Cover Page for Protocol – J18119

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TITLE: A Phase 2 study Evaluating Response and Biomarkers in Patients with Microsatellite Stable (MSS) Advanced Colorectal Cancer treated with Nivolumab in Combination with Relatlimab

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Bristol-Myers Squibb Supplied Agents: Nivolumab (BMS-936558; anti-PD-1 mAb)
Relatlimab (BMS-986016, anti-LAG-3 mAb)

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Amendment 5/Version 6.0/June 16, 2020
Amendment 6/Version 7.0/August 19, 2020
Amendment 7/Version 8.0/ August 3, 2021
Amendment 8/Version 9.0/March 31, 2022

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1. OBJECTIVES

1.1. Primary Objective

Cohort A/B: To estimate the objective response rate (ORR) in patients with metastatic or locally advanced microsatellite stable (MSS) colorectal cancer that have a positive and negative composite PD-L1/Mucin (CPM) score treated with nivolumab and relatlimab.

Cohort C: To estimate the objective response rate (ORR) in patients with metastatic or locally advanced microsatellite stable (MSS) colorectal cancer without prospective biomarker selection treated with nivolumab and relatlimab.

1.2. Secondary Objective

1.2.1. To assess safety and characterize toxicities of nivolumab in combination with relatlimab.

1.3. Exploratory Objectives

1.3.1. To assess the overall survival (OS), progression free survival (PFS), time to-progression (TTP), disease control rate (DCR), best overall response (BOR), duration of response (DOR), duration of clinical benefit (DCB), and time to objective response (TTOR) of patients with metastatic or locally advanced microsatellite stable (MSS) colorectal cancer that have a positive and negative CPM score treated with nivolumab and relatlimab.

1.3.2. To assess immune objective response rate (iORR) by immune-related RECIST criteria (iRECIST).

1.3.3. To evaluate CPM score and determine the cut-off threshold as a predictive marker for I-O treatment in patients with MSS CRC.

1.3.4. To collect pre- and on-treatment biopsies to explore the association of features of the tumor microenvironment with response to therapy, including assessment of T cell subset markers (CD4, CD8, FoxP3, Granzyme A/B, CD69), immune regulation (PD-L1, PD-L2, CTLA4, LAG-3, IDO1, TIM-3), and immune cell population markers (NK, DC, B cell, MDSC).

1.3.5. To evaluate molecular determinants such as KRAS and BRAF status

1.3.6. To evaluate molecular determinants of response using next generation sequencing and other sequencing techniques.

- Characterize the tumor mutational landscape through exomic sequencing for mutation analysis and MANA prediction.

1.3.7. To assess tumor burden dynamics using standard protein biomarkers when available as well as circulating biomarkers (i.e. ctDNA).

1.3.8. To collect peripheral blood lymphocytes to explore the association of lymphocyte activation markers with clinical response.

1.3.9. To evaluate clonal T cell populations in the tumor and in the periphery through T cell receptor sequencing, and to functionally assess mutation associated neoantigen-specific T cells.

1.3.10. To collect stool and oral wash (and/or buccal mucosal) samples at baseline and throughout treatment to explore the association of changes in the host microbiome and clinical outcome.

- Microbial community analysis to correlate gut microbiome composition with response (OS, PFS and best overall response).

- Whole metagenome functional profiling analysis via shotgun sequencing to correlate microbiome composition and microbial functions and pathways with response (OS, PFS and best overall response).

1.4. Study Design

This is an open-label, two stage, phase 2 study to evaluate the safety and clinical activity of nivolumab and relatlimab in patients with metastatic or locally advanced microsatellite stable (MSS) colorectal cancer that have a positive and negative composite PD-L1/Mucin (CPM) score. The primary endpoint is objective response rate (ORR) assessed using RECIST 1.1.

The trial will enroll two cohorts of MSS mCRC patients receiving 480mg nivolumab/160mg relatlimab: patients with MSS colorectal adenocarcinomas who have a positive CPM score (Cohort A); and patients with MSS colorectal adenocarcinomas who have a negative CPM score (Cohort B). The cutoff threshold $\geq$ 15% of CPM will be used to determine CPM positivity. An additional cohort of MSS mCRC patients without biomarker selection will be enrolled to receive either 480mg nivolumab/960mg relatlimab or 480mg nivolumab/480mg relatlimab (Cohort C). As of Amendment 6, enrollment will begin to Cohort C. Enrollment to Cohorts A and B will resume once enrollment to Cohort C is complete.

As of Amendment 7, newly enrolled patients in Cohort C will receive 480mg nivolumab/480mg relatlimab Q4W. Patients previously treated in Cohort C at 960mg relatlimab will either be dose reduced to relatlimab 160mg, 480mg, or continue to receive relatlimab 960mg if they are past the 8 week safety window at the discretion of the Principal Investigator. [redacted]. Patients receiving relatlimab 480mg or 960mg will have an increase in the frequency of safety monitoring per **Section 9**.

Each cohort will enroll up to 32 evaluable patients. The primary endpoint is objective response rate (ORR) per RECIST 1.1, and the three cohorts will be analyzed separately for the primary analysis of rate of ORR. For each cohort, the treatment will be considered inactive and of no interest for further evaluation if the ORR is 5% or less and considered active if the ORR is 20% or greater. This design allows for the simultaneous evaluation of the efficacy of the treatment and CPM as a predictive marker.

Simon two-stage minimax design is planned for each cohort. Initially, 18 patients per cohort will be treated in Stage 1. Patients will be considered evaluable if they receive at least one dose of study drug. If there is at least 1 response in the initial 18 patients in a cohort, then an additional 14 patients will be enrolled in Stage 2 for a total of 32 (18 + 14 = 32) patients in that cohort. If a total of 4 or more responses are observed in Stages 1 and 2 combined, we conclude the regimen is promising and warrants further study. This design has 90% power to reject the null response rate of 5% in favor of 20% response rate, with one-sided type 1 error 0.1.

We expect that the prevalence of a positive CPM score is 10-15% among MSS CRC patients. Therefore, we will need to pre-screen 220-320 MSS CRC patients in order to identify 32 marker positive MSS CRC patients. Assuming 95% of CRC patients are MSS, we will pre-screen a total of 235-340 CRC patients.

The study will consist of a pre-screening period (for Cohorts A and B), a screening period (within 28 days of the first dose), a treatment period, and a follow-up period. Subjects will receive treatment on 28 day cycles, and will come to clinic for dosing and/or assessments on Day 1 of each cycle and additional days for safety and immune monitoring follow up as per the study schedule in **Section 9.** No dose escalations or reductions of nivolumab or relatlimab are allowed. Complete information on study drug administration, schedule, and dosing can be found in **Section 4.1.**

The study will include a safety run-in for the first six patients for Cohorts A and B only. If more than 1 of the first 6 patients experiences an unacceptable toxicity within the first cycle, then enrollment will be halted and the overall risk-benefit ratio of the study will be reconsidered. At any time thereafter, if more than 33% of patients are observed to experience unacceptable toxicity within the first cycle, enrollment will be halted and the safety of the combination will be re-evaluated. Complete unacceptable toxicity criteria can be found in **Section 4.7**.

Treatment may continue per investigator discretion, or until discontinuation due to toxicity, lack of clinical benefit as determined by the investigator, subject withdrawal, or termination of the study by the IND sponsor. Subjects may continue on treatment with radiographic disease progression if subject is clinically stable and investigator believes the treatment is providing benefit. Criteria for removal from treatment are found in **Section 4.10**.

Tumor biopsies, PBMC, serum and plasma collection, microbiome samples, and computed tomography (CT) scans or magnetic resonance imaging (MRI), if CT is contraindicated, will be obtained at baseline and during treatment for clinical assessments and correlative analyses. Tumor assessments will be made using RECIST 1.1 and iRECIST.

