

2.2 Institutional Review Board/Independent Ethics Committee

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

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

2.3 Informed Consent

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

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

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

Investigators must:

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

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

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

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

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

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

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

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

[redacted]

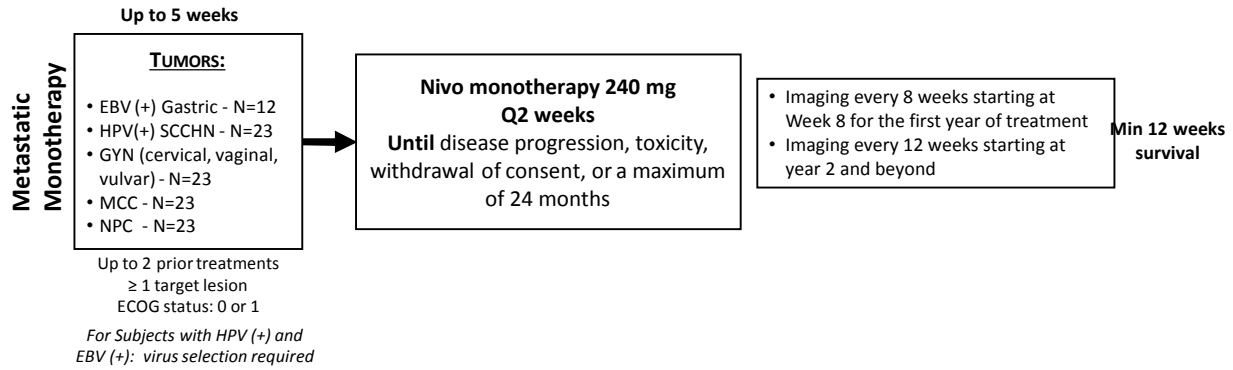
Metastatic Monotherapy Cohorts:

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

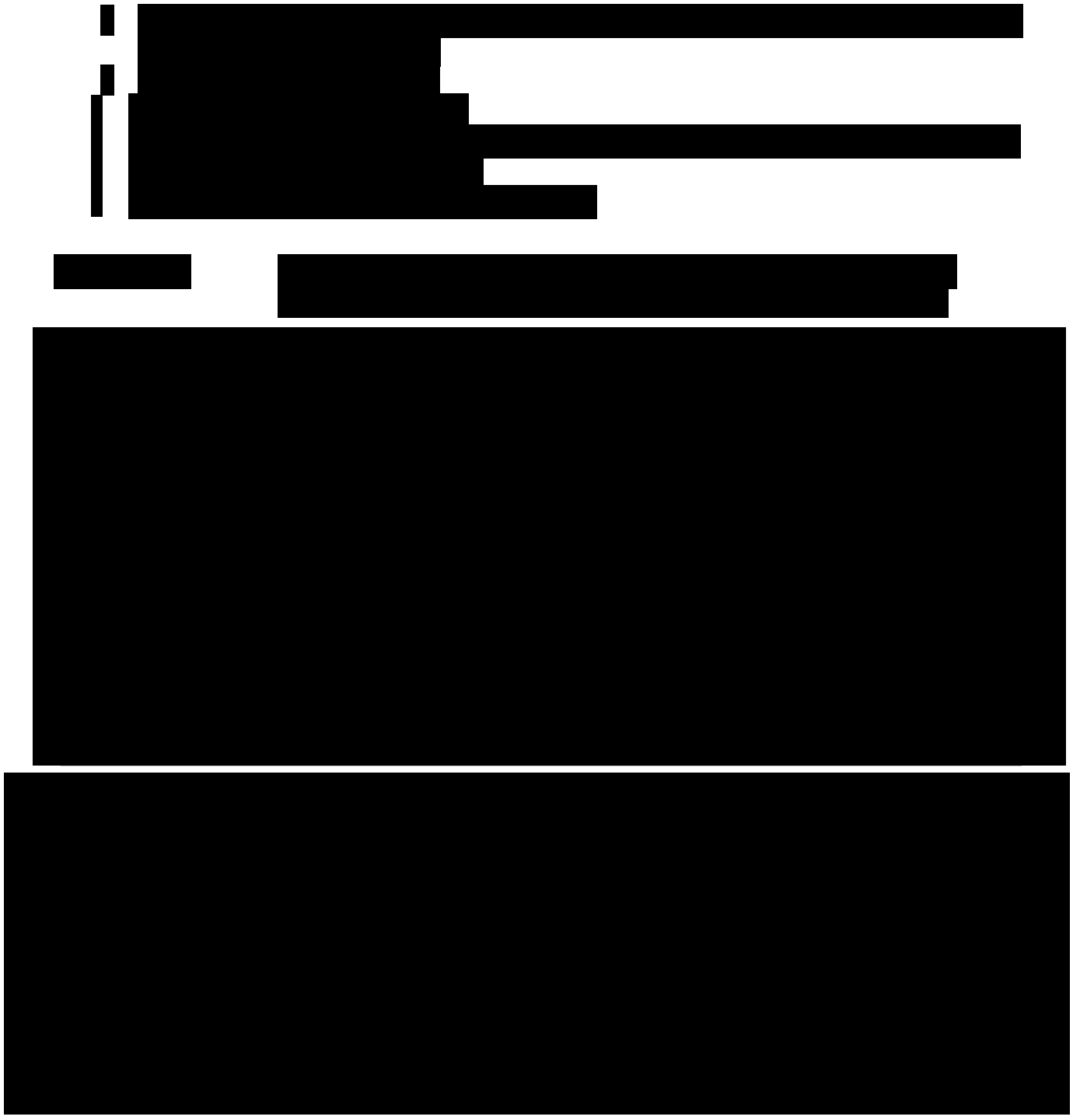
[redacted]

[redacted]

Figure 3.1-2: Study Design Schematic for the Metastatic Monotherapy Cohort



[redacted]



[redacted]

Table 3.1-1: Tumor Types by Cohort

Tumor Type	Cohort
[redacted]	[redacted]
[redacted]	[redacted]
• GYN (cervical, vaginal, vulvar)	Metastatic Monotherapy Cohort
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

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

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

3.1.1 Viral Status Determination Prior to Entry

[redacted]

[redacted]

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

[redacted]

Metastatic monotherapy cohort: Gastric and SCCHN subjects will be tested for viral status prior to study drug assignment. Gastric subjects must be EBV positive, and SCCHN subjects must be HPV positive to enroll in this cohort. MCC, NPC, and Gyn (cervical, vaginal, vulvar) subjects will not require viral screening prior to study entry. With the exception of gastric cancer (n=12), each specific tumor type in the metastatic monotherapy cohort will contain 23 subjects. Subjects will be treated with nivolumab 240 mg IV every 2 weeks until disease progression, unacceptable toxicity, or 24 months of treatment. Viral positivity will be tested retrospectively for MCC, NPC, and Gyn tumor types.

[redacted]

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

[redacted]

[redacted]

3.1.3 Subjects in the Metastatic Monotherapy Cohort

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

criteria. Exploratory endpoints include complete and partial remission rates and durations based on radiological assessments. Individual tumors types will be analyzed separate from each other.

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

[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]

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

- **For subjects in the metastatic cohorts (monotherapy and combination)**
  - Progressive metastatic or recurrent disease treated with no more than 2 prior systemic therapies or regimens in the metastatic setting.
  - Measurable disease by CT or MRI per RECIST 1.1 criteria (Appendix 3) (radiographic tumor assessment must be performed within 35 days prior to first dose).
  - Subjects who actively refuse chemotherapy or other standard therapies for the treatment of unresectable or metastatic disease (advanced Stage III or Stage IV), despite being informed by the investigator about the treatment options may enroll. The subject's refusal must be thoroughly documented. The investigator will discuss each individual subject refusing chemotherapy with the sponsor's medical monitor or study director to confirm eligibility. Written approval from the sponsor's medical monitor is required for eligibility.
  - The following tumor types

[redacted]

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

[redacted]

[redacted]

[redacted] **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.

- o **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)
  - ♦ Cardiac Troponin T (cTnT) or I (cTnI) ≤ 2 × institutional ULN. Subjects with cTnT or cTnI levels between > 1 to 2 × ULN will be permitted if repeat levels within 24 hours are ≤ 1 ULN (**Combo C only**)
    - o If cTnT or cTnI levels are >1 ULN at 24 hours, the subject may undergo a cardiac evaluation and be considered for treatment, following a discussion with the BMS Medical Monitor or designee.
- o **Subject Re-enrollment**: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been randomized / has not been treated). If re-enrolled, the subject must be re-consented.
- o LVEF assessment with documented LVEF ≥ 50% by either TTE or MUGA (TTE preferred test) within 6 months from first study drug administration (**Combo C only**)

3. Age and Reproductive Status

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

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

c) Women must not be breastfeeding

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

[redacted] 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 T cell co-stimulation or checkpoint pathways is also prohibited. **Exception**: **Combo C** SCCHN prior anti-PD-1/anti-PD-L1/anti-CTLA-4 exposure tumor types.

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

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

[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.

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

- **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.

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

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

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

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

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

Only non-target lesions included in the planned radiation field or CNS lesions may receive palliative radiotherapy. Details of palliative radiotherapy should be documented in the source records and electronic case report form (eCRF). Details in the source records should include: dates of treatment, anatomical site, dose administered and fractionation schedule, and adverse events. Subjects receiving limited field palliative radiation therapy will be considered to have unequivocal progression of disease in the non-target lesion. Symptoms requiring palliative radiotherapy should be evaluated for objective evidence of disease progression. Administration of additional study drug to subjects who received limited field palliative radiation should follow guidelines specified in Section 4.7.8 Treatment Beyond Disease Progression.

3.4.3 Surgical Resection Following Initial Response

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

and shipment of these specimens will be provided in a separate Procedure Manual at the time of study initiation.

3.4.4 Other Restrictions and Precautions

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

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

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

[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
- For discontinuation criteria related to nivolumab-and/or ipilimumab, BMS-986016 (relatlimab) or daratumumab-related adverse events, please refer to Section 4.7.6.

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

- Subjects will have two follow-up visits for safety. Follow-up visit 1, 35 days from the last dose or from the date decision is made to discontinue subject from the study (only applicable for early treatment discontinuation) (± 7 days) and follow-up visit 2 80 days (± 7 days) after follow-up visit 1. After follow-up visit 2, subjects will be followed every 3 months for ongoing drug-related adverse events until resolved, return to baseline or deemed irreversible, or until lost to follow-up, withdrawal of study consent, or start of a subsequent anti-cancer therapy.
- Subjects who discontinue study therapy for reasons other than disease progression will continue to have radiographic assessments as per defined schedule until disease progression, lost to follow-up, or withdrawal of study consent.
- PK and immunogenicity samples will be collected at the first 2 follow-up visits.

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

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

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

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

3.6 Post Study Drug Study Follow-up

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

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

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-up

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

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

[redacted]

Table 4.-1: Product Description: Treatment Period

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

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

[redacted]

4.1 Investigational Product

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

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

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

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

4.2 Non-investigational Product

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

Standard of care treatment will be procured by the investigator.

4.3 Storage and Dispensing

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

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

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

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

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

Nivolumab is to be administered as an IV infusion. Nivolumab infusion must be promptly followed by a flush of diluent to clear the line.

[redacted]

[redacted]

4.4 Method of Assigning Subject Identification

The subject number will be assigned through an interactive response technology (IRT) system once the subject has signed the informed consent form and is registered. Every subject that signs the informed consent form must be assigned a subject number in IRT. Specific instructions for using IRT will be provided to the investigational site in a separate document.

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

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

Once enrolled subjects have met all eligibility criteria the IRT must be contacted again for treatment assignment, drug vial [redacted] and to confirm that the Cohort/Tumor Type that the subject would qualify for is not closed for the study.

[redacted]

The following information is required for drug vial assignment:

- Subject number
- Date of birth
- [redacted]

[redacted]

[redacted]

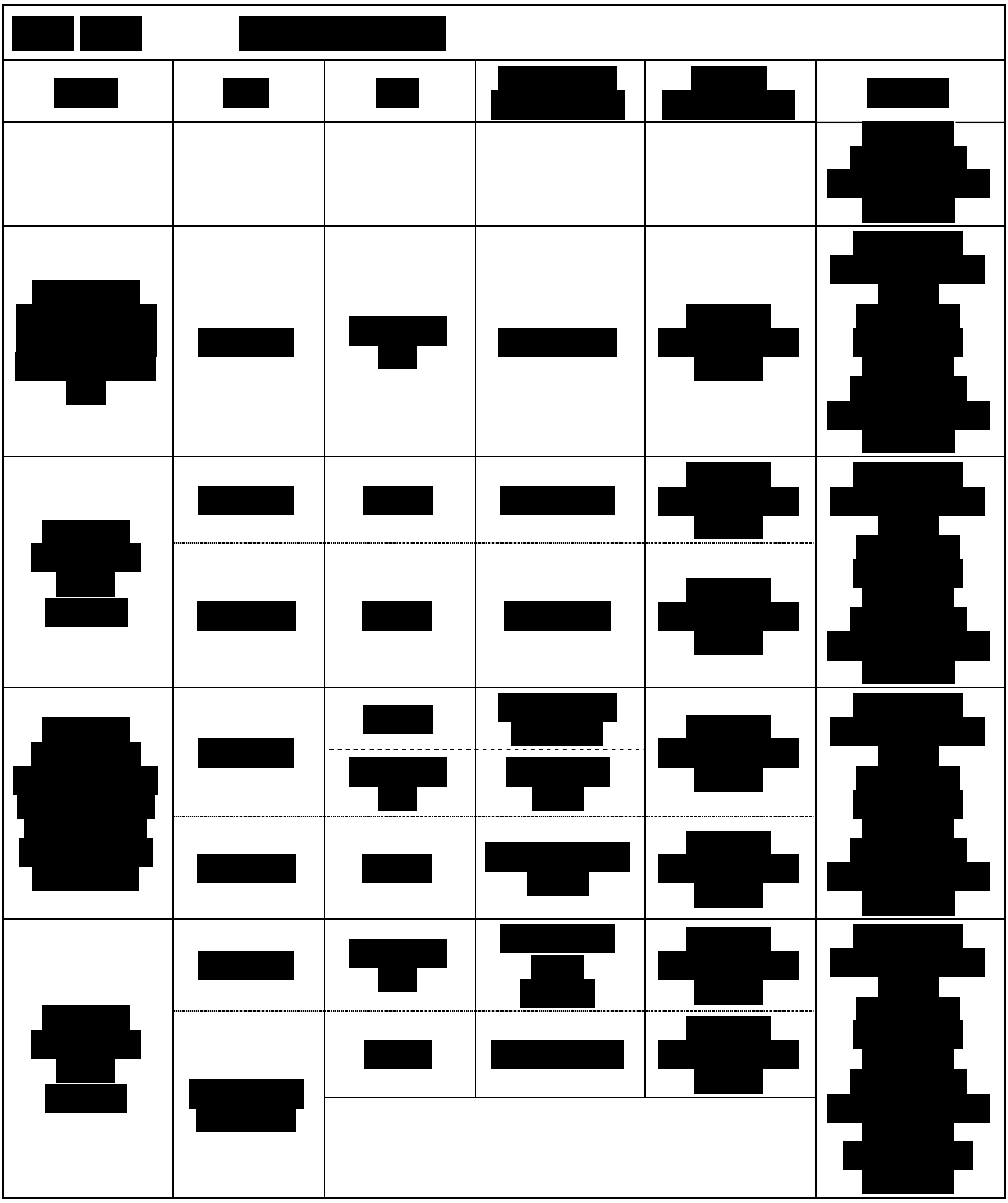
If the Cohort/Tumor Type that the subject would qualify for has already met the maximum number of subjects, the subject will not be able to enter the treatment phase of the study and will be considered an enrollment failure.

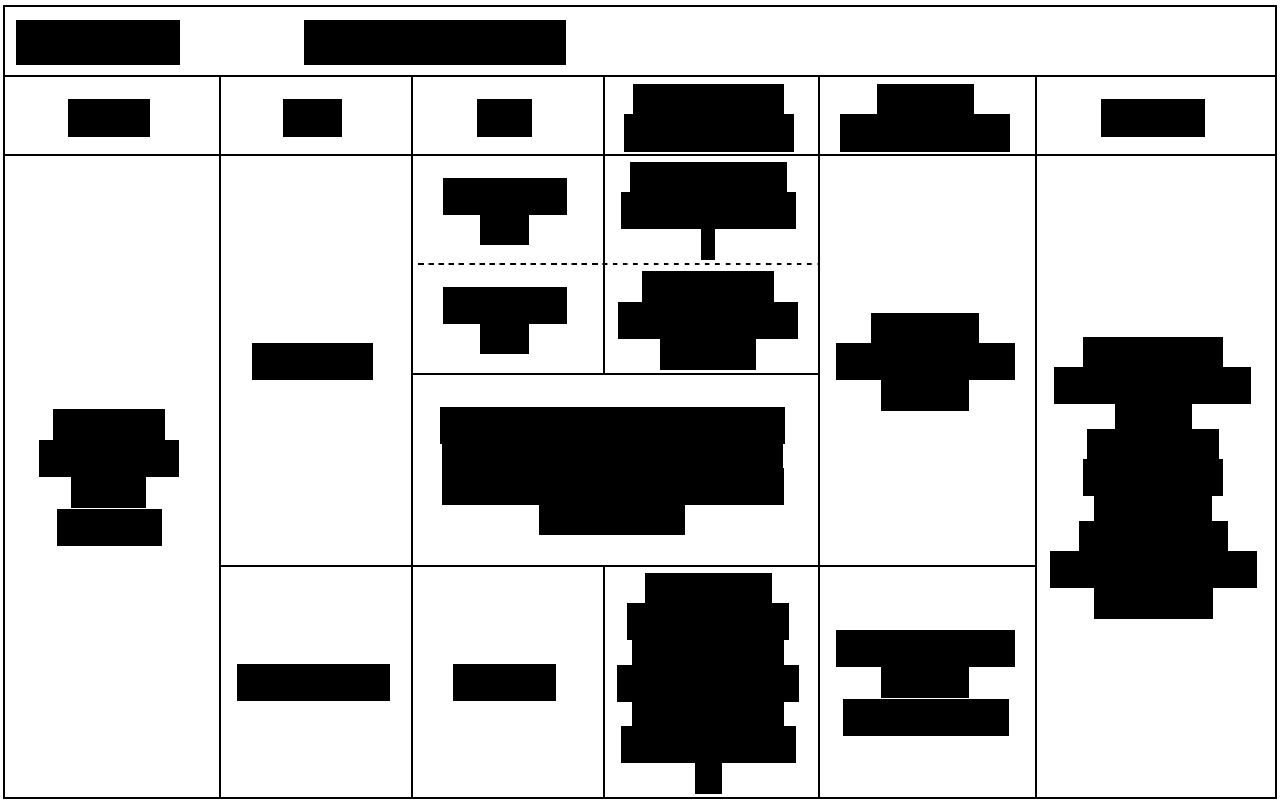
The exact procedures for using the IRT will be detailed in the IRT manual.

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
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic Monotherapy	Nivolumab	240 mg flat dose	every 2 weeks	30 minute Intravenous (IV) infusion	Maximum of 24 months or until disease progression, unacceptable





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

[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, ipilimumab, and BMS-986016 (relatlimab). 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. Nivolumab, ipilimumab, BMS-986016 (relatlimab), and daratumumab are considered immuno-oncology agents in this protocol. Early recognition and management of adverse events associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of adverse events:

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

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

4.7.3 Dose Delay Criteria

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

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

[redacted]

[redacted]

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

[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]

[redacted]

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

4.7.7 Treatment of Study Drug-related Infusion Reactions

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

[redacted]

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

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

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

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

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

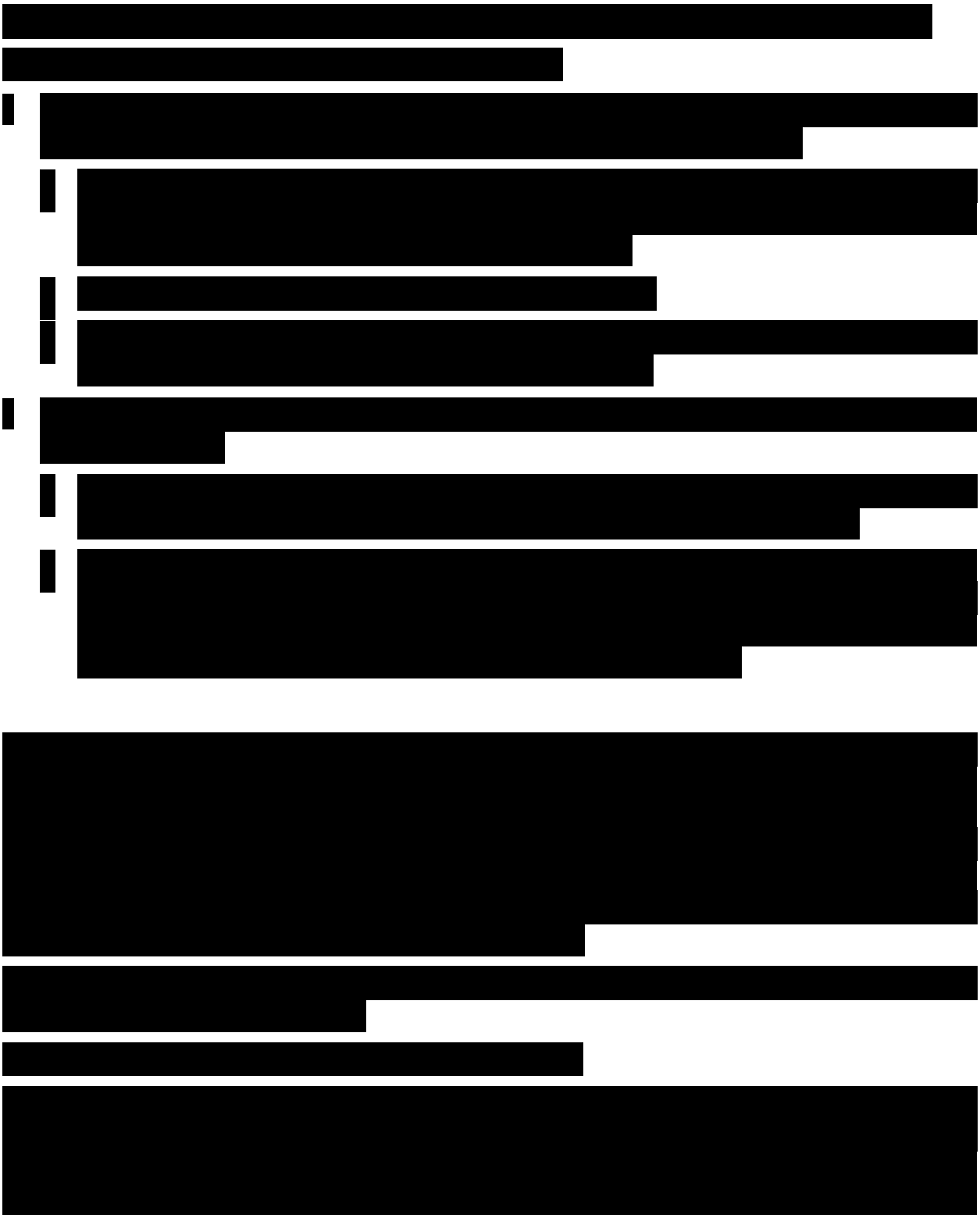
The following prophylactic premedications are recommended for future infusions:

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

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

- Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Study drug will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms.

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



[redacted]

4.7.8 Treatment Beyond Disease Progression

Accumulating clinical evidence indicates some subjects treated with immune system stimulating agents may develop progression of disease (by conventional response criteria) before demonstrating clinical objective responses and/or stable disease. This phenomenon was observed in approximately 10% of subjects in the Phase 1 study of nivolumab and also with ipilimumab monotherapy.[186] Two hypotheses have been put forth to explain this phenomenon. First, enhanced inflammation within tumors could lead to an increase in tumor size which would appear as enlarged index lesions and as newly visible small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease leading to overt signs of clinical improvement. Alternatively, in some individuals, the kinetics of tumor growth may initially outpace anti-tumor immune activity. With sufficient time, the anti-tumor activity will dominate and become clinically apparent. Therefore, subjects will be allowed to continue study therapy after

initial investigator-assessed RECIST 1.1 defined progression as long as they meet the following criteria:

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

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

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

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

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

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

For statistical analyses that include the investigator-assessed progression date, subjects who continue treatment beyond initial investigator-assessed, RECIST 1.1-defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event.

4.8 Destruction of Study Drug

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

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

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

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

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

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

4.9 Return of Study Drug

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

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

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

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

Procedure	Screening Visit[a]	Notes
Eligibility Assessments		
Informed Consent	X	Register in Interactive Response Technology (IRT) system to obtain subject number. Pre-screening informed consent will be obtained to perform viral testing for Gastric and SCCHN subjects. Register subject in IRT. Once viral status is confirmed positive, informed consent will be obtained for full eligibility assessments. See Viral Testing row below in this table for additional details.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to first dose
Medical History	X	
Serious Adverse Event Assessment	X	Serious Adverse Events from time of consent. See Section 6.
Prior Systemic Therapy	X	
Safety Assessments		
Physical Examination	X	Within 14 days prior to first dose
Physical Measurements	X	Include Height and Weight Within 14 days prior to first dose
Vital Signs	X	Temperature, BP and HR Within 72 hours of first dose
Performance Status (ECOG)	X	Within 14 days prior to first dose See Appendix 1 for ECOG scale
[redacted]	[redacted]	[redacted]

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

Procedure	Screening Visit[a]	Notes
ECG	X	Within 14 days prior to first dose
Assessment of Signs and Symptoms	X	After obtaining Informed Consent, assess all signs and symptoms within 14 days prior to first dose.
Concomitant Medication Collection	X	Within 14 days prior to first dose
Laboratory Tests	X	CBC with differential and platelet count, Chemistry panel including LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, P, glucose, bicarbonate or total CO2 (if locally available), albumin, amylase, lipase, TSH (reflex to free T3, free T4 for abnormal TSH result), hepatitis B surface antigen (HBV sAg, Australia antigen), and hepatitis C antibody (HCV Ab or RNA) Within 14 days prior to first dose. [redacted]
Viral Testing	X	See Section 5.6.1. Pre-screening informed consent will be obtained prior to viral testing [redacted] • See the Efficacy/Biomarker Assessment section of this table for additional information regarding other tumor types.
Pregnancy Test	X	Serum or urine pregnancy testing to be done at screening visit and repeated within 24 hours of first dose.
[redacted]	[redacted]	[redacted]

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

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

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

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

[a] Within 35 days prior to first dose

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

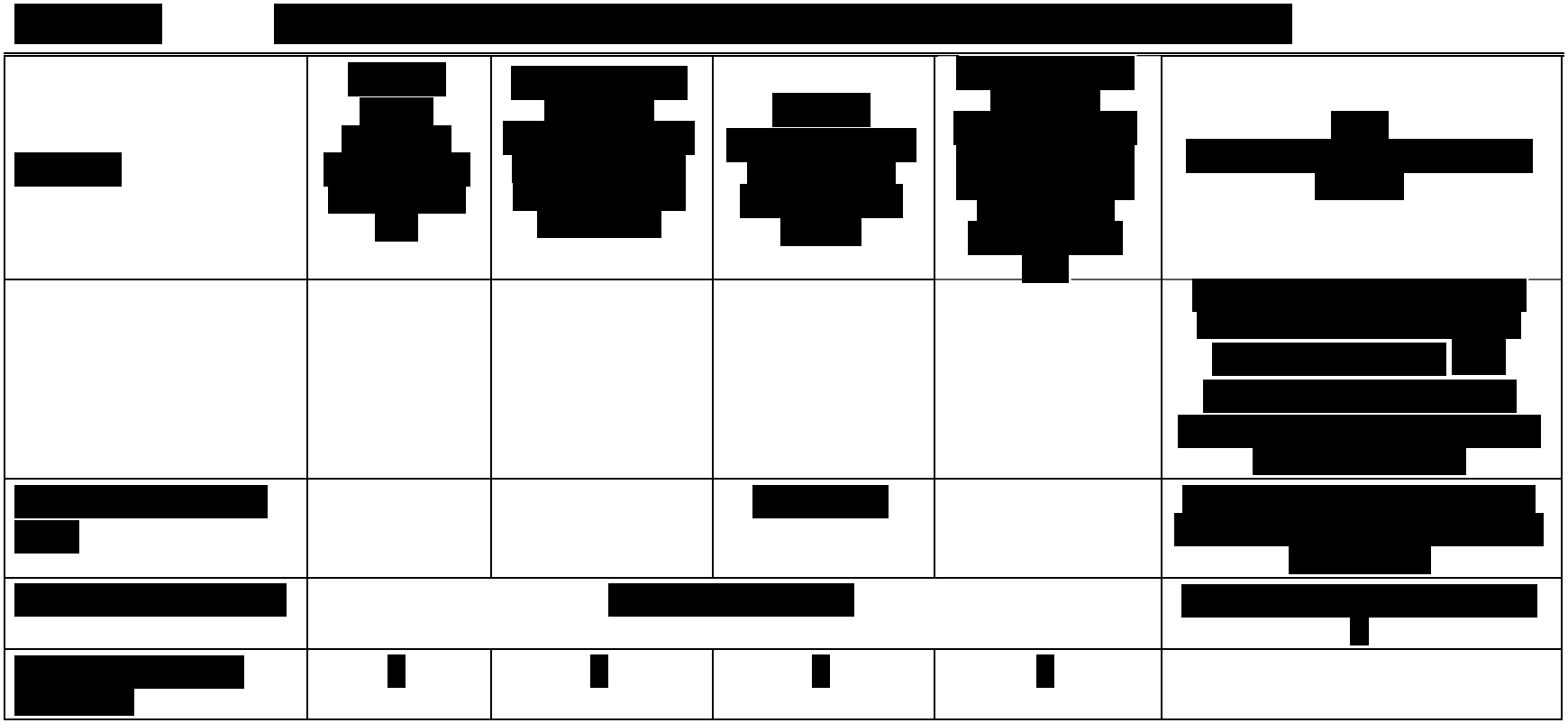
Procedure	Cycle 1 Day 1 (C1D1)	Each Cycle (every 2 Weeks) on Day 1 (± 3 days)	Notes
Safety Assessments			
Targeted Physical Examination	X	X	Targeted examination must include at a minimum the following body systems: • Cardiovascular • Gastrointestinal • Pulmonary • Neurological exam for subjects with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

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

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

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

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



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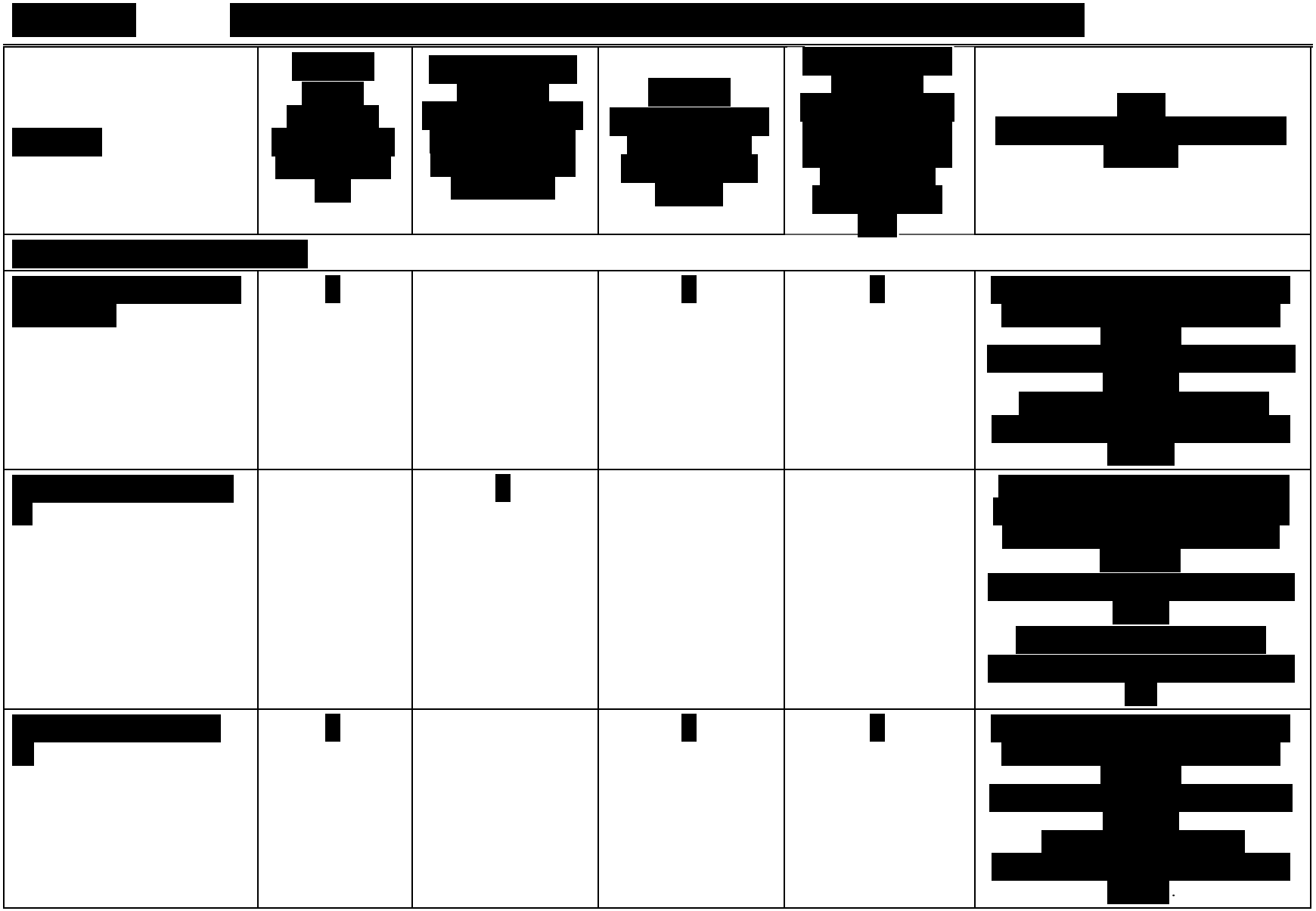