Subjects will return to the study site 30 (+/- 7) days after the final administration of study treatment for an end of treatment (EOT) evaluation. Subjects will be considered in the treatment period until 30 days after the last dose of study drug. After completion of treatment and EOT assessments, all subjects will continue to be followed per **Section 4.12**.

Information on progression-free survival and overall survival may continue to be gathered for supplementary analyses after the completion of the primary analysis.

2. BACKGROUND

2.1. Study Disease

As the third leading cause of cancer in both men and woman in the United States, it is estimated that 50,630 people will die from colorectal cancer (CRC) in 2018[1]. The majority of CRC cases are due to spontaneous genetic changes, which can include microsatellite instability (MSI), chromosomal instability (CIN), and the CpG island methylator phenotype (CIMP)[2]. Approximately 15 percent of all CRC (4% in metastatic CRC) are considered microsatellite instability (MSI-high), whereas 85 percent of all CRC cases are microsatellite stable (MSS) or MSI-low. The immune system has long been known to play a role in CRC, where intratumoral immune infiltration has been shown to correlate with improved prognosis[3-11]. While durable objective responses (OR) following T cell checkpoint inhibition in the treatment of refractory solid tumors[12-16] are a proof of principle that endogenous adaptive immune responses can be harnessed by immunotherapy[17-20], no objective clinical responses with anti-PD-1 (nivolumab)[21] or an anti-PD-L1 antibody (BMS936559/MDX-1105)[13] were observed in CRC patients with the rare exception in an MSI-H CRC patient[22].

2.2. Dual Blockade of PD-1 and LAG-3

Lymphocyte-activation gene 3 (LAG-3) is a cell surface molecule expressed on activated T cells, and has a negative regulatory effect on T cell function. While the mechanism by which it modulates T lymphocyte activity is incompletely understood, it has structural homology with CD4 and binds its primary ligand, MHC class II with higher affinity than CD4, thereby mediating a state of T cell exhaustion. Relatlimab (BMS-986016) is fully human monoclonal immunoglobulin (Ig) G4 antibody that binds to a defined epitope on LAG-3 with high affinity and specificity and potently blocks the interaction of LAG-3 with MHC class II, resulting in a reversal of LAG-3-mediated T-cell downregulation.

In preclinical models and early clinical studies, anti-LAG-3 antibodies have demonstrated minimal anti-tumor activity as a single agent but synergistic activity when combined with anti-PD-1 antibody. The combination of the PD-1 inhibitor nivolumab plus the LAG-3 inhibitor relatlimab is being tested in the ongoing phase 1/2a trial CA224020. As of April 2017, 268 subjects had been treated with relatlimab monotherapy (N=25) or combination with nivolumab (N=243), with acceptable safety profile observed at all doses tested. Of 48 evaluable patients in the PD-1/PD-L1 experienced melanoma cohort, an ORR of 12.5% and DCR of 54% was observed [23].

2.3. Relatlimab Dose Selection

Nivolumab was recently approved for use at a dosing of 480 mg flat dosing every 4 weeks in multiple cancers, based on clinical data and population PK (PPK) simulations and exposure-response analyses suggesting no significant impact on toxicity or efficacy. Similarly, a Q4 weekly dosing of relatlimab is highly desirable from an economic standpoint and for patient convenience. The justification for the flat dosing of relatlimab at 160 mg Q4 weekly is based on PPK simulation predicting similar exposure to that seen with Q2W dosing. The safety of relatlimab 160 mg Q4W in combination with nivolumab 480 mg Q4W is being evaluated in the ongoing Phase 1/2a study CA224020, and will be further evaluated in the present study. Please see the Relatlimab Investigator's Brochure for more information regarding experience and safety of nivolumab/relatlimab 160/480 Q4W dose.

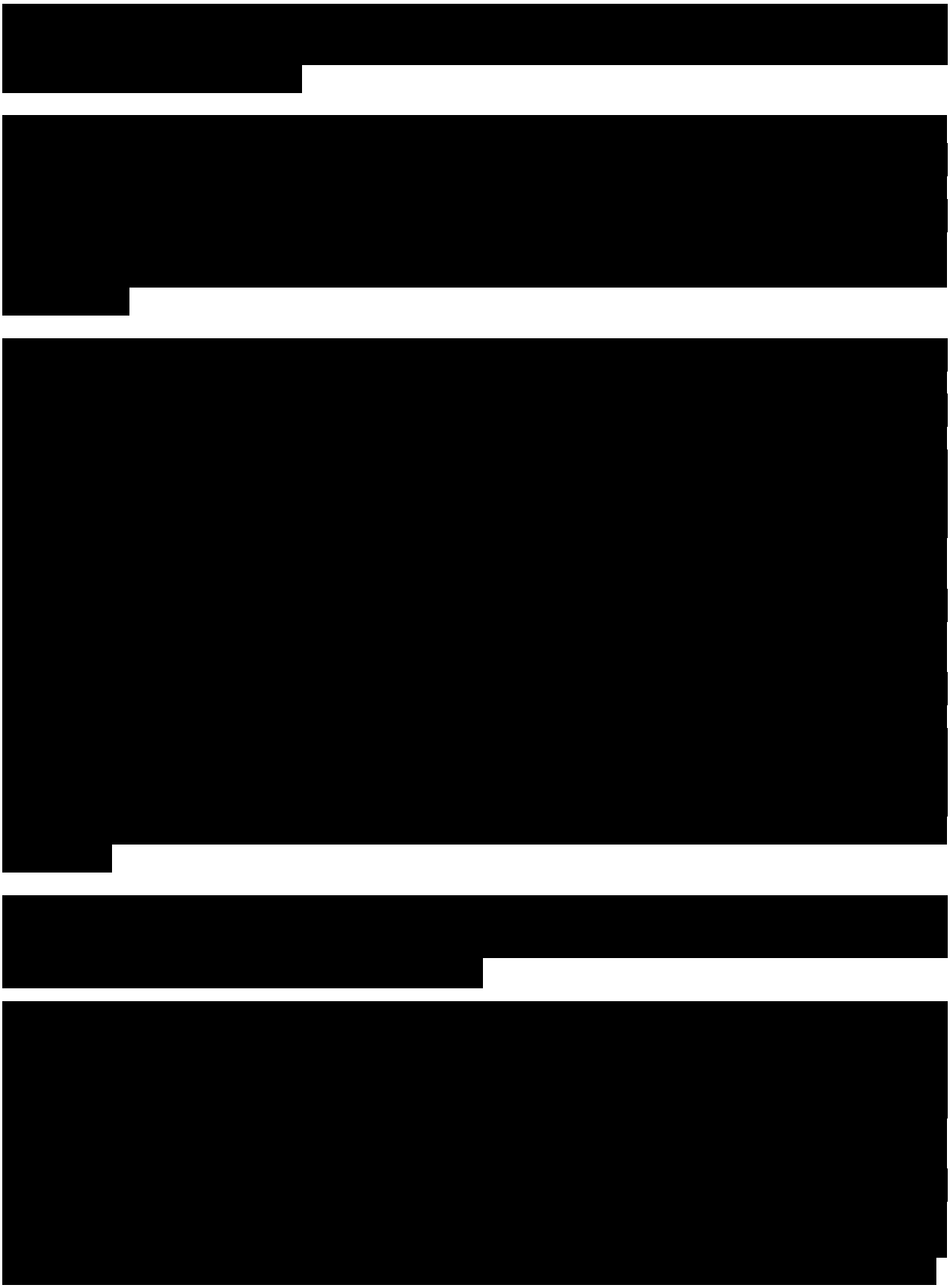
2.3.1. Justification for 480 or 960 mg Q4W

The target dose of relatlimab 480 mg Q4W dose is based on the consideration of clinical safety and target engagement will provide meaningful clinical activity. The relatlimab dose was selected after consideration of several factors including relatlimab PK, pharmacodynamics, population pharmacokinetic (PPK) model predicted exposure metrics, benefit/risk assessment of relatlimab and nivolumab co-administration, and extensive nivolumab monotherapy clinical experience.

[redacted]

[redacted]

Safety:



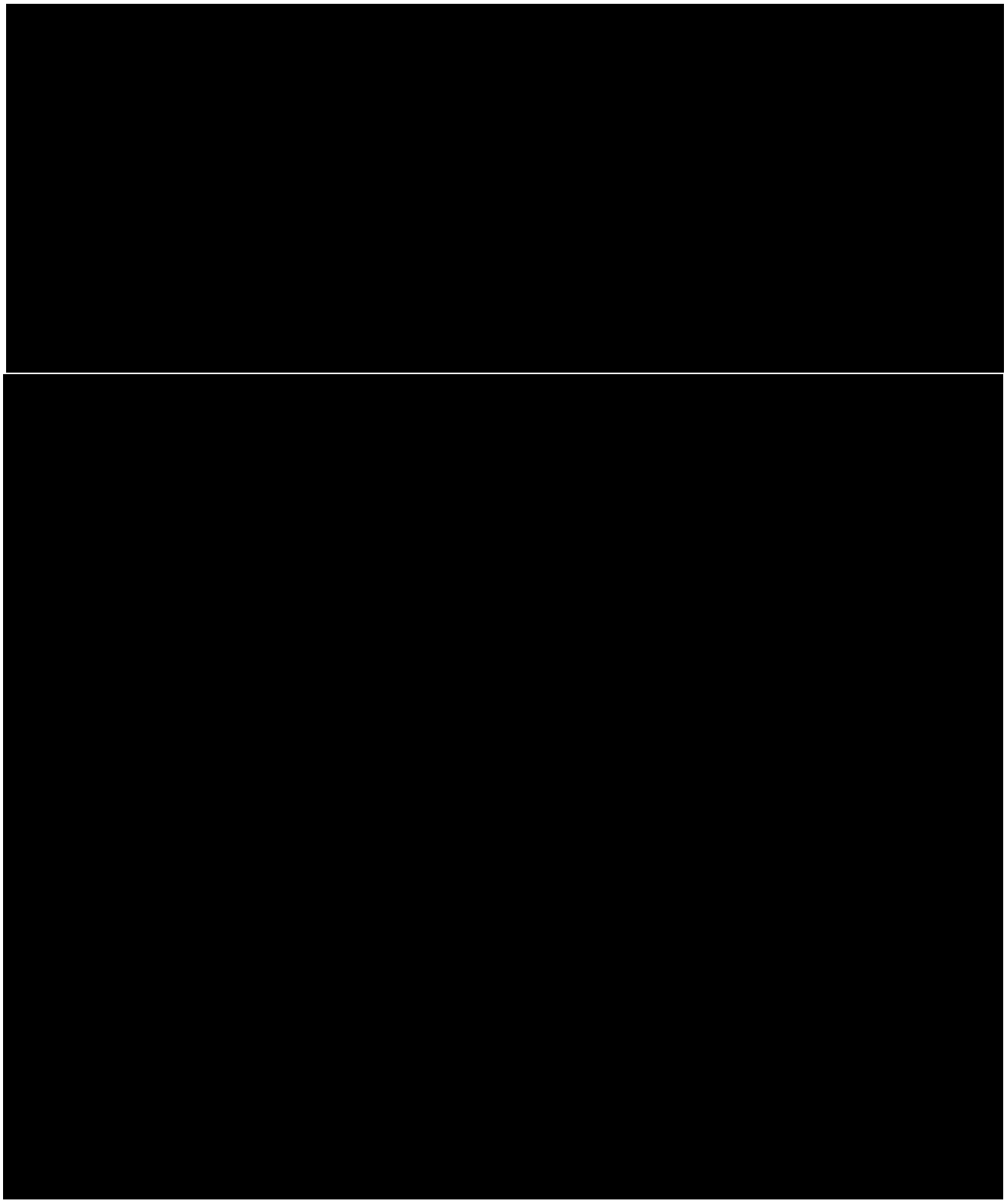
[redacted]

Please see the Relatlimab Investigator's Brochure for more information regarding experience and safety of relatlimab 480 mg Q4W dose.

2.4. Rationale

Mismatch repair (MMR) deficient tumors, also termed MSI-high, harbor hundreds to thousands of mutation-associated neoantigens (MANAs) that can be recognized and targeted by T cells. Several studies have revealed that anti-CTLA-4 or anti-PD-1 therapies can unleash and amplify preexisting MANA-specific tumor-infiltrating T cells in the tumor and peripheral blood[25, 26]. Data from a phase II trial by Le et al demonstrated that 90 percent of MSI-high patients (9/10) experienced either an objective response or disease stabilization, as compared to only 11 percent of MSS patients (2/18), with disease stabilization being the best response seen in MSS patients[27]. The updated overall response rate (ORR) was 53% in MSI-H CRC[28]. In a separate clinical trial, nivolumab resulted in a 31% response rate and the combination of nivolumab and ipilimumab led to a 55% ORR[29, 30]. One explanation that could account for why some MSI-high patients progress after checkpoint blockade and conversely, why some MSS patients exhibit disease control could potentially be found in the differences in tumor immune microenvironment (TiME).

We recently established that the high density of somatic mutations found in MSI-high CRC tumors exhibit robust IFNγ^{hi}PD-1^{hi}CD8^{+} T cell infiltration that is associated with myeloid expression of the PD-1 ligand, PD-L1, in response to IFNγ production in the TiME[31]. Upregulated expression of several T cell checkpoints, including LAG-3, CTLA-4, and PD-1, suggest that MSI-high CRC tumors trigger an endogenous anti-tumor immune response that is counter-regulated by the expression of a variety of immunoregulatory ligands[31]. [redacted]



This study aims to target immune checkpoints PD-1 and LAG-3 to synergistically improve T cell activation and proliferation by circumventing T cell exhaustion and regulation that promote immune evasion by tumors. This study will be an open label, phase II study to evaluate ORR in patients with metastatic or locally advanced MSS CRC that have a positive and negative CPM score treated with nivolumab and relatlimab.

3. PATIENT SELECTION

3.1. Eligibility Criteria

3.1.1. Age ≥18 years.

3.1.2. ECOG performance status of 0-1 (**Appendix A**).

3.1.3. Patients with histologically proven metastatic or locally advanced microsatellite stable (MSS) colorectal adenocarcinoma.

3.1.4. Cohort A: Primary lesion has a composite PD-L1/Mucin (CPM) score ≥ 15%.

3.1.5. Cohort B: Primary lesion has a composite PD-L1/Mucin (CPM) score < 15%.

3.1.6. Cohort C: Prior surgical resection of primary tumor. Prospective biomarker evaluation not required.

3.1.7. Patients who have received at least one prior cancer chemotherapy regimen in the locally advanced/metastatic setting. Adjuvant therapy can only be counted if recurrence occurred within 6 months of completing systemic chemotherapy.

Radiosensitizing doses of chemotherapy are not considered systemic chemotherapy. Patients should be considered for standard therapies.

3.1.8. Presence of at least one lesion with measurable disease as defined by 10 mm in longest diameter for a soft tissue lesions or 15 mm in short axis for a lymph node by RECIST 1.1.

3.1.9. Patients must have available archival tissue from the surgical resection of their primary tumor for CPM score determination.

3.1.10. Patient's acceptance to have a tumor biopsy of an accessible lesion at baseline and on treatment if the lesion can be biopsied with acceptable clinical risk (as judged by the investigator).