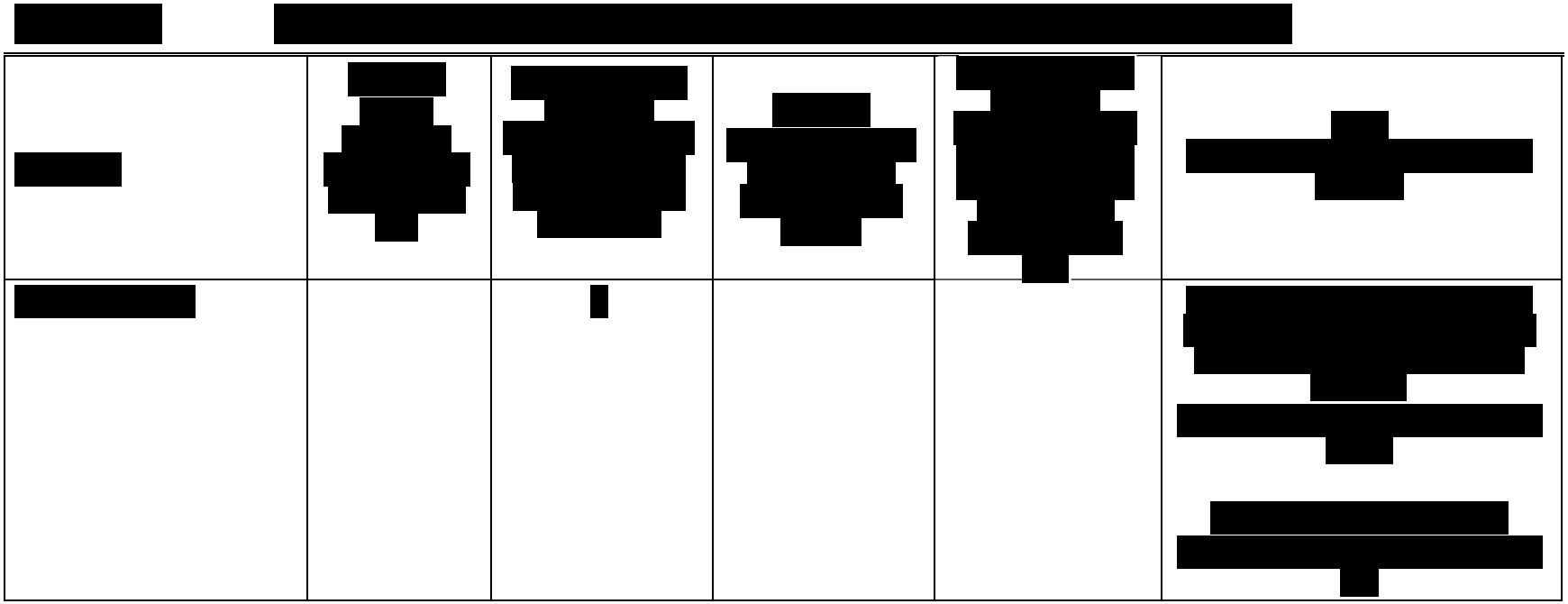

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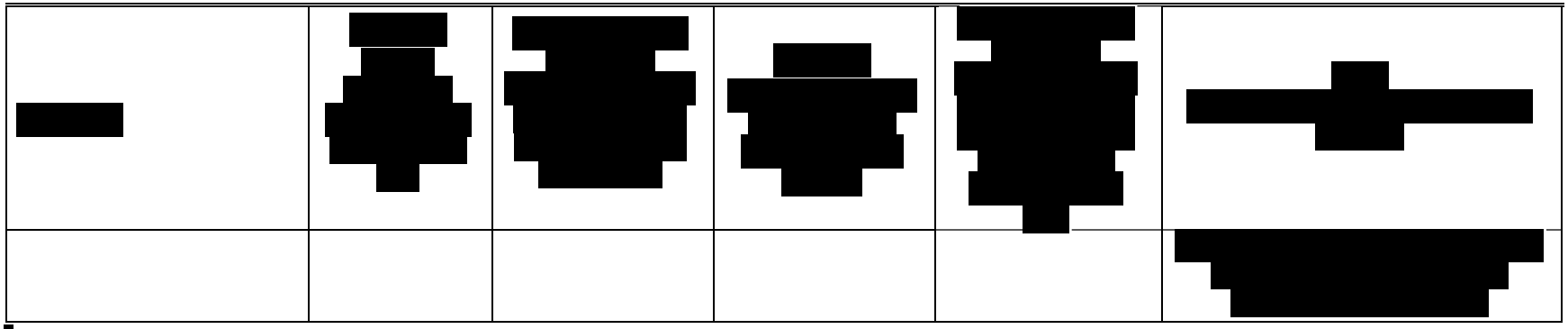

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Table 5.1-5: Eligibility Assessments and On-Treatment Assessments - Subjects Receiving Study Drug Post-Standard of Care (CA209358)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

5.1.1 Retesting During Screening or Lead-in Period

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

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

5.2 Study Materials

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

5.3 Safety Assessments

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

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

[redacted]

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

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

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

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

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

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

5.4 Efficacy Assessments

5.4.1 Imaging Assessments for the Study

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

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

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

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

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

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

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

[redacted]

For the Metastatic Cohorts (monotherapy and combination therapy), baseline tumor assessments should be performed within 35 days prior to the first dose. Subjects will then be evaluated for

tumor response beginning 8 weeks from the date of first dose (± 1 wk.), then every 8 weeks (± 1 wk.) thereafter up to 48 weeks, then it will be every 12 weeks (± 2 weeks) until disease progression is documented, or when treatment is discontinued (whichever occurs later).

5.4.2 Primary Efficacy Assessment

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

ORR is defined as the number of subjects with a best overall response (BOR) of confirmed complete response (CR) or partial response (PR) divided by the number of all treated subjects. BOR is defined as the best response designation recorded between the date of first dose and the date of the initial objectively documented tumor progression per investigator assessment using RECIST 1.1 criteria or the date of subsequent therapy, whichever occurs first.

5.4.3 Secondary Efficacy Assessments

Not applicable

5.5 Pharmacokinetic Assessments

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

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

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

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

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

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

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

[redacted]

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

[redacted]

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

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

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

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

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

[redacted]

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

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

[redacted]

[redacted]

5.5.1 Pharmacokinetic Sample Analysis

Serum samples will be analyzed for nivolumab, [redacted] by a validated method. In addition, selected samples may be analyzed by an exploratory analytical method that measures nivolumab, [redacted]

[redacted] for technology exploration purposes; exploratory results will not be reported.

5.6 Biomarker Assessments

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

5.6.1 Determination of Tumor's Viral Positivity

[redacted]

Cervical, vaginal, vulvar, anal canal and penile: HPV positivity is defined by FDA approved tests (Cobas HPV Test; Digene Hybrid Capture 2 High-Risk HPV DNA Test; Cervista™ HPV HR and Genfind™ DNA Extraction Kit; Cervista™ HPV 16/18; APTIMA® HPV Assay) or other well validated commercially available tests (such as Ventana Inform HPV ISH test) comprising in situ hybridization, real-time PCR, or immunohistochemistry (IHC). High-risk HPV positivity includes the following subtypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. Virus testing will

be performed retrospectively only if results from prior accepted testing are not available. If the HPV status is known please report this information on the provided case report form.

[redacted]

[redacted]

5.6.9 Tumor Samples

[redacted]

Tumor tissue specimen requirements for the Metastatic Cohort (Monotherapy and Combination Therapy) are as follows:

- At Baseline (Prior to first dose of study drug): Biopsy and submission of fresh tumor tissue, or submission of archived tumor tissue, is mandatory for all subjects. Biopsy is indicated for subjects with accessible lesions where biopsy is deemed safe by the Investigator.
- An on-treatment biopsy and submission of fresh tumor tissue is mandatory for subjects in each tumor type in the metastatic cohort to ensure an adequate number of paired samples to perform meaningful analyses to support biomarker objectives. Subjects with accessible lesions where biopsy is deemed safe by the Investigator should undergo biopsy per protocol.
- All other time points where tumor tissue collections are indicated, aside from baseline and the one mandatory on-treatment biopsy, are described in Table 5.6.9-2 and Table 5.6.9-3.

Tumor tissue specimen requirements for Subjects Treated with Study Drug Post-Standard of Care are as follows:

- At Cycle 1 Day 1 biopsy and submission of fresh tumor tissue is strongly encouraged for subjects with accessible lesions where biopsy is deemed safe by the Investigator.
- All other time points where tumor tissue collections are indicated, aside from Cycle 1 Day 1, are described in Table 5.6.9-4.

Submission of fresh tumor tissue collected via biopsy is required for TILs isolation for ex-vivo functional assays (RPMI media preparation), and also for gene expression profiling (RNALater samples). Please refer to Central Lab Manual for detailed sample requirements.

Submission of tissue samples (FFPE tumor tissue block or slides) is required for characterization of tumor infiltrating lymphocytes (TILs) and tumor, utilizing immunohistochemistry (IHC) methods. A minimum of 1 FFPE tumor tissue block (preferred) OR minimum of 15 FFPE unstained sections are required for this purpose. Tissue for this purpose may be obtained during the screening phase, prior to resection, or collected as a standard of care procedure within 90 days prior to obtaining informed consent, and is mandatory. Please refer to Central Lab Manual for detailed sample requirements.

Tissue for protocol purposes should be obtained via excision, incision or core needle. Fine needle aspirates are prohibited.

Tumor samples obtained from bone metastases are not considered acceptable for PD-L1 testing because the PD-L1 assay does not include a decalcification step. For any cases where the only tumor tissue available is from a bone metastasis lesion, please discuss further with the study Medical Monitor.

All subjects may volunteer to undergo tumor biopsies at any time during therapy, if clinically indicated. When tumor biopsy is performed during these times, submission of tumor biopsy is strongly encouraged.

All tumor tissue sample submission upon progression is optional, and can be taken within 7 days at the discretion of the investigator.

Tumor-Based Biomarker Measures

Tumor biopsy specimens will be obtained from consenting subjects prior to administration of study drug to characterize immune cell populations and expression of selected tumor markers. Tumor biopsy collection and submission is mandatory for subjects with accessible lesions prior to therapy. Tumor tissue (obtained during the screening phase or collected as a standard of care procedure within 90 days prior to obtaining informed consent) will be provided for biomarker analysis if accessible and deemed safe by the investigator. For subjects where tumor tissue cannot be provided due to issues related to safety, the reason must be clearly documented in the medical record AND the BMS Medical Monitor must be contacted. Archival tissue should be submitted for these subjects. Submission of archival tissue is also encouraged for all subjects, irrespective of whether fresh biopsy tissue is available.

For cases when a complete response occurs, and an on-treatment biopsy is required but not feasible, these cases must be clearly documented in the medical record AND the BMS Medical Monitor must be contacted.

A tumor biopsy sample of subjects that have confirmed progression is optional, but strongly encouraged for the purposes of understanding mechanisms of resistance to therapy.

Biopsy samples may be used for the following assessments:

Characterization of tumor infiltrating lymphocytes (TILs) and tumor. Immunohistochemistry (IHC) will be used to assess the number and composition of immune infiltrates in order to define the immune cell subsets present within formalin-fixed, paraffin-embedded (FFPE) tumor tissue before and after exposure to therapy. These IHC analyses may include, but not necessarily be limited to, the following markers: PD-L1, PD-L2, PD-1, LAG3, IDO, GITR, T cell and macrophage markers. For the neo-adjuvant arm only TILs may also be assessed in fresh baseline biopsies and surgical resections by cytometry. Analysis of cytokines including but not limited to IFN-g, IL-4, IL-13, IL-10, IL-17, and IL-32g may be done with multiplex qRT-PCR and/or amplified in situ hybridization (ISH) using fixed tumor tissue.

Tumor genotyping, mutational analysis, and tumor antigen profiling

RNA and DNA from tumor samples may be analyzed using whole-exome and transcriptome sequencing or another technology to determine the number of mutations found within a given sample relative to a normal host tissue, such as adjacent non-transformed cells or PBMC. Mutations that are detected will be analyzed for their ability to bind the MHC I and MHC II proteins using prediction algorithms. Evaluating the ability of tumor mutations to bind MHC molecules will provide evidence that these mutations are serving as antigens that are recognized the immune system and are potential rejection antigens.

In addition to viral positivity, chromosomal translocations, aberrant expressions, and epigenetic modifications within tumor cells may be characterized and explored by IHC and RNA/DNA analysis of tumor biopsies. Associations of altered tumor cell genetic structure with nivolumab efficacy will be performed. This includes, but is not limited to, assessments of 9p24 copy number alterations.

Characterization of T cell repertoire. As described above, DNA sequencing may be performed on pre- and post-treatment tumor tissue to assess the composition of the T cell repertoire. DNA may be isolated from either the FFPE tumor block or from RNAlater, or equivalent preparations.

Gene expression profiling. Tumor biopsies that are collected in RNAlater or equivalent fixative maybe examined for mRNA and miRNA gene expression by nanostring, RNAseq, microarray, and/or quantitative real-time polymerase chain reaction (qPCR) to detect expression of selected immune related genes and regulatory pathways.

Ex vivo Functional Assays. To explore whether nivolumab may restore T cell activation and function, Tumor infiltrating Lymphocytes (TILs) will be isolated. Assays for phenotypic

characteristic as well as functional status of effector T cells may be performed, including but not limited to, flow cytometry and peptide restimulation.

[redacted]

[redacted]

Table 5.6.9-2: CA209358 Biomarker Sampling Schedule (Metastatic Monotherapy Cohorts and Metastatic Cohort Combo A and B)

Collection Time[a]	Serum	Plasma	PBMC (US and European Sites Only)		Tumor Biopsy	Whole Blood		
Study Day	Soluble Biomarker		Immuno-phenotyping	Ex-vivo Functional		Gene Expression	MDSC	SNP
Screening					X[b]			
Week 1 Day 1	X	X	X	X		X	X	X
Week 3 Day 1	Mono [redacted] c		Mono & Combo A[c]			Mono [redacted] c		
[redacted]	[redacted]		[redacted]		[redacted]	[redacted]		
Week 5 Day 1	Mono [redacted] c		Mono [redacted] c		[redacted]			
Week 7 Day 1	X		X	X		X	X	
[redacted]	[redacted]		[redacted]	[redacted]		[redacted]		
CR Evaluation	X		X		X (optional)[e]	X		
During Treatment (when clinically indicated)[e]					X[e]			
Upon Progression[f]	X (optional)		X (optional)	X (optional)	X (optional)	X (optional)	X (optional)	

[a] Serum, PBMC, Plasma, and whole blood samples may be obtained ± 3 days of the indicated time **except** for Cycle 1 Day 1 samples which must be collected prior to treatment.

[b] Submission of fresh tumor tissue is required for gene expression profiling (RNALater samples).

[c] For Monotherapy [redacted]

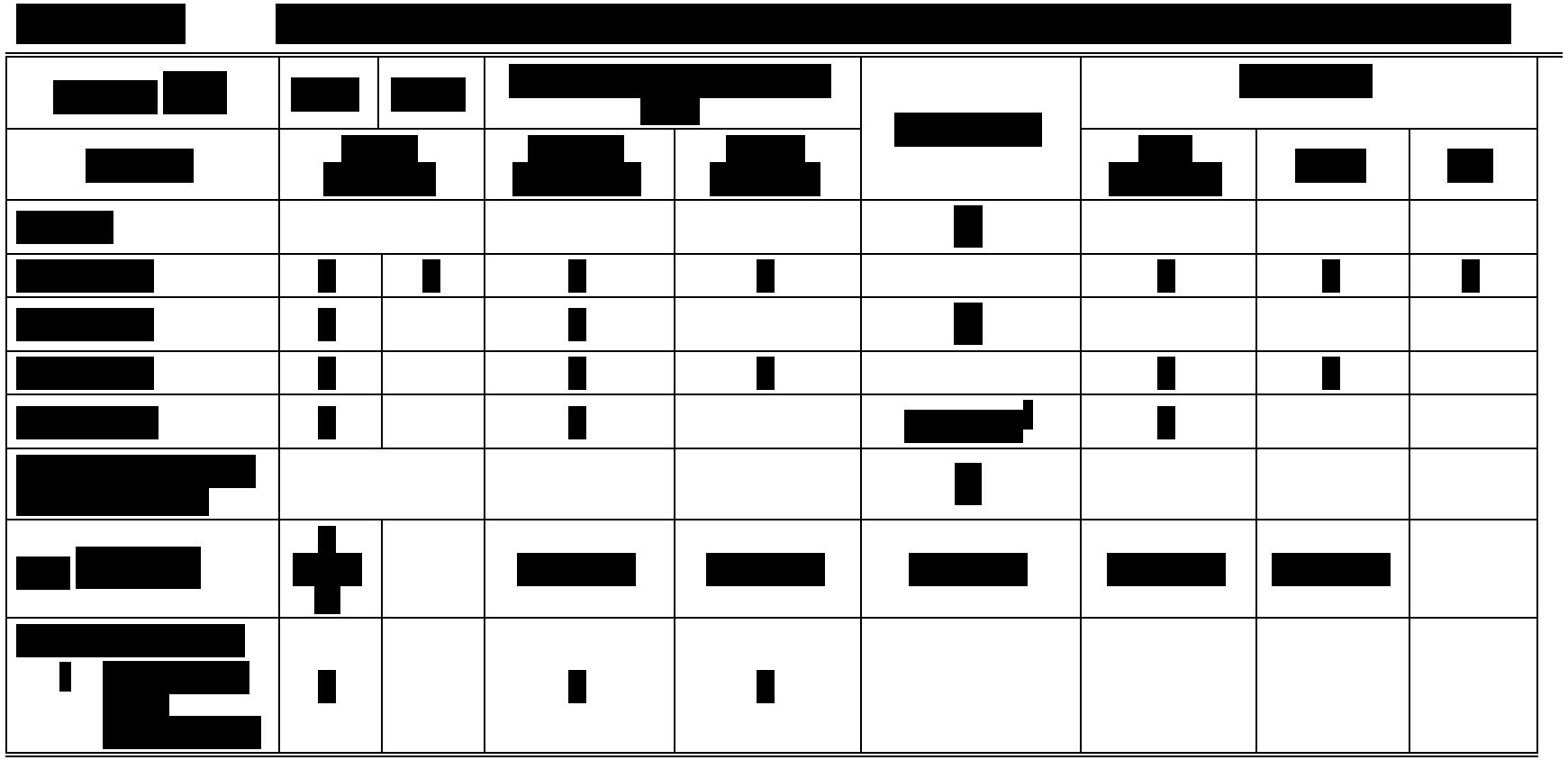
[d] For cervical cancer and anogenital HPV associated tumors (vulvar/vaginal/anal canal/penile) only

[e] All subjects may volunteer to undergo tumor biopsies at any time during therapy if clinically indicated. When tumor biopsy is performed, submission of tumor biopsy is strongly encouraged.

[f] All sample submission upon progression is optional and can be taken at any time after progression at the discretion of the investigator.