3.1.11. Life expectancy of greater than 3 months.

3.1.12. Patients must have normal organ and marrow function as defined below:

- Leukocytes	$\geq$ 2,000/mm^3
- Absolute neutrophil count	$\geq$1,500/mm^3
- Platelets	$\geq$100,000/mm^3
- Hemoglobin	$\geq$8.5 g/dL
- Total bilirubin	$\leq$ 1.5 x ULN except subjects with Gilbert's Syndrome, who must have normal direct bilirubin
- AST(SGOT) and ALT(SGPT)	$\leq$ 3.0 x ULN
- Albumin	$\geq$ 2.8 g/dl
- Lipase and amylase	< 1.5 x ULN Subjects with values > 1.5 ULN may enroll if there are neither clinical nor radiographic signs of a pancreatitis.
- Creatinine	$\leq$ 1.5 x ULN or creatinine clearance (CrCl) $\geq$ 40 mL/min (if using the Cockroft-Gault formula below):

$$\textit{Female}\ \text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

$$\textit{Male}\ \text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$$

3.1.13. LVEF assessment with documented LVEF $\geq$ 50% by either TTE or MUGA (TTE preferred) within 6 months from first study drug administration.

3.1.14. 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 3 days prior to start of study drug. In a case of a positive HCG test, a vaginal ultrasound must be used to confirm a lack of pregnancy. WOCBP is defined in

Section 4.8. WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drugs plus an additional 165 days (approximately 24 weeks) after the last dose of nivolumab and/or relatlimab. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drugs plus an additional 225 days (approximately 33 weeks) after the last dose of study drug.

3.1.15. Patient understands the study regimen, its requirements, risks and discomforts and is able and willing to sign the informed consent form in accordance with regulatory and institutional guidelines must be obtained before the performance of any protocol related procedures that are not part of normal patient care. Subjects must be competent to report AEs, understand the drug dosing schedule and use of medications to control AEs.

3.2. Exclusion Criteria

3.2.1. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 1 week prior to initiation of study treatment. This is not applicable to patients with primary brain tumors.

3.2.2. Patient is expected to require any other form of systemic or localized antineoplastic therapy while on study.

3.2.3. Patients with a history of prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA4, or anti-Lag-3 antibodies.

3.2.4. Any of the following procedures or medications:

- Within 2 weeks prior to initiation of study treatment:
  - Systemic or topical corticosteroids at immunosuppressive doses (> 10 mg/day of prednisone or equivalent). Inhaled or topical steroids, and adrenal replacement steroid doses ≤ 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
  - Palliative radiation or gamma knife radiosurgery.
  - Chemotherapy
- Within 4 weeks prior to initiation of study treatment:
  - Any investigational cytotoxic drug. Exposure to any non-cytotoxic drug within 4 weeks or 5 half-lives (whichever is shorter) is prohibited. If 5 half-lives is shorter than 4 weeks, agreement with IND Sponsor is mandatory.
  - Non-oncology vaccines containing live virus.

- Allergen hyposensitization therapy.
- Growth factors, e.g. granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), erythropoietin
- Major surgery

3.2.5. History of severe hypersensitivity reaction to any monoclonal antibodies or related compounds or to any of their components (e.g., history of severe hypersensitivity reactions to drugs formulated with polysorbate 80).

3.2.6. Uncontrolled intercurrent acute or chronic medical illness.

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

3.2.8. Has a diagnosis of immunodeficiency.

3.2.9. Prior tissue or organ allograft or allogeneic bone marrow transplantation. Exceptions can be approved by the IND Sponsor if loss of the graft is not a clinical concern.

3.2.10. A known or underlying medical condition that, in the opinion of the Investigator, could make the administration of study drug hazardous to the subject or could adversely affect the ability of the subject to comply with or tolerate study.

3.2.11. Patients with a history of interstitial lung disease.

3.2.12. Requirement for daily supplemental oxygen.

3.2.13. Uncontrolled or significant cardiovascular disease (i.e. cardiomyopathy, congestive heart failure with New York Heart Association (NYHA) functional classification III-IV, pericarditis, significant pericardial effusion, significant coronary stent occlusion), including, but not limited to any of the following:
- Myocardial infarction (MI) or stroke/transient ischemic attack within the 6 months prior to consent
- Uncontrolled Angina within the 3 months prior to consent
- Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes)
- QTc prolongation > 480 msec
- Cardiovascular disease-related requirement for daily supplemental oxygen
- History of two or more MIs OR two or more coronary revascularization procedures
- Subjects with history of myocarditis, regardless of etiology.

3.2.14. Troponin T (TnT) or I (TnI) >2 x ULN. Subjects with TnT or TnI levels between >1 to 2 x ULN will be permitted if repeat levels within 24 hours are ≤ 1 x ULN. If TnT or TnI levels are >1 to 2 x ULN within 24 hours, the subjects may undergo a cardiac evaluation and be considered for treatment, following a discussion with the IND Sponsor. When repeat levels within 24 hours are not available, a repeat test should be conducted as soon as possible. If TnT or TnI repeat levels beyond 24 hours are ≤ 2 x ULN, the subject may undergo cardiac evaluation and be considered for treatment, following discussion with the IND Sponsor.

3.2.15. Has a confirmed history of encephalitis, meningitis, or uncontrolled seizures in the year prior to informed consent.

3.2.16. Positive blood screen for Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies) or known acquired immunodeficiency syndrome (AIDS).

3.2.17. Any positive test for Hepatitis B or Hepatitis C virus indicating presence of virus, e.g. Hepatitis B surface antigen or Hepatitis C antibody positive (except if HCV-RNA negative).

3.2.18. Has active infection requiring systemic antibacterial, antiviral, or antifungal therapy ≤ 7 days prior to initiation of study drug.

3.2.19. Subjects unable to undergo venipuncture and/or tolerate venous access.

3.2.20. Any other sound medical, psychiatric, and/or social reason as determined by the Investigator.

3.2.21. Patient is, at the time of signing informed consent, a regular user (including "recreational use") of any illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol).

3.2.22. Women who are pregnant or nursing.

3.2.23. Women with a positive pregnancy test on enrollment or prior to investigational product administration.

3.2.24. WOCBP and men with female partners (WOCBP) who are not willing to use contraception.

3.3. Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

3.4. Composite PD-L1/Mucin (CPM) Score

3.5. MSI Testing

Microsatellite instability (MSI), a form of genomic instability, occurs through the insertion or deletion of repeating nucleotides during DNA replication and failure of the mismatch repair system to correct errors in nucleotide repeat markers. All MSI testing will be performed in a CLIA-certified laboratory for mismatch repair deficiency (MRD) or MSI using IHC, PCR, or next generation sequencing (NGS). MMRd or MSI status is determined by examining either 1) protein expression by IHC of 4 MMR enzymes (MLH1/MSH2/MSH6/PMS2) or 2) 3-5 tumor microsatellite loci using PCR-based assay, respectively. Tumors are classified as MSS when no allelic shifts among the 3-5 analyzed microsatellite markers are detected by PCR, or presence of all 4 mismatch repair protein expression is detected by IHC. Subjects that are MSS will be enrolled in this study.

4. TREATMENT PLAN

4.1. Agent Administration

Treatment will be administered on an outpatient basis. Appropriate dosing delays are described in **Section 5.** No investigational or commercial agents or therapies other than those described below in **Table 2** may be administered with the intent to treat the patient's malignancy.

Table 2: Regimen Description

REGIMEN DESCRIPTION						
Agent	***Premedications; Precautions***	***Administration Type***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Cohort A/B: Nivolumab/ Relatlimab	No prophylactic pre-medication will be given unless indicated by previous experience in an individual subject per **Section 4.2**	Co-administration	480mg/160mg	IV infusion over 60 (+/-15) min*	Day 1	28 days
Cohort C: Nivolumab/ Relatlimab		Sequential**	480mg/960mg or 480mg/480mg ***	Each drug infused IV over 30 (+/-10) min*		
		Co-administration	480mg/160mg ***			

*Infusion times are approximate and may be adjusted based on subject tolerability.
** Order of administration is nivolumab followed by relatlimab. Subjects should be observed for a minimum of 30 minutes between each infusion.