Submission of tissue samples (FFPE tumor tissue block or slides) is required for characterization of tumor infiltrating lymphocytes (TILs) and tumor, utilizing immunohistochemistry (IHC) methods. Tissue for this purpose may be obtained during the screening phase, prior to resection, or collected as a standard of care procedure within 90 days prior to obtaining informed consent. On-treatment tumor biopsies are mandatory. On-treatment tumor biopsy may be collected +/- 7 days.

[redacted]



[redacted]

Table 5.6.9-4: CA209358 Biomarker Sampling Schedule (Subjects Treated with Study Drug Post-Standard of Care)

Collection Time[a]	Serum	PBMC (US and European Sites Only)		Tumor Biopsy	Whole Blood	
Study Day	Soluble Biomarker	Immuno-phenotyping	Ex-vivo Functional		Gene Expression	MDSC
Cycle 1 Day 1	X	X	X	X[b]	X	X
Cycle 2 Day 1	X	X			X	
Cycle 3 Day 1	X	X				
Cycle 4 Day 1	X	X	X		X	X
CR Evaluation	X	X		X (optional)[c]	X	
During Treatment (when clinically indicated)[c]				X[c]		
Upon Progression[d]	X (optional)	X (optional)	X (optional)	X (optional)	X (optional)	X (optional)

[a] Serum, PBMC and whole blood samples may be obtained ± 3 days of the indicated time except for Cycle 1 Day 1 samples which must be collected prior to treatment.

[b] Submission of tumor tissue is strongly encouraged, if feasible.

[c] All subjects may volunteer to undergo tumor biopsies at any time during therapy if clinically indicated. When tumor biopsy is performed, submission of tumor biopsy is strongly encouraged.

[d] All sample submission upon progression is optional and can be taken at any point after progression at the discretion of the investigator.

5.7 Outcomes Research Assessments

The Outcomes research data including health related quality of life and subject reported symptom burden provide a more complete understanding of the impact of treatment by incorporating the subjects' perspective. These data offer insights into the subject experience that may not be captured through physician reporting. Generic health related quality of life scales provide data necessary in calculating utility values for health economic models.

The EQ-5D will be collected in order to assess the impact of study drug on generic health related quality of life and the data will be used for populating health economic models most notably, cost effectiveness analysis. The EQ-5D descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels: no problems, some problems, and severe problems.

The EORTC QLQ-C30 will be collected in order to assess cancer specific health related quality of life. The combination of the generic scale for general health status and economic evaluation and the cancer specific scale will provide a robust outcomes research package.

The EORTC QLQ-C30 is one the most commonly used QoL instrument in oncology studies. The EORTC QLQ-C30 is a 30-item instrument comprising six functional scales (physical functioning, cognitive functioning, emotional functioning, role functioning, social functioning and global quality of life) as well as nine symptom scales (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Except for the overall health status and global quality of life items, responses for all items are 4-point categorical scales ranging from 1 (Not at all) to 4 (Very much). The overall health status/quality of life responses are 7-point Likert scales. General health status will be measured using the EQ-5D. The EQ-5D is a standardized instrument for use as a measure of self-reported general health status. The EQ-5D comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety) and a visual analog rating scale (VAS). The utility data generated from the EQ-5D is recommended for and commonly used in cost effectiveness analysis.

5.8 Immunogenicity Assessments

Serum samples collected at time points identified from Table 5.5-1 to Table 5.5-8 will be analyzed by validated immunoassay methods. Additional characterization (ie, neutralizing antibodies) for any detected anti-drug antibodies (ADA) response to study drug may also be performed. All samples collected for detection of anti-drug antibodies will also be assessed for the respective serum drug concentrations to enable interpretation of the antibody data. All on-treatment PK time points are intended to align with days on which nivolumab is administered. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected, but the dose is subsequently delayed, an additional predose sample should not be collected. Selected serum samples may be analyzed by an exploratory method that measures anti-nivolumab, anti-ipilimumab, anti-BMS-986016 (relatlimab), or anti-daratumumab antibodies for technology exploration purposes; exploratory results will not be reported.

In addition, serum samples designated for PK or biomarker assessments may also be used for immunogenicity analysis if required (eg, if there is insufficient volume for complete immunogenicity assessment or to follow up on suspected immunogenicity related AE).

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE).The causal relationship can be one of the following:

> Related: There is a reasonable causal relationship between study drug administration and the AE.
>
> Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

6.1 Serious Adverse Events

A S***erious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs, (See Section 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see Section 6.1.1 for reporting details).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 100 days of the last dose of study drug. For participants assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of treatment assignment. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

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

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

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

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Immune-mediated adverse events are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor

progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the participant's case report form.

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

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

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

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

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

6.4 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least approximately 5 half-lives after product administration plus 30 days, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug after a thorough discussion of benefits and risk with the subject

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

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

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

All occurrences of overdose must be reported as SAEs (see Section 6.1.1 for reporting details).

6.6 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

Potential drug induced liver injury is defined as:

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

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

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

6.7 Other Safety Considerations

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

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Not applicable

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

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

[redacted]

[redacted]

2) Recurrent/metastatic monotherapy cohort:

HPV+ SCCHN, GYN, MCC and NPC tumor types in the recurrent/metastatic cohort will contain approximately 23 subjects. Table 8.1-1 shows the probabilities of observing 0, 1 or 2 responders and ≥ 3 responders assuming 5%, 20% and 30% true response rate of ORR. Table 8.1-2 shows the two-sided 95% exact CI using Clopper-Pearson methods based on observed 3, 4 and 5 responders out of 23 subjects.

EBV+ Gastric tumor type will contain approximately 12 subjects, due to the low prevalence. Table 8.1-5 shows the precision of the estimation of ORR based on the two sided 95% exact CI using Clopper-Pearson methods based on 1, 2, 3, 4 and 5 responders out of 12 subjects.

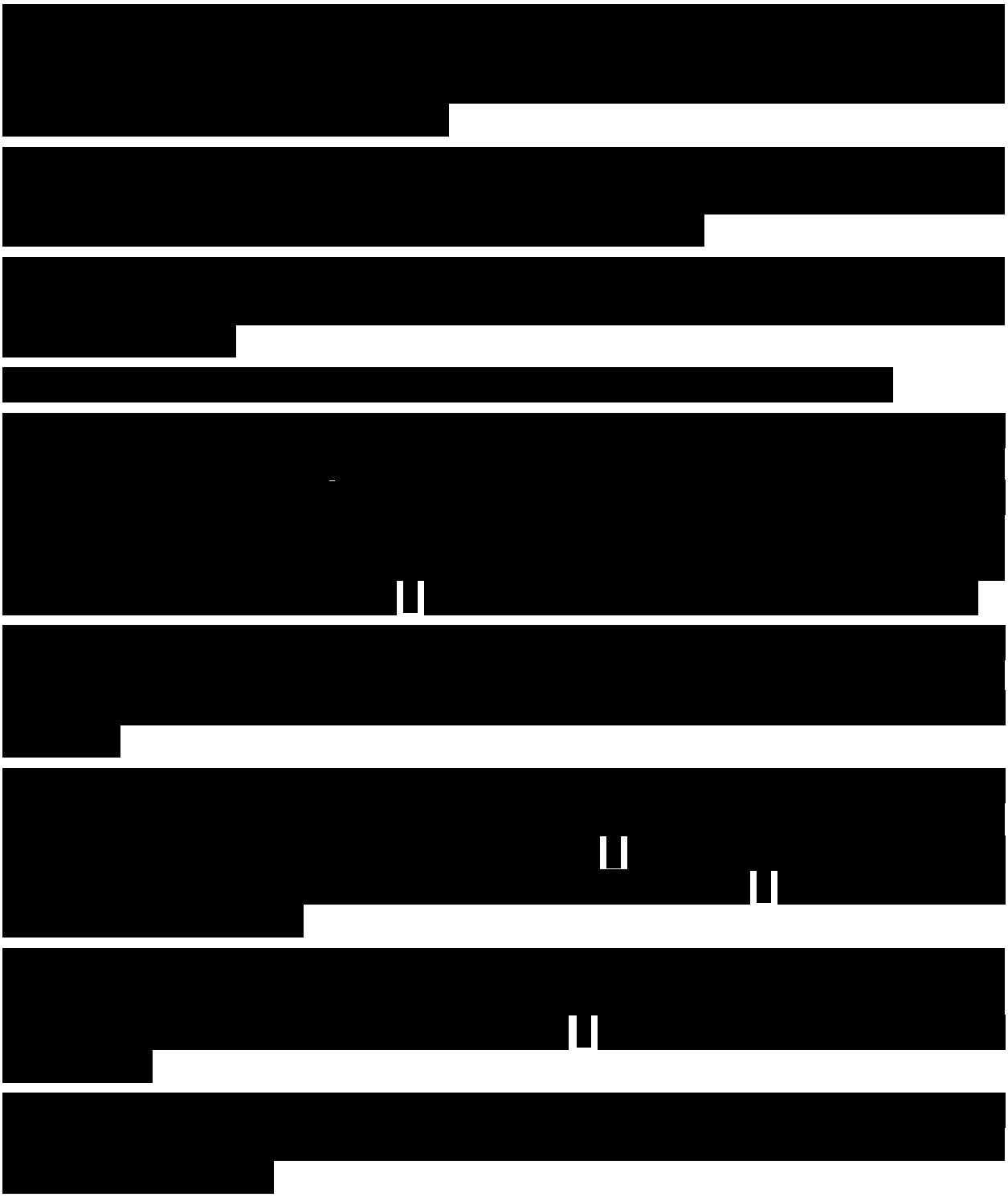
Table 8.1-1: Probability of Observing Responses Given True ORR for Sample Size of 23 Subjects

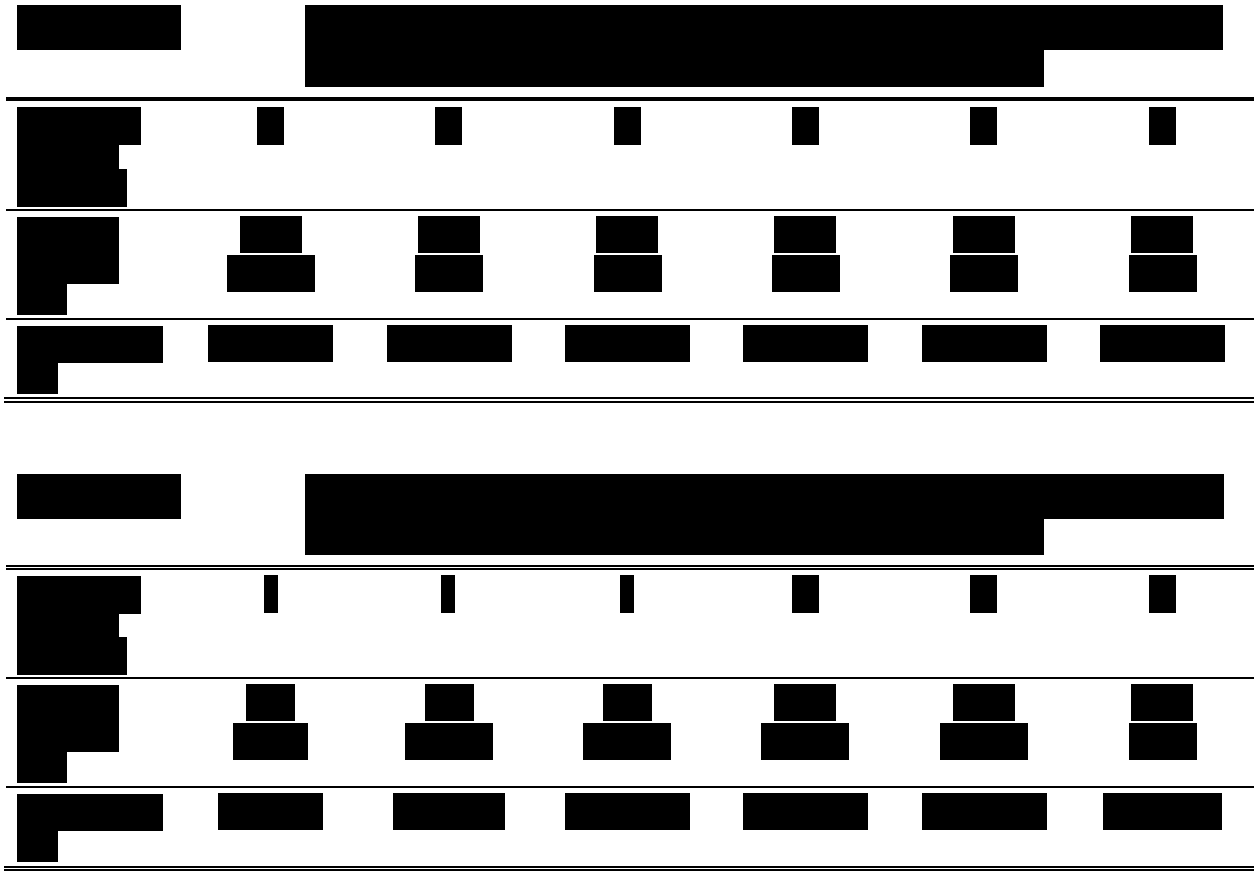
True ORR	Probability of observing 0, 1 or 2 responses	Probability of observing ≥ 3 responses
5%	89.5%	10.5%
20%	13.3%	86.7%
30%	1.6%	98.4%

Table 8.1-2: Two-sided 95% Exact CI Using Clopper-Pearson Method Based on Number of Observed Responses out of 23 Subjects

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

[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.
  - All Response Evaluable Subjects: All treated subjects in recurrent/metastatic cohorts (monotherapy and combination therapy) who have a BOR of CR, PR, SD, Non-CR/Non-PD or PD, and target lesion(s) assessed at baseline, and one of the following: i) at least one on-study time point (before sub-sequent therapy) with all baseline target lesion(s) assessed; ii) clinical progression or death before any on-study tumor assessment.
  - All Evaluable Neoadjuvant Subjects: All treated subjects in neoadjuvant cohorts who have available paired tissue samples at Screening and Day 29.
- Outcome Research Subjects: All treated subjects who have an assessment at baseline and at least one post-baseline assessment.
- Pharmacokinetic Subjects: All subjects who receive at least one dose of study drug and have available serum concentration data.

- Immunogenicity Subjects: All treated subjects with baseline and at least 1 post-baseline immunogenicity assessment for nivolumab, ipilimumab and BMS-986016 (relatlimab); All treated subjects with at least 1 post-baseline immunogenicity assessment for daratumumab.
- Biomarker Subjects: All treated subjects who have available biomarker data.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

[redacted]

Metastatic cohorts (monotherapy and combination therapies):

- The investigator-assessed objective response rate (ORR). ORR is defined as the number of subjects with a best overall response (BOR) of confirmed complete response (CR) or partial response (PR) divided by the number of treated subjects. BOR is defined as the best response designation recorded between the date of first dose and the date of the initial objectively documented tumor progression per investigator assessment using RECIST 1.1 criteria or the date of the last tumor assessment date prior to subsequent therapy. In this study, an ORR in excess of 10% will be considered of clinical interest, and an ORR of 25% or greater will be considered of strong clinical interest.

8.3.2 Secondary Endpoint(s)

Metastatic cohorts (monotherapy and combination therapies):

- Duration of response (DOR) is defined as the time from first confirmed response (CR or PR) to the date of the initial objectively documented tumor progression as determined per investigator assessment using RECIST 1.1 criteria or death due to any cause, whichever occurs first. Subjects who did not start subsequent anti-cancer therapy and die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on the date they were treated. Subjects who started any subsequent anti-cancer therapy prior to death and without a prior reported progression will be censored at the last tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy. DOR will only be evaluated in subjects with objective response of CR or PR.
- Overall survival (OS) is defined as the time from first dosing date to the date of death. A subject who has not died will be censored at last known date alive.
- Investigator-assessed progression free survival (PFS) is defined as the time from first dosing date to the date of the first documented tumor progression, as determined by investigators (per

RECIST 1.1), or death due to any cause. Subjects who did not start subsequent anti-cancer therapy and die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on the date they were treated. Subjects who started any subsequent anti-cancer therapy prior to death and without a prior reported progression will be censored at the last tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy.

8.3.3 Exploratory Endpoint(s)

[redacted]

Metastatic cohorts (monotherapy and combination therapies):

- The safety and tolerability objective will be measured by the incidence of adverse events, serious adverse events, deaths and laboratory abnormalities.

[redacted]

[redacted] **Metastatic cohorts (monotherapy and combination therapies):**

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

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

8.4 Analyses

All analyses for neoadjuvant cohort will be performed as it completes safety follow-up. All analyses for each metastatic cohort (nivolumab monotherapy or combo A, B, C, or D) will be performed as it completes efficacy follow-up. All analyses will be performed independently by cohort, by tumor type, and regimen.

The randomization of the patients with metastatic cervical cancer and anogenital HPV associated (vulvar/vaginal/anal canal/penile) tumor types to combo A, B, or D is for administration purposes, not for comparison. Analyses will be done for each dosing schema separately.

8.4.1 Demographics and Baseline Characteristics

Demographic and baseline laboratory results will be summarized using descriptive statistics for all treated subjects.

8.4.2 Efficacy Analyses

8.4.2.1 Primary Endpoint Methods

[redacted]

Metastatic cohort (monotherapy and combination therapies):

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

8.4.2.2 Secondary Endpoints Methods

Metastatic cohort (monotherapy and combination therapies):

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

8.4.2.3 Exploratory Endpoints Methods

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

8.4.3 Safety Analyses

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

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

8.4.4 Pharmacokinetic Analyses

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

8.4.5 Biomarker Analyses

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

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

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

8.4.6 Outcomes Research Analyses

8.4.6.1 EQ-5D

Subject's overall health state on a visual analog scale (EQ-VAS) at each assessment time point will be summarized using descriptive statistics (N, mean, standard deviation, median, first and

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

A by-subject listing of EQ-5D with the problem levels for each of the 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), health state (5 dimensions digits combined in a 5-digit number) and EQ-VAS will be provided. Each dimension has three levels: no problems, some problems, and severe problems.