***Patients enrolling during or after Amendment 7 will receive nivolumab/relatlimab 480mg/480mg. Patients who enrolled prior to Amendment 7 and are within 8 weeks of their first dose will be dose reduced to nivolumab/relatlimab 480mg/160mg or 480mg/480mg at the discretion of the Principal Investigator. Patients who are past 8 weeks from their first dose may continue to receive nivolumab/relatlimab 480mg/960mg or be dose reduced to nivolumab/relatlimab 480mg/160mg or 480mg/480mg at the discretion of the Principal Investigator.

Please see **Section 5.2** for guidance regarding dosing delays.

Antiemetic medications should not be routinely administered prior to dosing of drugs. See **Section 4.2.1** for subsequent premedication recommendations following an infusion reaction.

4.2. General Concomitant Medication and Supportive Care Guidelines

Nivolumab and relatlimab are fully human monoclonal immunoglobulin (Ig) G4 antibodies. Subjects should be closely monitored for potential AEs during antibody infusion and potential AEs throughout the study.

4.2.1. Infusion Reactions

Since nivolumab and relatlimab contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce an infusion or hypersensitivity reaction. 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 allergic-like reactions. All grade 3 or 4 infusion reactions should be reported within 24 hours to the IND Sponsor, Regulatory Specialist, and BMS and reported as an SAE if criteria are met. Infusion reactions should be graded according to CTCAE (version 5.0) guidelines.

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 acetaminophen 325 to 1000 mg at least 30 minutes before additional administrations.

For grade 2 symptoms (moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g., 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 acetaminophen 325 to 1000 mg; 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, 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 case report form (CRF).

The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg should be administered at least 30 minutes before study drug infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

For grade 3 or grade 4 symptoms (severe reaction, grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]; grade 4: (life threatening; pressor or ventilator 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. All study drugs 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 (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

4.2.2. Nivolumab and Relatlimab-Related Adverse Events

Blocking PD-1 or LAG-3 function may permit the emergence of auto-reactive T cells and resultant clinical autoimmunity. Rash/pruritus, diarrhea/colitis, pneumonitis, hepatitis, and hypothyroidism were drug-related, presumptive autoimmune events noted in previous nivolumab studies.

For the purposes of this study, a nivolumab- or relatlimab-related AE is defined as an AE of unknown etiology, associated with drug exposure and is consistent with an immune

phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes. Serological, immunological, and histological (biopsy) data should be used to support the diagnosis of an immune-mediated toxicity. Suspected nivolumab- or relatlimab-related AEs must be documented on an AE or SAE CRF. Identification and treatment of nivolumab- and relatlimab-related AEs can be found in **Appendix B**. Additional guidance can be found in the nivolumab and relatlimab Investigator's Brochures (IB).

Subjects who experience a grade 2 or higher nivolumab- or relatlimab-related AE should be discussed with the IND Sponsor immediately.

4.3. Prohibited and/or Restricted Treatments

The following medications are prohibited during the study:

- Immunosuppressive agents unless they are utilized to treat an AE or as specified in **Sections 4.2** and **4.5**.
- Concurrent administration of any anticancer therapies (investigational or approved) with the exception of subjects in the survival period of the study.
- Use of growth factors unless prior discussion and agreement with the IND Sponsor.
- Use of allergen hyposensitization therapy

Palliative radiotherapy is permitted only under certain conditions as described in **Section 4.5.**

4.4. Other Restrictions and Precautions

Any vaccination containing attenuated or inactivated virus may be permitted if clinically indicated. However, this must be discussed and documented with the IND Sponsor prior to administration and may require a study drug washout period prior to and after administration of the vaccine. Inactivated influenza vaccination will be permitted on study without restriction.

It is the local imaging facility's responsibility to determine, based on subject attributes (e.g., 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 (i.e., estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m2) 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 IRB/Ethics Committee.

4.5. Permitted Therapy

Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Immunosuppressive agents and the use of systemic corticosteroids are permitted in the context of treating AEs, prophylaxis prior to a diagnostic procedure (e.g., contrast MRI/CT scans) or as specified in **Section 4.2**. A brief course of corticosteroids for prophylaxis (e.g., contrast dye allergy) is permitted.

Subjects may continue to receive hormone replacement therapy (HRT).

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

The potential for overlapping toxicities with radiotherapy and relatlimab ± nivolumab is currently not known. Therefore, palliative radiotherapy is not recommended while receiving any of these drugs, alone or in combination. If palliative radiotherapy in short courses and for isolated fields is required to control symptoms, then drug administration should be withheld, if possible, for at least 1 week before radiation and for at least 1 week after its completion. Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy. Prior to resuming study drug treatment, radiotherapy-related AEs should resolve to ≤Grade 1 or baseline and subjects must meet relevant eligibility criteria as determined by the IND Sponsor. The IND Sponsor must be consulted prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks after the last dose.

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 AEs. Subjects receiving palliative radiation of target lesions will have the evaluation of ORR just prior to radiotherapy but such subjects will no longer be evaluable for determination of response subsequent to the date palliative radiation occurs.

For subjects who need to undergo elective surgery (not tumor-related) during the study, it is recommended to hold study drug(s) for at least 2 weeks before and 2 weeks after surgery, or until the subject recovers from the procedure, whichever is longer. Prior to resuming study drug treatment, surgically-related AEs should resolve to ≤Grade 1 or baseline and subjects must meet relevant eligibility criteria as determined by the IND Sponsor. The IND Sponsor must be consulted prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks after the last dose.

4.6. Definition of an Overdose for this Protocol

Overdose of nivolumab or relatlimab is defined as:

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. Appropriate supportive treatment should be provided if clinically indicated.

All reports of overdose (with and without an AE) must be reported within 24 hours to the IND Sponsor, Regulatory Specialist, and Bristol-Myers Squibb (BMS) as an SAE per **Section 6**.

4.7. Unacceptable Toxicity

Unacceptable toxicities are defined as:

1. Any treatment-related ≥ grade 3 AEs. Exceptions include:

    - Asymptomatic laboratory abnormalities
    - Grade 3 fatigue
    - Diarrhea, nausea, or vomiting that resolves to < grade 3 within 24 hours of intervention
    - Grade 3-4 hyperglycemia or grade 3 endocrinopathies where symptoms are controlled on hormone replacement therapy

2. Treatment related blood bilirubin > 5 x ULN or concurrent blood bilirubin > 2 x ULN and AST or ALT > 3 x ULN

3. Treatment related eye pain ≥ grade 2 or reduction of visual acuity that does not respond to topical therapy and does not improve to ≤ grade 1 severity within 2 weeks of starting therapy, or requires systemic therapy is an unacceptable toxicity.

If more than 1 of the first 6 patients experiences an unacceptable toxicity within the first cycle, then enrollment will be halted, and the overall risk-benefit ratio of the study will be reconsidered. At any time thereafter, if more than 33% of patients are observed to experience unacceptable toxicity within the first cycle, then enrollment will be suspended until further review and consideration by the IND Sponsor. There will be no dose reductions for nivolumab or relatlimab.

4.8. WOCBP, Contraception, Use in Pregnancy, Use in Nursing

4.8.1. Definition of 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 in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a documented serum follicle stimulating hormone (FSH) level > 40mIU/mL to confirm menopause.

Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels.

- 1 week minimum for vaginal hormonal products (e.g., rings, creams, gels)

- 4 weeks minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/mL at any time during the washout period, the woman can considered postmenopausal.