8.4.6.2 EORTC QLQ-C30

The analysis of EORTC QLQ-C30 will be performed in all treated subjects who have an assessment at baseline and at least one subsequent assessment.

All scales and single items are scored on a categorical scale and linearly transformed to 0-to-100 scales with higher scores for a functional scale representing higher levels of functioning, higher scores for the global health status/quality of life representing higher levels of global health status/quality of life, and higher scores for a symptom scale representing higher level of symptoms.

Baseline and change from baseline in EORTC QLQ-C30 global health status/QoL composite scale data and the remaining EORTC QLQ-C30 scale data will be summarized by time point using descriptive statistics for each cohort (N, mean, standard deviation, median, first and third quartiles, minimum, maximum). In addition, the percentage of subjects demonstrating a clinically meaningful deterioration (defined as a 10 point change from baseline) will be presented for each scale at each assessment time point. Percentages will be based on number subjects assessed at assessment time point.

8.4.7 Other Analyses

8.4.7.1 Immunogenicity Analyses

Immunogenicity may be reported for ADA positive status (such as persistent positive, neutralizing positive, only last sample positive, baseline positive and other positive) and ADA negative status, relative to baseline. Effect of immunogenicity on safety, efficacy, biomarkers and PK may be explored. Additional details will be described in the SAP.

8.5 Interim Analyses

Under the circumstance that data of some tumor types mature faster than others or a strong signal is observed in some tumor types, interim analyses may be performed prior to the completion of the study in order to facilitate program decisions and to support presentations or publication. These interim analyses will not impact the study duration and the trial will continue as planned.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any

deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

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

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

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

9.1.2 Monitoring

BMS representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source documents.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

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

9.1.2.1 Source Documentation

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures.

Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

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

BMS will notify the investigator when the study records are no longer needed.

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

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include investigational product. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

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

9.2.3 Case Report Forms

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

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

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

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

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

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

9.3 Clinical Study Report and Publications

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

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

- External Principal Investigator designated at protocol development
- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing [Study site or Investigator] participation in the study. These

requirements include, but are not limited to, submitting proposed publications to BMS at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	If one form of contraception is required, Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. If two forms of contraception is required, Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. **Expanded definition** Complete abstinence as defined as complete avoidance of heterosexual intercourse is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence

11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
ACLS	advanced cardiac life support
AI	accumulation index
AI_AUC	AUC Accumulation Index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose
AI_Cmax	Cmax Accumulation Index; ratio of Cmax at steady state to Cmax after the first dose
AI_Ctau	Ctau Accumulation Index; ratio of Ctau at steady state to Ctau after the first dose
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
A-V	atrioventricular
β-HCG	beta-human chorionic gonadotrophin
BA/BE	bioavailability/bioequivalence
%BE	percent biliary excretion
BID, bid	bis in die, twice daily
BLQ	below limit of quantification
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
BRt	Total amount recovered in bile

Term	Definition
%BRt	Total percent of administered dose recovered in bile
BUN	blood urea nitrogen
C	Celsius
C12	concentration at 12 hours
C24	concentration at 24 hours
Ca++	calcium
Cavg	average concentration
CBC	complete blood count
Cexpected-tau	expected concentration in a dosing interval
CFR	Code of Federal Regulations
cHL	classical Hodgkin's lymphoma
CI	confidence interval
C1-	chloride
CLcr	creatinine clearance
CLD	Dialysate clearance of drug from plasma/serum
CLNR	nonrenal clearance
CLR	renal clearance
CLT	total body clearance
CLT/F (or CLT)	apparent total body clearance
CLT/F/fu or CLT/fu	Apparent clearance of free drug or clearance of free if (if IV)
cm	centimeter
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	trough observed concentration
CNS	Central nervous system
CRC	Clinical Research Center
CRF	Case Report Form, paper or electronic
Ct	Expected concentration at a certain time, usually at the end of an expected future dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
Ctau	Concentration in a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)

Term	Definition
Ctrough	Trough observed plasma concentration
CV	coefficient of variation
CYP	cytochrome p-450
D/C	discontinue
dL	deciliter
DRt	Total amount recovered in dialysate
%DRt	Total percent of administered dose recovered in dialysate
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4th Edition)
EA	extent of absorption
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEG	electroencephalogram
eg	exempli gratia (for example)
ESR	Expedited Safety Report
F	bioavailability
Fb	fraction of bound drug
FDA	Food and Drug Administration
FI	fluctuation Index ([Cmax-Ctau)/Cavg])
FRt	total amount recovered in feces
%FRt	total percent of administered dose recovered in feces
FSH	follicle stimulating hormone
%FE	percent fecal excretion
fu	fraction of unbound drug
g	gram
GC	gas chromatography
GCP	Good Clinical Practice
G criteria	adjusted R2 value of terminal elimination phase
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
h	hour

Term	Definition
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCO3-	bicarbonate
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
Ig	immunoglobulin
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IO	immuno-oncology
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	International Unit
IV	intravenous
K	slope of the terminal phase of the log concentration-time curve
K3EDTA	potassium ethylenediaminetetraacetic acid
K+	potassium
kg	kilogram
λz	terminal disposition rate constant
L	liter
LAG-3	lymphocyte activation gene 3
LC	liquid chromatography
LDH	lactate dehydrogenase
ln	natural logarithm

Term	Definition
Lz_Start	The time point starting the log-linear elimination phase defining the terminal half life
Lz_End	The time point ending the log-linear elimination phase defining the terminal half life
Lz_N	Number of time points in the log-linear elimination phase defining the terminal half life
LVEF	left ventricular ejection fraction
MEL	melanoma
mg	milligram
Mg++	magnesium
MIC	minimum inhibitory concentration
min	minute
mL	milliliter
mmHg	millimeters of mercury
MR_AUC(0-T)	Ratio of metabolite AUC(0-T) to parent AUC(0-T), corrected for molecular weight
MR_AUC(INF)	Ratio of metabolite AUC(INF) to parent AUC(INF), corrected for molecular weight
MR_AUC(TAU)	Ratio of metabolite AUC(TAU) to parent AUC(TAU), corrected for molecular weight
MR_Cmax	Ratio of metabolite Cmax to parent Cmax, corrected for molecular weight
MR_Ctau	Ratio of metabolite Ctau to parent Ctau, corrected for molecular weight
MRT	mean residence time
MS	mass spectrometry
MTD	maximum tolerated dose
µg	microgram
N	number of subjects or observations
Na+	sodium
N/A	not applicable
ng	nanogram
NIMP	non-investigational medicinal products
NSAID	nonsteroidal anti-inflammatory drug

Term	Definition
NSCLC	non-small cell lung cancer
pAUCe	Extrapolated partial AUC from last quantifiable concentration to infinity
Pb	percent of bound drug
PD	pharmacodynamics
PK	pharmacokinetics
PO	per os (by mouth route of administration)
PT	prothrombin time
PTT	partial thromboplastin time
Pu	percent of unbound drug
QC	quality control
QD, qd	quaque die, once daily
R2	coefficient of determination
RBC	red blood cell
RCC	renal cell carcinoma
SAE	serious adverse event
SCC	squamous cell cancer
SCLC	small cell lung cancer
SD	standard deviation
SEB	staphylococcal enterotoxin B
SOC	standard of care
SOP	Standard Operating Procedures
sp.	species
Subj	subject
t	temperature
T	time
TAO	Trial Access Online, the BMS implementation of an EDC capability
T-HALF	Half life
T-HALFeff_AUC	Effective elimination half-life that explains the degree of AUC accumulation observed
T-HALFeff_Cmax	Effective elimination half-life that explains the degree of Cmax accumulation observed)

Term	Definition
TID, tid	ter in die, three times a day
TIL	tumor infiltrating lymphocytes
Tmax, TMAX	time of maximum observed concentration
TR_AUC(0-T)	AUC(0-T) treatment ratio
TR_AUC(INF)	AUC(INF) treatment ratio
TR_Cmax	Cmax treatment ratio
UR	urinary recovery
%UR	percent urinary recovery
URt	total amount recovered in urine
%URt	total percent of administered dose recovered in urine
UV	ultraviolet
Vss/F (or Vss)	apparent volume of distribution at steady state
Vz	Volume of distribution of terminal phase (if IV and if multi-exponential decline)
W	washout
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
x g	times gravity

12 REFERENCES

1 Freeman GJ, Long AJ, Iwai Y, Bourque K, Chernova T, Nishimura H, et al. Engagement of the PD 1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med 2000;192(7):1027-34.

2 Nishimura H, Honjo T. PD-1: an inhibitory immunoreceptor involved in peripheral tolerance. Trends Immunol. 2001; 22: 265-8.

3 Latchman Y, Wood CR, Chernova T, Chaudhary D, Borde M, Chernova I, et al., PD-L2 is a second ligand for PD-1 and inhibits T cell activation. Nat Immunol. 2001;2(3):261-268.

4 Carter LL, Fouser LA, Jussif J, Fitz L, Deng B, Wood CR, et al. PD-1:PD-L inhibitory pathway affects both CD4+ and CD8+ T cells and is overcome by IL-2. Eur J Immunol. 2002;32(3):634-43.

5 Chemnitz JM, Parry RV, Nichols KE, et al. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol. 2004; 173: 945-54.

6 Sheppard KA, Fitz LJ, Lee JM, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKC-theta. FEBS Letters. 2004; 574: 37-41.

7 Nishimura H, Nose M, Hiai H, et al. Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. Immunity. 1999; 11:141-51.

8 Nishimura H, Okazaki T, Tanaka Y, et al. Autoimmune dilated cardiomyopathy in PD-1 receptor-deficient mice. Science. 2001; 291: 319-22.

9 Okazaki T, Tanaka Y, Nishio R, et al. Autoantibodies against cardiac troponin I are responsible for dilated cardiomyopathy in PD-1-deficient mice. Nat Med. 2003; 9: 1477-83.

10 Salama AD, Chitnis T, Imitola J, et al. Critical role of the programmed death-1 (PD-1) pathway in regulation of experimental autoimmune encephalomyelitis. J Exp Med. 2003; 198: 71-8.

11 Blazar BR, Carreno BM, Panoskaltsis-Mortari A, et al. Blockade of programmed death-1 engagement accelerates graft-versus-host disease lethality by an IFN-α-dependent mechanism. J Immunol. 2003; 171: 1272-7.

12 Ansari MJ, Salama AD, Chitnis T, Smith RN, Yagita H, Akiba H, et al. The programmed death-1 (PD-1) pathway regulates autoimmune diabetes in nonobese diabetic (NOD) mice. J Exp Med. 2003 Jul 7;198(1):63-9.

[13] Iwai Y, Terawaki S, Honjo T. PD-1 blockade inhibits hematogenous spread of poorly immunogenic tumor cells by enhanced recruitment of effector T cells. Int Immunol. 2004; 17: 133-44.

[14] Iwai Y, Ishida M, Tanaka Y, et al. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-1 blockade. Proc Natl Acad Sci USA. 2002; 99: 12293-7.

[15] Strome SE, Dong H, Tamura H, et al. B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma. Cancer Res. 2003; 63: 6501-5.

[16] Dong H, Strome SE, Salomao DR, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med. 2002; 8: 793-800.

[17] Hirano F, Kaneko K, Tamura H, et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. Cancer Res. 2005 Feb 1;65(3):1089-96.

[18] Blank C, Brown I Peterson AC, et al. PD-L1/B7H-1 inhibits the effector phase of tumor rejection by T cell receptor (TCR) transgenic CD8+ T cells. Cancer Res. 2004; 64: 1140-45.

[19] Keir M, Butte M, Freeman G, Sharpe A. PD-1 and its ligands in tolerance and immunity. Ann Rev Immunol. 2008;26:677-704.

[20] Konishi J, Yamazaki K, Azuma M, et al. B7-H1 expression on non-small cell lung cancer cells and its relationship with tumor-infiltrating lymphocytes and their PD-1 expression. Clin Cancer Res. 2004; 10: 5094-100.

[21] Thompson RH, Gillett MD, Cheville JC, et al. Costimulatory B7-H1 in renal cell carcinoma subjects: indicator of tumor aggressiveness and potential therapeutic target. Proc Natl Acad Sci USA. 2004; 101: 17174-9.

[22] Ohigashi Y, Sho M, Yamada Y et al. Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand-2 expression in human esophageal cancer. Clin Cancer Res. 2005; 11: 2947-53.

[23] Tsushima F, Tanaka K, Otsuki N, et al. Predominant expression of B7-H1 and its immunoregulatory roles in oral squamous cell carcinoma. Oral Oncol. 2006; 42: 268-74.

[24] Thompson RH, Weber WS, Cheville JC, et al. B7-H1 glycoprotein blockade: a novel strategy to enhance immunotherapy in subjects with renal cell carcinoma. Urology. 2005; 66: 10-4.

[25] Thompson RH, Gillett MD, Cheville JC, et al. Costimulatory molecule B7-H1 in primary and metastatic clear cell renal cell carcinoma. Cancer. 2005; 104: 2084-91.

[26] Dong H, Chen L. B7-H1 pathway and its role in the evasion of tumor immunity. J Mol Med. 2003; 81: 281-7.

[27] Chemnitz JM, Parry RV, Nichols KE, et al. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol. 2004; 173: 945-54.

[28] Azuma T, Yao S, Zhu G, et al. B7-H1 is a ubiquitous antiapoptotic receptor on cancer cells. Blood. 2008; 111: 3635-43.

[29] Thompson RH, Gillett MD, Cheville JC, et al. Costimulatory B7-H1 in renal cell carcinoma subjects: indicator of tumor aggressiveness and potential therapeutic target. Proc Natl Acad Sci USA. 2004; 101: 17174-9.

[30] Effect of MDX-1106 on CD4+ T cells during an allogeneic mixed lymphocyte reaction (MLR) (Medarex Study No. MDX-1106-026-R). Bristol-Myers Squibb Pharmaceutical Research Institute; 2006. Document Control No. 930046581.

[31] Ferlay J, Soerjomataram I, Ervik M. et al. GLOBOCAN 2012 v1.0, cancer incidence and mortality worldwide. IARC Cancer Base 11, http://globocan.iarc.fr, Accessed on 13 August 2014.

[32] Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2011, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2011/, based on November 2013 SEER data submission, posted to the SEER web site, April 2014.

[33] Karpeh MS, Leon L, Klimstra D, et al. Lymph node staging in gastric cancer: islocation important than number? An analysis of 1038 patients. Ann Surg 2000;232:362-371.

[34] The Cancer Genome Atlas Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature 2014;513:202–209.

[35] Murphy G, Pfeiffer R, Camargo MC, et al. Meta-analysis shows that prevalence of Epstein-Barr virus-positive gastric cancer differs based on sex and anatomic location. Gastroenterology. 2009; 137:824-33.

[36] WHO Classification of Tumours of the Digestive System 4th edition (International Agency for Research on Cancer, 2010).

[37] Carmargo MC, Kim WH, Chiaravalli AM, et al. Improved survival of gastric cancer with tumor Epstein-Barr virus positivity: an international pooled analysis. Gut. 2014;63:236-43.

[38] Lee JH, Kim SH, Han SH, et al. Clinicopathological and molecular characteristics of Epstein-Barr virus-associated gastric carcinoma: a meta-analysis. J Gastroenterol Hepatol 2009; 24:354-65.

[39] Atula S, Auvinen E, Grenman R, et al. Human papillomavirus and Epstein-Barr virus in epithelial carcinomas of the head and neck region. Anticancer Res 1997; 17:4427.

[40] Pathmanathan R, Prasad U, Sadler R, et al. Clonal proliferations of cells infected with Epstein-Barr virus in preinvasive lesions related to nasopharyngeal carcinoma. N Engl J Med 1995; 333:693.

[41] Chien YC, Chen JY, Liu MY, et al. Serologic markers of Epstein-Barr virus infection and nasopharyngeal carcinoma in Taiwanese men. N Engl J Med 2001; 345:1877.

[42] Pathology and genetics of head and neck tumors. In: World Health Organization Classification of Tumours, Barnes L, Eveson JW, Reichart P, Sidransky D (Eds), IARC Press, Lyon 2005.

[43] Leung SF, Zee B, Ma BB, et al. Plasma Epstein-Barr viral deoxyribonucleic acid quantitation complements tumor-node-metastasis staging prognostication in nasopharyngeal carcinoma. J Clin Oncol 2006; 24:5414-18.

[44] Lin JC, Wang WY, Chen KY, et al. Quantification of plasma Epstein-Barr virus DNA in patients with advanced nasopharyngeal carcinoma. N Engl J Med. 2004;350:2461-70.

[45] Lin JC, Wang WY, Liang WM, et al. Long-term prognostic effects of plasma epstein-barr virus DNA by minor groove binder-probe real-time quantitative PCR on nasopharyngeal carcinoma patients receiving concurrent chemoradiotherapy. Int J Radiat Oncol Biol Phys. 2007;68:1342-8.

[46] Lee AW, Sze WM, Au JS, et al. Treatment results for nasopharyngeal carcinoma in the modern era: the Hong Kong experience. Int J Radiat Oncol Biol Phys. 2005;61:1107-16.

[47] Jin Y, Cai XY, Shi YX, et al. Comparison of five cisplatin-based regimens frequently used as the first-line protocols in metastatic nasopharyngeal carcinoma. J Cancer Res Clin Oncol. 2012;138:1717-25.

[48] Chua DT, Sham JS, Au GK. A phase II study of capecitabine in patients with recurrent and metastatic nasopharyngeal carcinoma pretreated with platinum-based chemotherapy. Oral Oncol. 2003;39:361-6.

[49] Poon D, Chowbay B, Cheung YB, et al. Phase II study of irinotecan (CPT-11) as salvage therapy for advanced nasopharyngeal carcinoma. Cancer. 2005;103:576-81.