4.8.2. Contraception

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 24 weeks after the end of study treatment.*****

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 9**.
- 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)

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

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 33 weeks 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 33 weeks 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.

4.8.3. Use in Pregnancy

The investigational agents used in this protocol may have adverse effects on a fetus; therefore, women with a positive pregnancy test at screening will not be eligible for enrollment. If a subject inadvertently becomes pregnant while on treatment, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated.

Pregnancy in female subjects throughout the study or within 24 weeks of completing treatment as well as any pregnancy in partners of male subjects throughout the study or within 33 weeks of completing the study should be reported initially as a serious adverse event (see SAE reporting procedures in **Section 6.5.1** and **6.5.4**) by the investigator within 24 hours of learning of its occurrence. Pregnancy information must be reported on the Pregnancy Form.

Protocol required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

Follow-up information regarding the course of the pregnancy, including any voluntary or spontaneous termination, perinatal and neonatal outcome and where applicable, offspring information must be reported on the Pregnancy Follow-up Form. Pregnancy outcomes must also be collected for the female partners of any males in this trial. Consent to report

information regarding these pregnancy outcomes should be obtained from the female partner.

4.8.4. Use in Nursing Women

Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

4.9. Duration of Therapy

Subjects who are clinically stable and meet dosing requirements (per **Section 5.2**) may continue to receive treatment per investigator discretion.

4.10. Criteria for Removal from Treatment

The reason for study removal and the date the subject was removed will be documented in the CRF. A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as parent or legal guardian) withdraws consent.

A subject must be discontinued from treatment (but may continue to be monitored in the post-treatment follow-up portion of the trial) for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent for treatment,
- Disease progression as defined in **Section 4.10.1**,
- Intercurrent illness that prevents further administration of treatment,
- Severe or life-threatening nivolumab- or relatlimab-related AE(s) (see **Section 4.10.2**),
- Need for >2 dose delays due to the same related toxicity as per the dose delay guidelines (see **Section 5.2**)
- If in the opinion of the Investigator, a change or temporal or permanent discontinuation of therapy would be in the best interest of the patient (The IND Sponsor should be included in this decision),
- Noncompliance with trial treatment or procedure requirements,
- Patient is lost to follow-up,
- Patient becomes pregnant, or
- Completed 24 months of treatment with nivolumab and relatlimab. Note: 24 months of study medication is calculated from the date of the first dose.

4.10.1 Disease Progression

Nivolumab and relatlimab are expected to trigger immune-mediated responses, which require activation of the immune system prior to the observation of clinical responses. Such immune activation may take weeks to months to be evident. Some subjects may have

objective volume increase of tumor lesions or other disease parameters within weeks following the start of immunotherapy. Such subjects may not have had sufficient time to develop the required immune activation or, in some subjects, tumor volume or other disease parameter increases may represent infiltration of lymphocytes into the original tumor. In conventional studies, such tumor volume or relevant laboratory parameter increases during the first 2-4 months of the study would constitute disease progression and lead to discontinuation of imaging to detect response, thus disregarding the potential for subsequent immune-mediated clinical response. This phenomenon was observed in approximately 10% of subjects in the Phase 1 study of nivolumab and has also been reported for ipilimumab monotherapy[38].

Subjects will be permitted to continue with treatment beyond RECIST 1.1 defined PD as long as they meet the following criteria:

- No symptoms or signs, including worsening of laboratory values, indicating disease progression*
- Investigator-assessed clinical benefit, and
- Subject is tolerating study drug.

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. The following criteria need to be taken into consideration:

- No decline in ECOG performance status.
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

*An exception to the above may be made for patients with PD who have only local symptoms that are amenable to radiation.

All decisions to continue treatment beyond PD must be discussed with the IND Sponsor and documented in the study records.

Tumor assessments will be made using RECIST 1.1 and iRECIST (**Appendix C and D**).

4.10.2 Nivolumab- and Relatlimab-Related Adverse Events Requiring Permanent Discontinuation

Permanent discontinuation of all study treatment should be considered for any of the following:

1. Severe or life-threatening related AEs, including, but not limited to, any of the following (the IND Sponsor and BMS must be notified in the event of these AEs):
    - Any grade 2 treatment-related uveitis, 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 AE lasting > 7 days or recurs, with the following exceptions:
    - Grade 3 treatment-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
    - Grade 3 treatment-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
    - Grade 3 treatment-related laboratory abnormalities do not require treatment discontinuation except:
        - Grade 3 treatment-related thrombocytopenia > 7 days OR that is associated with bleeding requires discontinuation
        - Any treatment-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
            - ALT or AST > 8 x ULN, regardless of duration, or
            - ALT or AST > 5 x and ≤ 8 x ULN, that fails to return to ≤ Grade 1 within 2 weeks despite medical intervention, or
            - Total bilirubin > 5 × ULN, or
            - Potential drug-induced liver injury (DILI) event **(Section 6.5.5)**
        - Elevated troponin ≥ Grade 3 requires discontinuation (except Grade 3 elevation without other signs of cardiac toxicity as determined by cardiac evaluation)
- Any grade 4 treatment-related AE or laboratory abnormality, except for the following events which do <u>not</u> require discontinuation:
    - Grade 4 neutropenia ≤ 7 days
    - Grade 4 lymphopenia and leukopenia.
    - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations.
    - 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 treatment-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose

intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the IND Sponsor.

- Any dosing interruption lasting > 6 weeks with the following exceptions:
  - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the IND Sponsor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
  - Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the IND Sponsor. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the IND Sponsor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab or relatlimab dosing.

In order to standardize the management of AEs for all subjects, treatment management algorithms are included in **Appendix B**. Additional AE treatment management algorithms included in the nivolumab and relatlimab IB might be considered for individual cases.

4.11. End of Treatment (EOT)

All subjects will return to the study site 30 days (± 7 days) after the last dose of study drug (or within 7 days prior to initiation of a new anti-cancer treatment, whichever comes first) for an EOT evaluation. Procedures and assessments performed at this visit and beyond should follow the respective guidelines described in **Sections 4.12 and 9** as appropriate.

4.12. Duration of Follow Up

4.12.1 Safety Follow-up

Subjects who discontinue treatment should be contacted by telephone or email at 100 days (+ 14 day reporting window) from their last dose of study drug or within 7 days before initiation of a new antineoplastic treatment (whichever comes first) to assess for treatment

related toxicities. In addition, all SAEs occurring during this time should be reported as well.

Subjects who are discontinued from the study treatment due to an unacceptable drug-related AE will be monitored for safety until the resolution of the AE to ≤ grade 1 or stabilization or until initiation of a new therapy for their cancer, whichever occurs first.

4.12.2 Clinical Follow-up

All enrolled subjects who discontinue treatment without disease progression will enter the clinical follow-up portion of the trial. Subjects will begin the clinical follow-up period after they complete the EOT visit. Clinical follow-up visits will occur every 12 weeks (± 2 weeks) until: 1) start of a new antineoplastic therapy (information of the new cancer therapy will be collected), 2) disease progression, 3) death, 4) withdrawal of consent, or 5) study closure, whichever occurs first. Refer to **Section 9** for the schedule of assessments that should be performed at each visit. After disease progression or start of a new antineoplastic therapy, subjects will enter the survival follow-up portion of the trial (**Section 4.12.3**).

4.12.3 Survival Follow-up

Subjects who discontinue treatment and have disease progression will enter the survival follow-up portion of the trial. Subjects should be contacted every 12 weeks (± 2 weeks) to monitor overall survival. Information of other cancer therapies after discontinuation from the study treatment will be collected as well.