[50] Ngeow J, Lim WT, Leong SS, et al. Docetaxel is effective in heavily pretreated patients with disseminated nasopharyngeal carcinoma. Ann Oncol. 2011;22(3):718-22.

[51] Chen C, Wang FH, Wang ZQ, et al. Salvage gemcitabine-vinorelbine chemotherapy in patients with metastatic nasopharyngeal carcinoma pretreated with platinum-based chemotherapy. Oral Oncol. 2012;48):1146-51.

[52] Yau TK, Shum T, Lee AW, et al. A phase II study of pemetrexed combined with cisplatin in patients with recurrent or metastatic nasopharyngeal carcinoma. Oral Oncol. 2012;48:441-4.

[53] Argiris A, Karamouzis MV, Raben D, et al. Head and neck cancer. Lancet 2008;371:1695-709.

[54] Pignon JP, Bourhis J, Domenge C, et al. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet 2000;355:949-55.

[55] Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014 ;64:9-29.

[56] Pignon JP, le Maitre A, Maillard E, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92:4-14.

[57] Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol 2003;21:92-8.

[58] Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006;354:567-78.

[59] Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol. 2010;11:21-8.

[60] Gold KA, Lee HY, Kim ES. Targeted therapies in squamous cell carcinoma of the head and neck. Cancer 2009;115:922-35.

[61] Chaturvedi AK, Engels EA, Anderson WF, et al. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. J Clin Oncol 2008;26:612-9.

[62] Gillison ML, D'Souza G, Westra W, et al. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. J Natl Cancer Inst 2008;100:407-20.

[63] Argiris A, Heron DE, Smith RP, et al. Induction Docetaxel, Cisplatin, and Cetuximab Followed by Concurrent Radiotherapy, Cisplatin, and Cetuximab and Maintenance Cetuximab in Patients With Locally Advanced Head and Neck Cancer. J Clin Oncol 2010;28:5294-300.

[64] Brizel DM, Albers ME, Fisher SR, et al. Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. N Engl J Med 1998;338:1798-804.

[65] Gilbert J, Li Y, Pinto HA, et al. Phase II trial of taxol in salivary gland malignancies (E1394): a trial of the Eastern Cooperative Oncology Group. Head Neck 2006;28:197-204.

[66] Leon X, Hitt R, Constenla M, et al. A retrospective analysis of the outcome of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck refractory to a platinum-based chemotherapy. Clin Oncol (R Coll Radiol) 2005;17:418-24.

[67] http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/125084s046LBL.pdf Accessed on 23 Sept 2103

[68] Price KAR and Cohen EE. Current Treatment Options for Metastatic Head and Neck Cancer. Curr Treat Options Oncol 2012;13:35-46.

[69] Guardiola E, Peyrade F, Chaigneau L, et al. Results of a randomised phase II study comparing docetaxel with methotrexate in patients with recurrent head and neck cancer. Eur J Cancer 2004;40:2071-6.

[70] Knoedler M, Gauler TC, Gruenwald V, et al. Phase II Study of Cetuximab in Combination with Docetaxel in Patients with Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck after Platinum-Containing Therapy: A Multicenter Study of the ArbeitsgemeinschaftInternisticshceOnkologie. Oncology 2013;84:284-89.

[71] Vermorken JB, Trigo J, Hitt R, et al. Open-Label, Uncontrolled, Multicenter Phase II Study to Evaluate the Efficacy and Toxicity of Cetuximab As a Single Agent in Patients With Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck Who Failed to Respond to Platinum-Based Therapy. JCO 2007;25:2171-77.

[72] Ang KK, Harris J, Wheeler R, et al. Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer. NEJM 2010;363:24-35.

[73] Posner MR, Hershock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 2007;357:1705-15.

[74] Fakhry C, Westra WH, Li S, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst 2008;100:261-9.

[75] Insinga RP, Liaw KL, Johnson LG, et al. A systematic review of the prevalence and attribution of human papillomavirus types among cervical, vaginal, and vulvar precancers and cancers in the United States. Cancer Epidemiol Biomarkers Prev. 2008l;17:1611-22.

[76] Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999;189:12-9.

[77] Iwasawa A, Nieminen P, Lehtinen M, et al. Human papillomavirus in squamous cell carcinoma of the vulva by polymerase chain reaction. J. Obstet Gynecol. 1997;89:81-4.

[78] http://www.cdc.gov/cancer/hpv/statistics/index.htm Accessed on 26 Dec 2014.

[79] Shylasree TS, Bryant A, Howells RE. Chemoradiation for advanced primary vulvar cancer. Cochrane Database Syst Rev. 2011;(4):CD003752.

[80] http://www.cancer.org/cancer/vulvarcancer/detailedguide/vulvar-cancer-survival-rates Accessed on 26 Dec 2014.

[81] Maggino T, Landoni F, Sartori E, et al. Patterns of recurrence in patients with squamous cell carcinoma of the vulva. A multicenter CTF Study. Cancer. 2000;89:116-22.

[82] http://www.cancer.org/cancer/cervicalcancer/detailedguide/cervical-cancer-survival Accessed on 26 Dec 2014.

[83] Tewari KS1, Sill MW, Long HJ, et al. Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med. 2014;370:734-43.

[84] Cancer Facts & Figures 2016. American Cancer Society. Available at http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-047079.pdf. Accessed: Sept 6, 2016.

[85] Palefsky JM. Anal human papillomavirus infection and anal cancer in HIV-positive individuals: an emerging problem. AIDS. 1994;8(3):283-95.

[86] Frisch M, Glimelius B, van den Brule AJ, et al. Sexually transmitted infection as a cause of anal cancer. N Engl J Med. 1997;337 (19):1350-8.

[87] SEER Stat Fact Sheets: Anal Cancer. NIH Surveillance, Epidemiology and End Results Program. Available at http://seer.cancer.gov/statfacts/html/anus.html.; Accessed: Sept. 6, 2016.

[88] Glynne-Jones R, Nilsson PJ, Aschele C, Goh V, Peiffert D, Cervantes A, Arnold D. Anal cancer: ESMO-ESSO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;40(10):1165-76.

[89] Long AP, Kroon BK, Gallee MP, et al. Pelvic lymph node dissection for penile carcinoma: extent of inguinal lymph node involvement as an indicator for pelvic lymph node involvement and survival. J Urol. 2007;177(3):947-52.

[90] Leijte JA, Kirrander P, Antonini N, Windahl T, Horenblas S. Recurrence patterns of squamous cell carcinoma of the penis: recommendations for follow-up based on a two-centre analysis of 700 patients. Eur Urol. 2008;54(1):161-8. Epub 2008 Apr 15.

[91] Connell CF, Berger NA. Management of advanced squamous cell carcinoma of the penis. Urol Clin North Am. 1994;21(4):745-56.

[92] Nicholson S, Hall E, Harland SJ, et al. Phase II trial of docetaxel, cisplatin and 5FU chemotherapy in locally advanced and metastatic penis cancer (CRUK/09/001). Br J Cancer. 2013;109(10):2554-9. Epub 2013 Oct 29.

[93] Haas GP, Blumenstein BA, Gagliano RG, et al. Cisplatin, methotrexate and bleomycin for the treatment of carcinoma of the penis: a Southwest Oncology Group study. J Urol. 1999;161(6):1823-5.

[94] Theodore C, Skoneczna I, Bodrogi I, et al. A phase II multicentre study of irinotecan (CPT 11) in combination with cisplatin (CDDP) in metastatic or locally advanced penile carcinoma (EORTC PROTOCOL 30992). Ann Oncol. 2008;19(7):1304-1307.

[95] Di Lorenzo G, Federico P, Buonerba C, et al. Paclitaxel in pretreated metastatic penile cancer: final results of a phase 2 study. Eur Urol. 2011;60(6):1280-4.

[96] Wang J, Pettaway CA, Pagliaro LC. Treatment for Metastatic Penile Cancer After First-line Chemotherapy Failure: Analysis of Response and Survival Outcomes. Urology. 2015;85(5):1104-10.

[97] Albores-Saavedra J, Batich K, Chable-Montero F, et al. Merkel cell carcinoma demographics, morphology, and survival based on 3870 cases: a population based study. J Cutan Pathol. 2010;27:20-7.

[98] Lemos BD, Storer BE, Iyer JG, et al. Pathologic nodal evaluation improves prognostic accuracy in merkel cell carcinoma: Analysis of 5823 cases as the basis of the first consensus staging system. J Am Acad Dermatol 2010;63:751–61.

[99] Howard RA, Dores GM, Curtis RE, et al. Merkel cell carcinoma and multiple primary cancers. Cancer Epidemiol Biomarkers Prev 2006;15:1545–9.

[100] Ascoli V, Minelli G, Kanieff M, et al. Merkel cell carcinoma: A population-based study on mortality and the association with other cancers. Cancer Causes Control 2011;22:1521–7.

[101] Gass JK, Chan SK, Rytina E, et al. Multiple primary malignancies in patients with merkel cell carcinoma. J Eur Acad Dermatol Venereol 2010;24:601–3.

[102] Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. Science 2008;319:1096-100.

[103] Sastre-Garau X, Peter M, Avril MF, et al. Merkel cell carcinoma of the skin: pathological and molecular evidence for a causative role of MCV in oncogenesis. J Pathol. 2009;218(1):48-56.

[104] Mojica P, Smith D, Ellenhorn JD. Adjuvant radiation therapy is associated with improved survival in Merkel cell carcinoma of the skin. Clin Oncol 2007;25:1043-47.

[105] http://www.nccn.org/professionals/physician_gls/pdf/mcc.pdf Accessed on 7 October 2014.

[106] Crown J, Lipzstein R, Cohen S, et al. Chemotherapy of metastatic Merkel cell cancer. Cancer Invest. 1991;9:129-32.

[107] Pectasides D, Moutzourides G, Dimitriadis M, et al. Chemotherapy for Merkel cell carcinoma with carboplatin and etoposide. Am J Clin Oncol. 1995 Oct;18:418-20.

[108] Redmond J, Perry J, Sowray P, et al. Chemotherapy of disseminated Merkel-cell carcinoma. Am J Clin Oncol. 1991;14:305-7.

[109] Rous P. A transmissible avian neoplasm. (sarcoma of the common fowl.). The Journal of experimental medicine 1910;12:696-705.

[110] Martin D, Gutkind JS. Human tumor-associated viruses and new insights into the molecular mechanisms of cancer. Oncogene 2008;27 Suppl 2:S31-42.

[111] Scheffner M, Huibregtse JM, Vierstra RD, et al. The HPV-16 E6 and E6-AP complex functions as a ubiquitin-protein ligase in the ubiquitination of p53. Cell 1993;75:495-505.

[112] Moody CA, Laimins LA. Human papillomavirus oncoproteins: pathways to transformation. Nature reviews Cancer 2010;10:550-60.

[113] Saha A, Robertson ES. Impact of EBV essential nuclear protein EBNA-3C on B-cell proliferation and apoptosis. Future microbiology 2013;8:323-52.

[114] Herrero JA, Mathew P, Paya CV. LMP-1 activates NF-kappa B by targeting the inhibitory molecule I kappa B alpha. Journal of virology 1995;69:2168-74.

[115] Dyson N, Bernards R, Friend SH, et al. Large T antigens of many polyomaviruses are able to form complexes with the retinoblastoma protein. Journal of virology 1990;64:1353-6.

[116] Treisman R, Novak U, Favaloro J, et al. Transformation of rat cells by an altered polyoma virus genome expressing only the middle-T protein. Nature 1981;292:595-600.

[117] Shuda M, Kwun HJ, Feng H, et al. Human Merkel cell polyomavirus small T antigen is an oncoprotein targeting the 4E-BP1 translation regulator. The Journal of clinical investigation 2011;121:3623-34.

[118] Lyngaa R, Pedersen NW, Schrama D, et al. T-cell responses to oncogenic merkel cell polyomavirus proteins distinguish patients with merkel cell carcinoma from healthy donors. Clinical cancer research: an official journal of the American Association for Cancer Research 2014;20:1768-78.

[119] Li J, Zeng XH, Mo HY, et al. Functional inactivation of EBV-specific T-lymphocytes in nasopharyngeal carcinoma: implications for tumor immunotherapy. PloS one 2007;2:e1122.

[120] Blackburn SD, Shin H, Haining WN, et al. Coregulation of CD8+ T cell exhaustion by multiple inhibitory receptors during chronic viral infection. Nature immunology 2009;10:29-37.

[121] Carthon BC, Wolchok JD, Yuan J, Kamat A, et al. Preoperative CTLA-4 blockade: tolerability and immune monitoring in the setting of a presurgical clinical trial. Clin Cancer Res. 2010 May 15;16(10):2861-71. doi: 10.1158/1078-0432.CCR-10-0569. Epub 2010 May 11.

[122] Lyngaa R1, Pedersen NW, Schrama D, et al. T-cell responses to oncogenic merkel cell polyomavirus proteins distinguish patients with merkel cell carcinoma from healthy donors. Clin Cancer Res. 2014 Apr 1;20(7):1768-78.

[123] Feichtenbeiner A1, Haas M, Büttner M, et al. Critical role of spatial interaction between $CD8^+$ and $Foxp3^+$ cells in human gastric cancer: the distance matters. Cancer Immunol Immunother. 2014 Feb;63(2):111-9.

[124] Paulson KG, Iyer JG, Simonson WT, et al. CD8+ lymphocyte intratumoral infiltration as a stage-independent predictor of Merkel cell carcinoma survival: a population-based study. Am J Clin Pathol. 2014 Oct;142(4):452-8.

[125] Lipson EJ, Vincet JG, Loyo M, et al. Expression in the merkel cell carcinoma microenvironment: Association with inflammation, merkel cell polyomavirus, and overall survival. Cancer Immunol Res 2013;1:1–10.

[126] Bristol-Myers Squibb Investigator Brochure: Ipilimumab, BMS-734016, MDX010.

[127] Curran MA, Montalvo W, Yagita H, et al. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. PNAS 2010; 107: 4275-80.

[128] Sznol M, Kluger HM, Callahan MK, et al. Survival, response duration, and activity by BRAF mutation (MT) status of nivolumab (NIVO, anti-PD-1, BMS-936558, ONO-4538) and ipilimumab (IPI) concurrent therapy in advanced melanoma (MEL). J Clin Oncol, 2014. 32:5s (suppl; abstr LBA9003).

[129] Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med 2015; 372:2006-2017.

[130] Scott JA, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancel Oncol 2016; 17:883-895.

[131] Investigator Brochure, Anti-PD-1 Human Monoclonal Antibody, BMS-936558, Version No. 12, 21-Jul-2014.

[132] Triebel F, Jitsukawa S, Baixeras E, et al. LAG-3, a novel lymphocyte activation gene closely related to CD4. J. Exp. Med. 1990; 171:1393–1405.

[133] Workman CJ, Wang Y, El Kasmi KC, et al. LAG-3 regulates plasmacytoid dendritic cell homeostasis. J Immunol;182(4):1885-91.

[134] Workman CJ, Vignali DA. Negative regulation of T cell homeostasis by lymphocyte activation gene-3 (CD223). J. Immunol. 2005; 174:688–695.

[135] Camisaschi C, Casati C, Rini F, et al. LAG-3 expression defines a subset of CD4(+) CD25 (high)Foxp3(+) regulatory T cells that are expanded at tumor sites. J Immunol. 2010; 184:6545-6551.

[136] Huang CT, Workman CJ, Flies D, et al. Role of LAG-3 in regulatory T cells. Immunity. 2004; 21:503–513.

[137] Grosso JF, Kelleher CC, Harris TJ, et al. LAG-3 regulates CD8+T cell accumulation and effector function in murine self- and tumor-tolerance systems. J. Clin. Invest. 2007; 117:3383–3392.

[138] Lyford-Pike S, Peng S, Young GD, et al. Evidence for a Role of the PD-1: PD-L1 Pathway in Immune Resistance of HPV-Associated Head and Neck Squamous Cell Carcinoma. Cancer Res. 2013 Mar 15;73(6):1733-41.

[139] Woo SR, Turnis ME, Goldberg MV, et al. Immune inhibitory molecules LAG-3 and PD-1 synergistically regulate T-cell function to promote tumoral immune escape. Cancer Res. 2012;72:917-927.

[140] Okazaki T, Okazaki IM, Wang J, et al. PD-1 and LAG-3 inhibitory co-receptors act synergistically to prevent autoimmunity in mice. J Exp Med. 2011; 208:395-407.

[141] Bettini M, Szymczak-Workman AL, Forbes K, et al. Cutting edge: accelerated autoimmune diabetes in the absence of LAG-3. J Immunol. 2011;187:3493-3498.

[142] Goding SR, Wilson KA, Xie Y, et al. Restoring Immune Function of Tumor-Specific CD4+ T Cells during Recurrence of Melanoma. J Immunol. 2013 Mar 27.

[143] Matsuzaki J, Gnjatic S, Mhawech-Fauceglia P, et al. Tumor-infiltrating NY-ESO-1-specific CD8+ T cells are negatively regulated by LAG-3 and PD-1 in human ovarian cancer. Proc Natl Acad Sci U S A. 2010;107:7875-7880.

[144] Gandhi MK, Lambley E, Duraiswamy J, et al. Expression of LAG-3 by tumor-infiltrating lymphocytes is coincident with the suppression of latent membrane antigen-specific CD8+ T-cell function in Hodgkin lymphoma patients. Blood. 2006;108:2280-2289.

[145] Waterhouse P, Penninger JM, Timms E, et al. Lymphoproliferative disorders with early lethality in mice deficient in CTLA-4. Science 1995;270:985-988.

[146] Grosso JF, Goldberg MV, Getnet D, et al. Functionally distinct LAG-3 and PD-1 subsets on activated and chronically stimulated CD8 T cells. J Immunol. 2009; 182:6659-6669.