5. DOSING DELAYS/DOSE MODIFICATIONS

5.1. Dose Modifications

Subjects will be monitored continuously for AEs while on study drug. Subjects will be instructed to notify their physician immediately for any and all AEs. Dose escalations or reductions of nivolumab or relatlimab will not be allowed.

[redacted], patients who enrolled prior to Amendment 7 and are within 8 weeks of their first dose will be dose reduced to 160mg or 480mg relatlimab at the discretion of the Principal Investigator. Patients who are past 8 weeks from their first dose may continue to receive relatlimab 960mg or be dose reduced to 160mg or 480mg at the discretion of the Principal Investigator.

5.2. Dose Delays

In some cases, the natural history of select AEs associated with immunotherapy can differ from and be more severe than AEs caused by other therapeutic classes. Early recognition and management may mitigate severe toxicity.

Guidance for Investigators is provided in the current relatlimab and nivolumab Investigator's Brochures. Additionally, management algorithms have been developed to assist Investigators with select toxicities and can be found in **Appendix B.** Toxicities for which management algorithms have been developed include:

- Pulmonary
- Gastrointestinal
- Hepatic
- Endocrine
- Dermatologic
- Neurologic
- Renal
- Myocarditis

Subjects who experience the following must have all study drugs held:

- Select drug-related AEs and drug-related laboratory abnormalities:
  - Grade ≥ 1 pneumonitis
  - Increase from baseline of ≥ one grade (to at least grade 2) of AST, ALT, and/or total bilirubin
  - Grade ≥ 2 creatinine
  - Grade ≥ diarrhea or colitis
  - Grade ≥ 2 neurological AE
  - Grade 4 amylase and/or lipase abnormalities regardless of symptoms or clinical manifestations
  - Troponin >ULN requires a dose delay to allow for prompt cardiac evaluation
    - Between > 1 to 2 × ULN will be permitted if a repeat assessment remains ≤ 2 × ULN and patient undergoes a cardiac evaluation
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study drug.

Subjects not meeting guidelines for permanent discontinuation will be permitted to resume therapy when the treatment-related AE(s) resolve to grade ≤1 or baseline value, with the following exceptions:

- If the toxicity resolves to ≤ Grade 1 or baseline > 6 weeks after last dose, but the subject does not otherwise meet criteria for permanent discontinuation, and the Investigator believes that the subject is deriving clinical benefit, then the subject may be eligible to resume the study drugs following the approval of the IND Sponsor.
- Subjects with grade 4 drug-related amylase and/or lipase increase that is not associated with symptoms or clinical manifestations of pancreatitis can be restarted on therapy once the levels have recovered to grade 3 or less.
- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects with baseline grade 1 AST, ALT or total bilirubin who require dose delays for reasons other than a drug-related hepatic event may resumed treatment in the presence of grade 2 AST, ALT or total bilirubin elevation.

- Subjects who require dose delays for drug-related elevations in AST, ALT, or total bilirubin may resume treatment when these values have returned to their baseline CTCAE grade or normal, provided the criteria for permanent discontinuation are not met.
- Treatment-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.

Subjects eligible to resume study drug will resume study drug at the treatment visit following their last received study drug dose.

The on treatment tumor assessments (i.e., CT/MRI, positron emission tomography [PET], etc.) will continue on an every 8-week schedule relative to the subject's first dose regardless of any treatment delay incurred. Subjects who are required to permanently discontinue both study drugs are listed in **Section 4.10.**

6. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

This study will use the descriptions and grading scales found in the revised CTCAE version 5.0 for AE reporting.

Information about all AEs, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected, recorded, and followed as appropriate.

6.1. Definitions

6.1.1 Adverse Event

An AE is defined as any undesirable sign, symptom or medical condition occurring after starting the study drug (or therapy) even if the event is not considered to be related to the study. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). Medical conditions/diseases present before starting the study treatment are only considered AEs if they worsen after starting the study treatment (any procedures specified in the protocol). New medical conditions / diseases occurring before starting the study treatment but after signing the informed consent form will not be recorded as AEs. Additionally, expected progression of the disease being studied will not be recorded as an adverse event.

Laboratory abnormalities: Laboratory abnormalities present at the screening visit will be recorded as pre-treatment signs and symptoms. After study treatment administration, all grade 3 and 4 clinical laboratory results that represent an increase in severity from baseline will be reported as AEs. A grade 1 or 2 clinical laboratory abnormality should be reported as an AE only if it is considered clinically significant by the investigator (induce clinical signs or symptoms or require corrective therapy), meets the definition of an SAE, or requires the participant to have study drug discontinued or interrupted. It is expected that

wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

6.1.2 Serious Adverse Event

A SAE is an undesirable sign, symptom or medical condition which:

- 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 for exceptions) for >24 hours
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (note: reports of congenital anomalies/birth defects must also be reported on the Pregnancy Form)
- 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 [e.g., 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.
- Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.
- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose
- Is a pregnancy or pregnancy outcome of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, or stillbirth.

Events **not** considered to be SAEs are hospitalizations for:

- 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)
- Admissions as per protocol for a planned medical/surgical procedure or to facilitate a procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission for purpose other than remedying ill health state and was 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 (e.g., lack of housing,

economic inadequacy, care-giver respite, family circumstances, administrative).

6.2. Relationship

The relationship of an AE to the administration of the study drug is to be assessed by the investigator according to the following definitions:

- No (unrelated, not related, no relation): The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.

- Yes (related): The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The following factors should also be considered:

- The temporal sequence from study drug administration - The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication - The other medications the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and pharmacokinetics of the study drug - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

Assessment of Grade:

The investigator will make an assessment of grade for each AE and SAE reported during the study, which will be recorded in the CRF. The assessment will be based on the National Cancer Institute's CTCAE (Version 5.0) and graded as shown below:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Any AE that changes in grade during its course will be recorded in the CRF at the highest level experience by the subject.

6.3. Expectedness

Unexpected AE: An AE, which varies in nature, intensity or frequency from information on the investigational drug/agent provided in the product IB, package insert or safety reports. Any AE that is not included in the IB, package insert, safety reports or informed consent is considered "unexpected". An expected AE with a fatal outcome should be considered unexpected unless the IB specifically states that the AE might be associated with a fatal outcome.

Expected (known) AE: An AE, which has been reported in the IB, package insert or safety reports. An AE is considered "expected", only if it is included in the IB document as a risk.

6.4. Handling of Expedited Safety Reports

In accordance with local regulations, the IND Sponsor (or designee) and BMS will notify investigators of all SAEs that are unexpected (i.e., not previously described in the IB), and related to nivolumab or relatlimab. An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of a SUSAR Report that is to be e-mailed to the investigators and the study coordinators. Upon receiving such notices, the investigator must review and retain the notice with the IB and where required by local regulations, the investigator will submit the SUSAR to the appropriate IRB. The investigator and IRB will determine if the informed consent requires revision. The investigator should also comply with the IRB procedures for reporting any other safety information.

6.5. Reporting

6.5.1 Adverse Events (AEs) and Serious Adverse Events (SAEs)

All AEs (both expected and unexpected) occurring from the first dose of study drug will be captured on the appropriate study-specific case report forms (CRFs).

A non-serious adverse event is an AE not classified as serious. All non-serious AEs (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days (+14 day reporting window) following the last dose of study treatment or before initiation of a new antineoplastic treatment (whichever comes first). Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of

study treatment as appropriate. Non-serious AEs are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [e.g., IND US trial] as part of an annual reporting requirement.

Subjects who experience a grade 2 or higher nivolumab or relatlimab-related AE should be discussed with the IND Sponsor.

Report AEs to the IND Sponsor within 24 hours once identified as an unacceptable toxicity (defined in Section 4.7).