[147] Saloura V, Zuo Z, Koeppen H, et.al. Correlation of T-cell inflamed phenotype with mesenchymal subtype, expression of PD-L1, and other immune checkpoints in head and neck cancer. J Clin Oncol 32:5s, 2014 (suppl; abstr 6009).

[148] Uozaki H, Fukayama M. Epstein-Barr virus and gastric carcinoma--viral carcinogenesis through epigenetic mechanisms. Int J Clin Exp Pathol 2008;1(3):198-216.

[149] Sittig SP, Køllgaard T, Grønbæk K, et.al. Clonal expansion of renal cell carcinoma-infiltrating T lymphocytes. Oncoimmunology 2013, 2:E26014.

[150] Giraldo NA, Becht E, Pagès F, Skliris G, et.al. Orchestration and Prognostic Significance of Immune Checkpoints in the Microenvironment of Primary and Metastatic Renal Cell Cancer. Clin Cancer Res. 2015, 21:3031-3040.

[151] D'Incecco A, Andreozzi M, Ludovini V, et.al. PD-L1 and PD-1 expression in molecularly selected non-small-cell lung cancer (NSCLC) patients. Journal of Thoracic Oncology (2014) 9 (Supplement 9): S7-S52.

[152] Herbst RS, Gordon MS, Fine GD, et al. A study of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic tumors. J Clin Oncol 2013;31(suppl; abstr 3000).

[153] Investigator Brochure, Anti-Lag3 Human Monoclonal Antibody, BMS-986016, Version No. 4, 30 Aug 2016.

[154] BMS-986016 Investigator Brochure, Version 4. Bristol-Myers Squibb Company; 2016. Document Control No. 930071620.

[155] de Weers M, Tai YT, van der Veer MS, et al. Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. J Immunol. 2011;186(3):1840-1848.

[156] Overdijk MB, Verploegen S, Bogels M, et al. Antibody-mediated phagocytosis contributes to the anti-tumor activity of the therapeutic antibody daratumumab in lymphoma and multiple myeloma. MAbs. 2015;7(2):311-321.

[157] Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with daratumumab monotherapy in multiple myeloma. N Engl J Med. 2015;373(13): 1207-1219.

[158] Lonial S, Weiss BM, Usmani SZ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. Lancet. 2016;387(10027):1551-1560.

[159] McKeage K. Daratumumab: first global approval. Drugs. 2016;76(2):275-281.

[160] Deaglio S, Mehta K, Malavasi F. Human CD38: a (r)evolutionary story of enzymes and receptors. Leuk.Res. 2001;25:1-12

[161] Vaisitti T, Aydin S, Rossi D et al. CD38 increases CXCL12-mediated signals and homing of chronic lymphocytic leukemia cells. Leukemia. 2010;24:958-969.

[162] Malavasi F, Deaglio S, Damle R et al. CD38 and chronic lymphocytic leukemia: a decade later. Blood. 2011;118:3470-3478.

[163] Overdijk MB, Verploegen S, Marijn B et al. Phagocytosis is a mechanism of action for daratumumab. ASH Annual Meeting Abstracts 2012;120:4054.

[164] Jansen JHM, Boross P, Overdijk MB et al. Daratumumab, a human CD38 antibody induces apoptosis of myeloma tumor cells via fc receptor-mediated crosslinking. ASH Annual Meeting Abstracts 2012;120:2974

[165] Krejcik J, Casneuf T, Nijhof IS et al. Daratumumab depletes CD38+ immune-regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. Blood 2016. pii: blood-2015-12-687749. [Epub ahead of print].

[166] Schadendorf D et al Efficacy and quality of life outcomes in patients with advanced melanoma (MEL) who discontinued treatment with nivolumab (NIVO) plus ipilimumab (IPI) due to toxicity in a phase III trial (CheckMate 067). 2016 Annual Meeting of the European Association of Dermato-Oncology; August 31-September 3, 2016; Vienna, Austria.

[167] Schadendorf D, et al. Pooled Analysis of Long-Term Survival Data from Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. J Clin Oncol 2015; 33: 1889-94.

[168] Brahmer J, et al. Five-year follow-up from the CA209-003 study of nivolumab in previously treated advanced non-small cell lung cancer: clinical characteristics of long-term survivors. Oral presentation presented at: American Association for Cancer Research (AACR) Annual Meeting; April 1-5, 2017; Washington, DC, USA.

[169] Felip E et al., Three-year follow-up from Checkmate 017/057: Nivolumab versus docetaxel in patients with previously treated advanced non-small lung cancer (NSCLC). Poster discussion presentation at the European Society of Medical Oncology Annual Meeting. 2017 Sep 8-12; Madrid, Spain. Poster 1301PD

[170] Herbst RS et al. KEYNOTE-010: Durable clinical benefit in patients with previously treated, PD-L1-expressing NSCLC who completed pembrolizumab. Poster presentation at the World Conference on Lung Cancer 2016 Dec 4-7; Vienna, Austria.

[171] Robert, C et al. Long-term outcomes in patients with ipilimumab-naive advanced melanoma in the phase 3 KEYNOTE-006 study who completed pembrolizumab treatment; Journal of Clinical Oncology 2017 35:15_suppl, 9504-9504

[172] Spigel DR, et al. Randomized results of continuous vs 1-year fixed-duration in patients with advanced non-small cell lung cancer. Oral presentation at the European Society of Medical Oncology Annual Meeting. 2017 Sep 8-12; Madrid, Spain.

[173] Robert C, Thomas L, Bondarenko et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med. 2011 Jun 30;364(26):2517-26.

[174] Hodi FS, O'Day SJ, McDermott DF, et al. Improved Survival with Ipilimumab in Patients with Metastatic Melanoma; N Engl J Med. 2010 Aug 19;363(8):711-23.

[175] Lokhorst H., Laubach JP, Nahi, H, Plesner T, Gimsing P, Hansson M, et al. Dose-dependent efficacy of daratumumab (DARA) as monotherapy in patients with relapsed or refractory multiple myeloma (RR MM). J Clin Oncol 2014. 32:5s, 8513. 2014.

[176] Lonial S, Usmani S, Singha UK, Chari A, Bahlis NJ. Phase II study of daratumumab (DARA) monotherapy in patients with = 3 lines of prior therapy or double refractory multiple myeloma (MM): 54767414MMY2002 (Sirius). J Clin Oncol. 2015;33 (supplement):LBA8512

[177] Nijhof IS, Groen RW, Noort WA et al. Preclinical evidence for the therapeutic potential of CD38-targeted immuno-chemotherapy in multiple myeloma patients refractory to lenalidomide and bortezomib. Clin.Cancer Res. 2014;21(12):2802-10.

[178] Nijhof IS, Noort W, van Bueren J, et al. CD38-targeted immunochemotherapy of multiple myeloma: preclinical evidence for its combinatorial use in lenalidomide and bortezomib refractory/intolerant mm patients. Blood 2013;122:277.

[179] van der Veer MS, de WM, van KB et al. Towards effective immunotherapy of myeloma: enhanced elimination of myeloma cells by combination of lenalidomide with the human CD38 monoclonal antibody daratumumab. Haematologica. 2011;96:284-290.

[180] Plesner T, Arkenau T, Lokhorst H et al. Preliminary safety and efficacy data of daratumumab in combination with lenalidomide and dexamethasone in relapsed or refractory multiple myeloma. Blood 2013;122:1986.

[181] Plesner T., Arkenau T, Lokhorst, H et al. Safety and efficacy of daratumumab with lenalidomide and dexamethasone in relapsed or relapsed, refractory multiple myeloma. Blood 2014;124(21):84.

[182] Dimopoulos M, Oriol A, Nahi H, San Miguel JF, Bahlis NJ, Rabin N, and Orlowski R. An open-label, randomized phase 3 study of daratumumab, lenalidomide, and dexamethasone (DRd) versus lenalidomide and dexamethasone (Rd) in relapsed or refractory multiple myeloma (RRMM): POLLUX. Haematologica 2016;EHA Abstr LB2238.

[183] Palumbo A, Chanan-Khan A, Weisel K, Nooka, AK, and Masszi T. Phase III randomized controlled study of daratumumab, bortezomib, and dexamethasone (DVd) versus bortezomib and dexamethasone (Vd) in patients (pts) with relapsed or refractory multiple myeloma (RRMM): CASTOR study. J Clin Oncol 2016;ASCO Abstr LBA4.

[184] DARZALEX [package insert]. Janssen Biotech, Inc, Horsham PA; 2017.

[185] Chapuy CI, Nicholson RT, Aguad MD et al: Resolving the daratumumab interference with blood compatibility testing. Transfusion 2015;55;1545–1554.

[186] Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. NEJM 2013;369:122-133.

[187] Manuel M, Tredan O, Bachelot T, et al. Lymphopenia combined with low TCR diversity (divpenia) predicts poor overall survival in metastatic breast cancer patients. Oncoimmunology. 2012;1(4):432-440.

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.

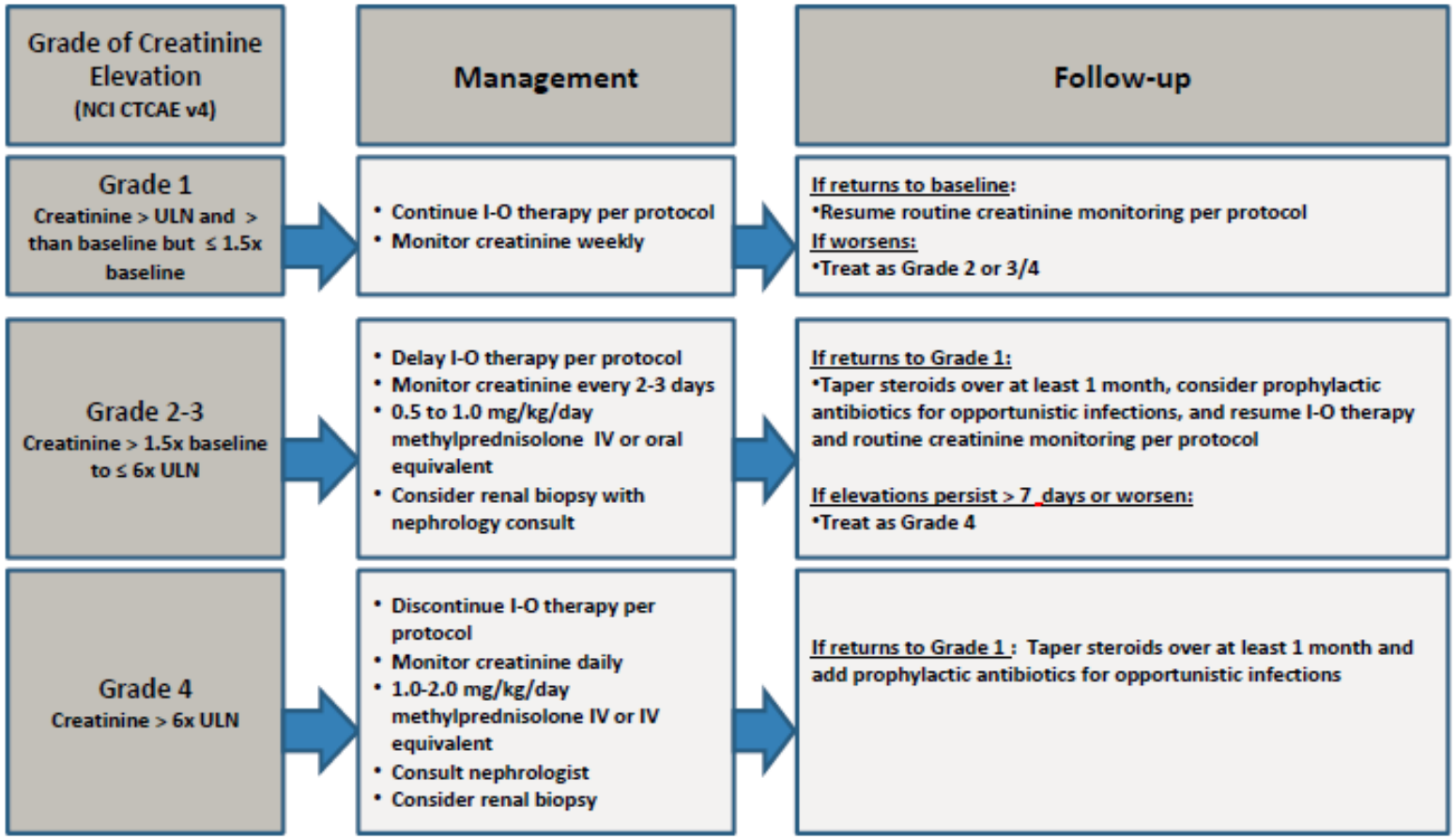
Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat 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

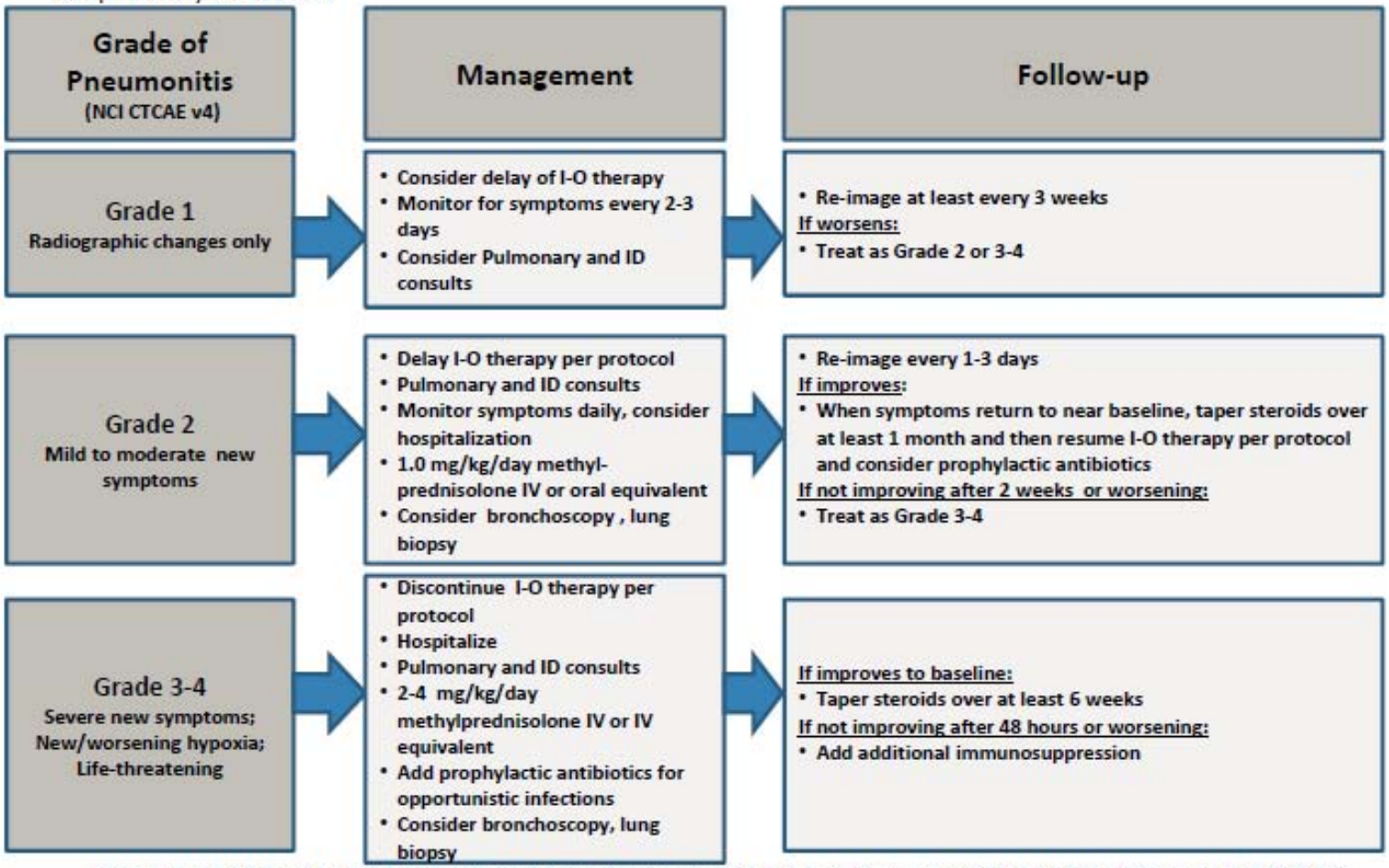


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

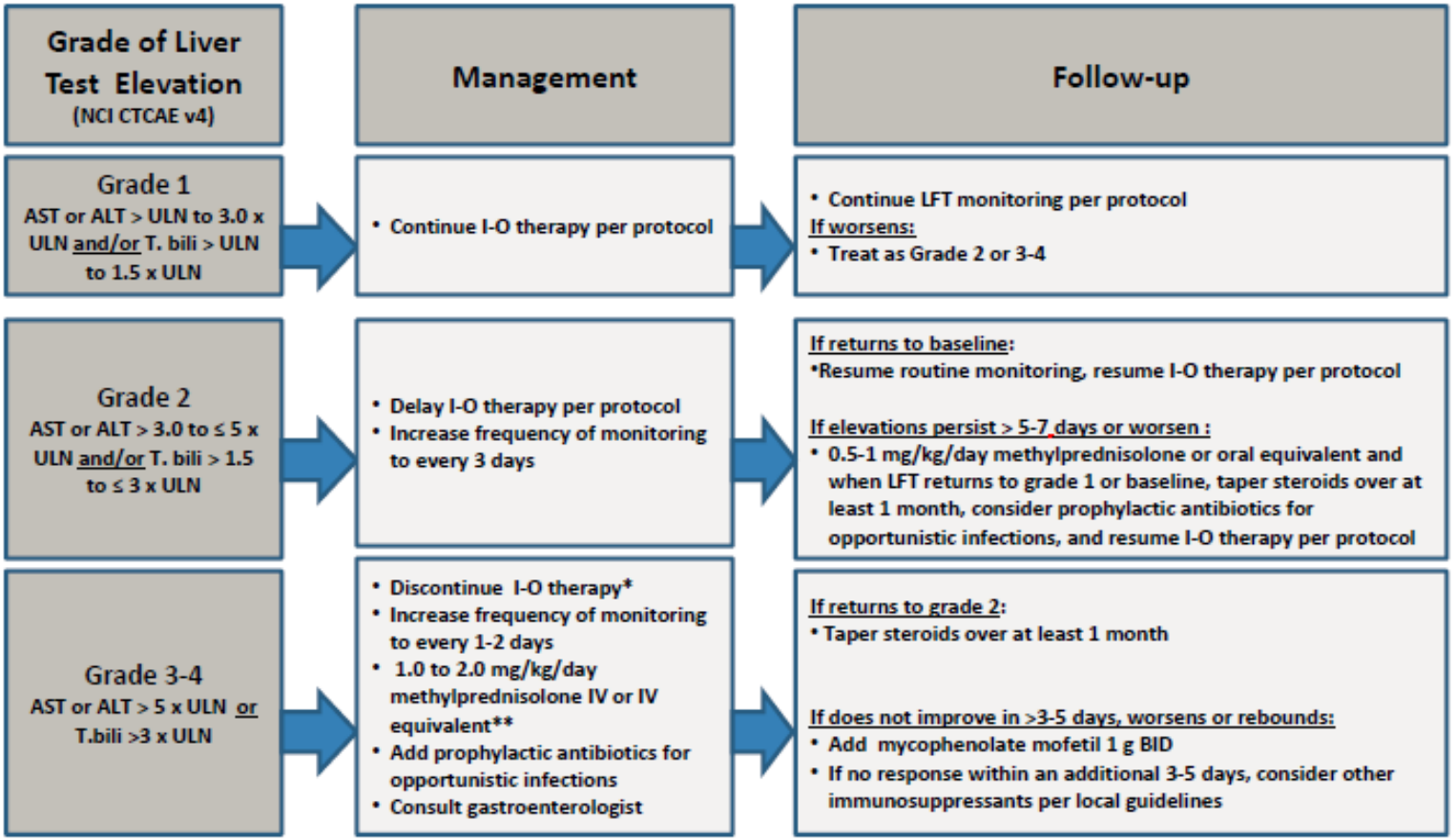


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



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

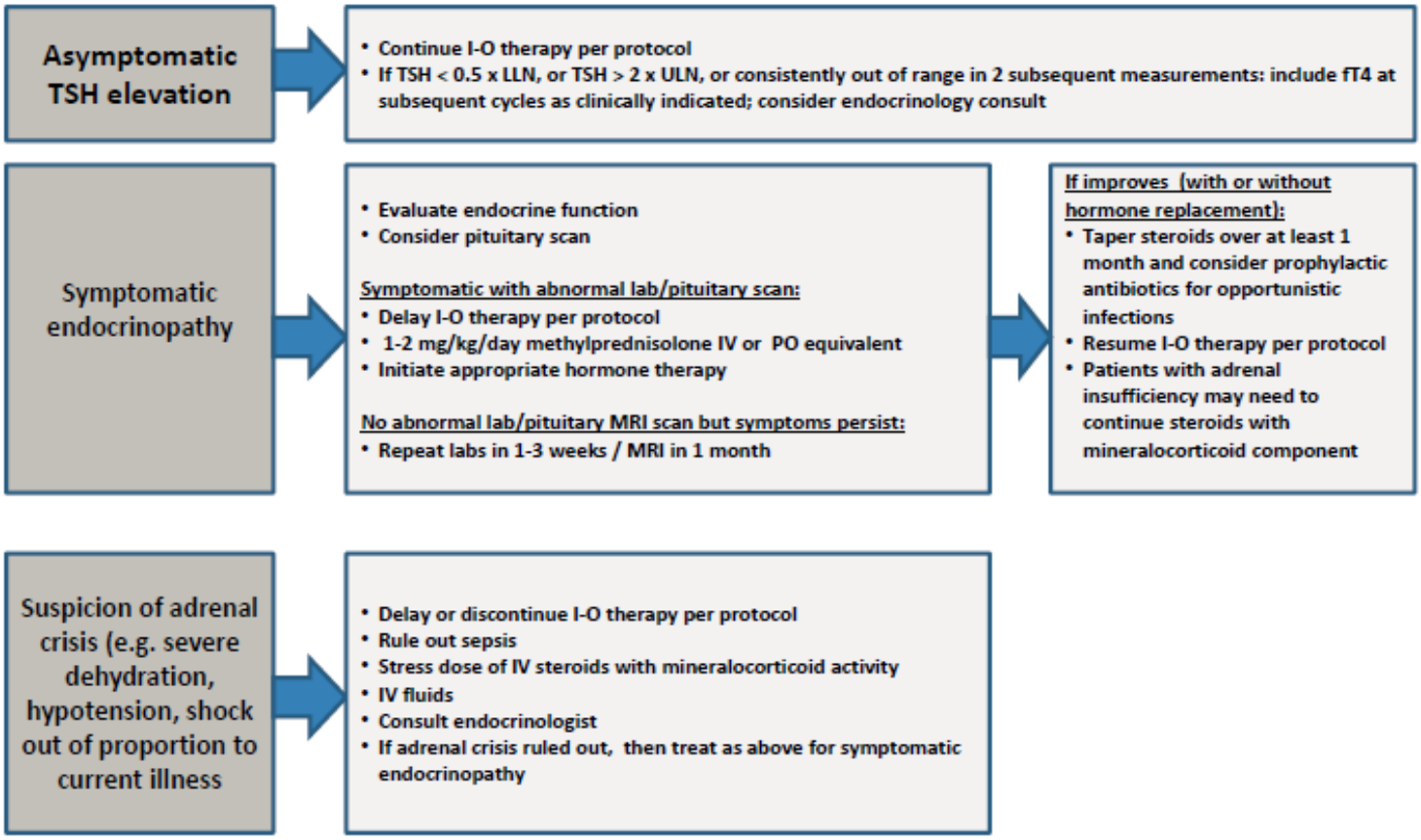
*I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.

**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Updated 05-Jul-2016

Endocrinopathy Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.

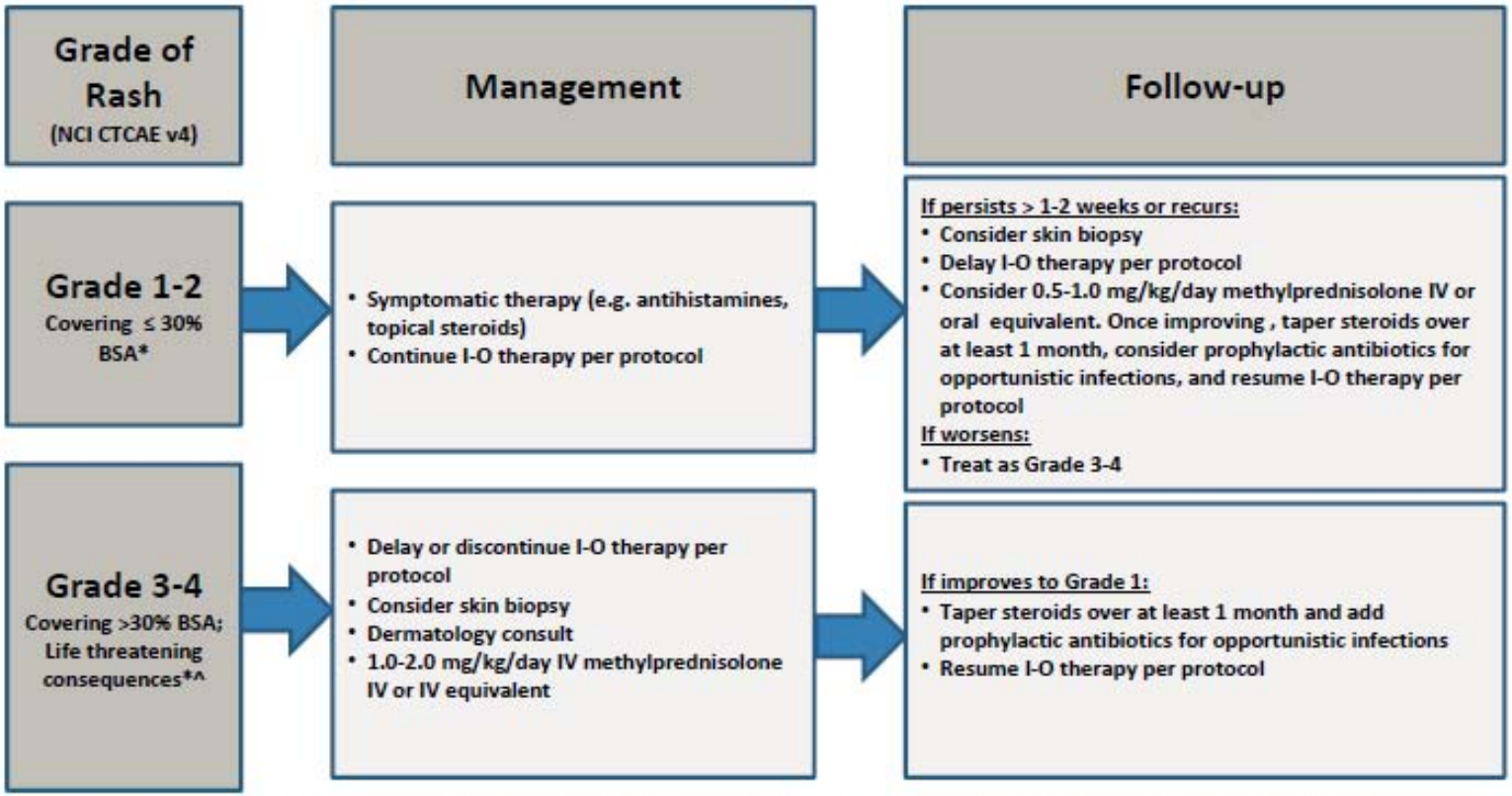


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

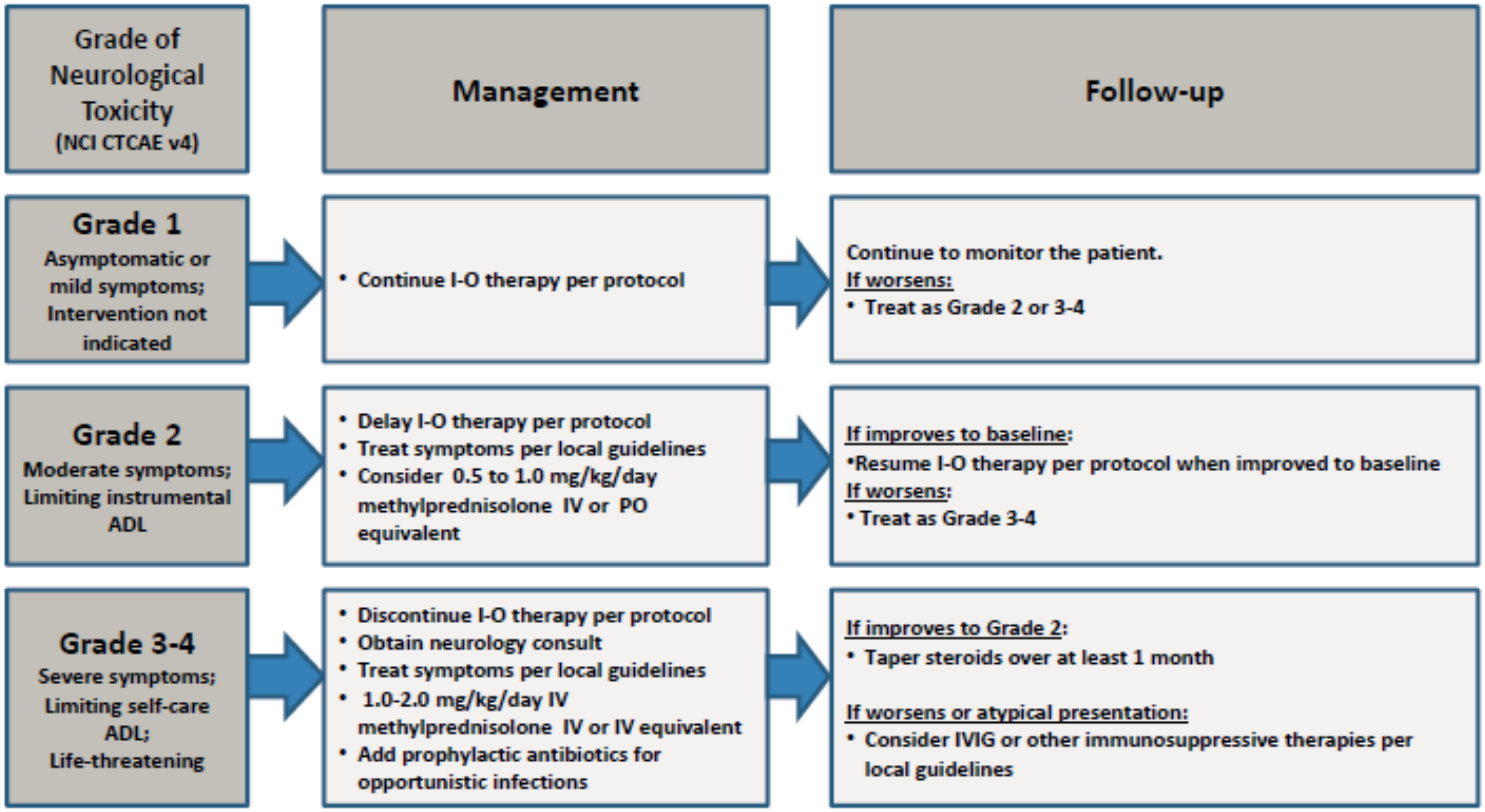


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Updated 05-Jul-2016

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

Updated 05-Jul-2016

APPENDIX 3 RECIST 1.1 GUIDELINES

1 EVALUATION OF LESIONS

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1 Measurable

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

1. 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
2. 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
3. 20 mm by chest x-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

1.2 Non-Measurable

All other lesions are considered non-measurable, including small lesions (longest diameter < 10mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

2 BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

3 RESPONSE CRITERIA

3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

3.1.1 Special Notes on the Assessment of Target Lesions

3.1.1.1 Lymph nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

3.1.1.2 Target lesions that become 'too small to measure'

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

3.1.1.3 Lesions that split or coalesce on treatment

When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

3.2 Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

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

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

3.2.1.1 When the patient also has measurable disease

In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy (see examples in Appendix 2 and further details below). A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

3.2.1.2 When the patient has only non-measurable disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While

it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

3.2.2 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
2. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

3.3 Response Assessment

3.3.1 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and

will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement.

3.3.2 Time Point Response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 3.3.2-1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 3.3.2-2 is to be used.

Table 3.3.2-1: Time Point Response: Patients With Target (+/- Non-Target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease and NE = inevaluable

Table 3.3.2-2: Time Point Response: Patients with Non-target Disease Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease and NE = inevaluable

[a] Non-CR/non-PD is preferred over SD for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

3.3.3 Best Overall Response

Best response determination of complete or partial response requires confirmation: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of ≥ 4 weeks later. In this circumstance, the best overall response can be interpreted as in Table 3.3.3-1.

Special note on response assessment: When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Table 3.3.3-1: Best Overall Response (Confirmation of CR&PR Required)

Overall Response First Time Point	Overall Response Subsequent Time Point	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD OR PR[a]
CR	SD	SD provided minimum criteria for SD duration[b] met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration[b] met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration[b] met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration[b] met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration[b] met, otherwise, NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

[b] Minimum criteria for SD duration is 6 weeks.

3.3.4 Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive repeat assessments that should be performed no less than 28 days after the criteria for response are first met. For this study, the next scheduled tumor assessment can meet this requirement.

Verification of Progression: Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered to not have progressive disease.

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 5 months after the end of study treatment.

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

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal

• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)[c] • Intrauterine device (IUD)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* – It is not necessary to use any other method of contraception when complete abstinence is elected. – WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. – Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence

NOTES:

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Unacceptable Methods of Contraception
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action • Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until end of relevant systemic exposure defined as 7 months after the end of study treatment.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of study treatment.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 6.1.1 and Section 6.4.

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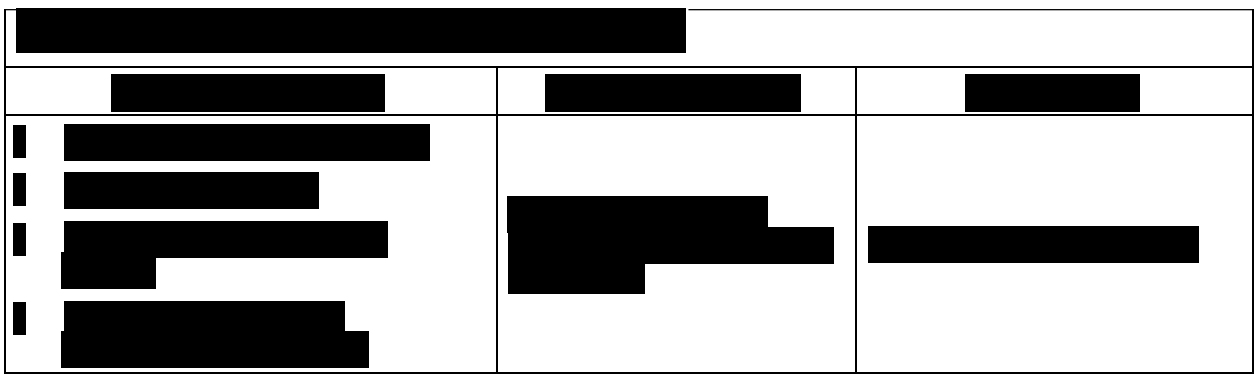

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