Dung Le: [redacted]

All SAEs (including deaths) occurring from the first dose of study drug, throughout the study, and 100 days (+14 day reporting window) after the last dose of study drug or before initiation of a new antineoplastic treatment (whichever comes first) must be reported. All SAEs that the investigator considers related to the study drug occurring after the follow-up periods must be reported.

SAEs will be reported promptly to the IND Sponsor, Regulatory Specialist, and BMS within 24 hours of recognition of the adverse event using the form found in **Appendix E**. If this falls on a weekend or holiday, an email notification is acceptable but must be followed by an SAE reporting form on the next business day.

SAE reports and any other relevant safety information are to be sent to:

Dung Le:
Jennifer Durham
BMS: [redacted]

6.5.2 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each subject and provide further information to the safety department concerning the subject's condition.

All AE(s) and SAE(s) will be followed until:

- Resolution
- The condition stabilizes
- The event is otherwise explained
- The subject is lost to follow-up
- Death

As soon as relevant information is available, a follow-up SAE report will be submitted to the IND Sponsor and BMS.

6.5.3 Reconciliation of SAEs

The Principal Investigator will reconcile the clinical database SAE cases (case level only) transmitted to the IND Sponsor and BMS Global Pharmacovigilance [redacted]. Frequency of reconciliation should be approximately every 3 months and prior to the database lock or final data summary. BMS GPV&E will email, upon request from the Principal Investigator, the reconciliation report. Requests for reconciliation should be sent to [redacted] and [redacted]. The data elements listed on the BMS GPV&E reconciliation report will be used for case identification purposes. If the Principal Investigator determines a case was not transmitted to the IND Sponsor and BMS GPV&E, the case should be sent immediately to the IND Sponsor and BMS.

6.5.4 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs.

6.5.5 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 under the seriousness category checked as 'other medically important event'. Potential drug induced liver injury is defined as:

1) 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 AST/ALT 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.

6.5.6 Pregnancy Reporting

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial or within 24 weeks following cessation of the study drugs, or pregnancy of a partner of a male subject within 33 weeks of cessation of the study drugs, must be reported by the investigator using the Pregnancy Surveillance Form. All subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion,

missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported to the IND Sponsor and BMS.

Any SAE occurring during pregnancy (pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth) must be recorded on the SAE report form and submitted to the IND Sponsor and BMS.

6.5.7 Institutional Review Board (IRB)

SAEs will be reported to the IRB per institutional guidelines. The following SAEs will be reported to the Johns Hopkins Medicine IRB per institutional guidelines:

1. Deaths, regardless of causality
2. Serious adverse events that are both related and unexpected

Follow-up information will be submitted to the IRB as soon as relevant information is available.

6.5.8 Food and Drug Administration (FDA)

All reporting to the FDA for the trial will be completed by the IND Sponsor.

6.5.8.1 Expedited IND Safety Reports

7 Calendar-Day Telephone or Fax Report:
The IND Sponsor is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the investigational agent. Such reports are to be emailed to the regulatory project manager and faxed [redacted] to the FDA within 7 calendar days of first learning of the event. Follow-up information will be submitted to the FDA as soon as relevant information is available.

15 Calendar-Day Written Report:
The IND Sponsor is required to notify the FDA of any SAE that is unexpected and related to the investigational agent in a written IND Safety Report.

Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed with the IND concerning similar events should be analyzed. The new report should contain comments on the significance of the new event in light of the previous, similar reports.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA within 15 calendar days of first learning of the event. Follow-up information

will be submitted to the FDA as soon as relevant information is available.

6.5.8.2 IND Annual Reports

In accordance with the regulation 21 CFR § 312.33, the IND Sponsor shall within 60 days of the anniversary date that the IND went into effect submit a brief report of the AEs and progress of the investigation. Please refer to Code of Federal Regulations, 21 CFR § 312.33 for a list of the elements required for the annual report. All IND annual reports will be submitted to the FDA by the IND Sponsor.

7. PHARMACEUTICAL INFORMATION

7.1. Agent Accountability

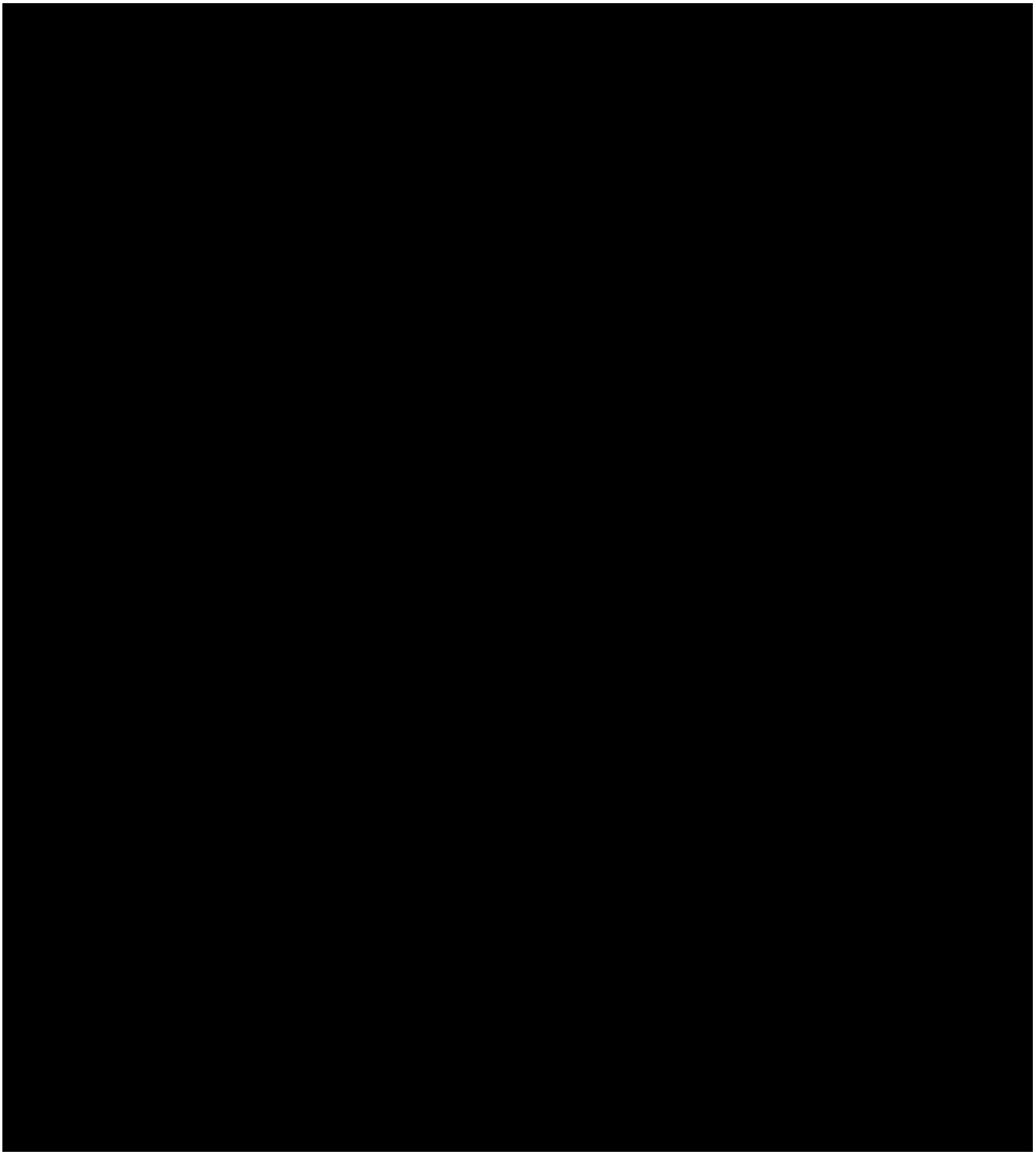
The IND sponsor or the IND Sponsor's representative shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

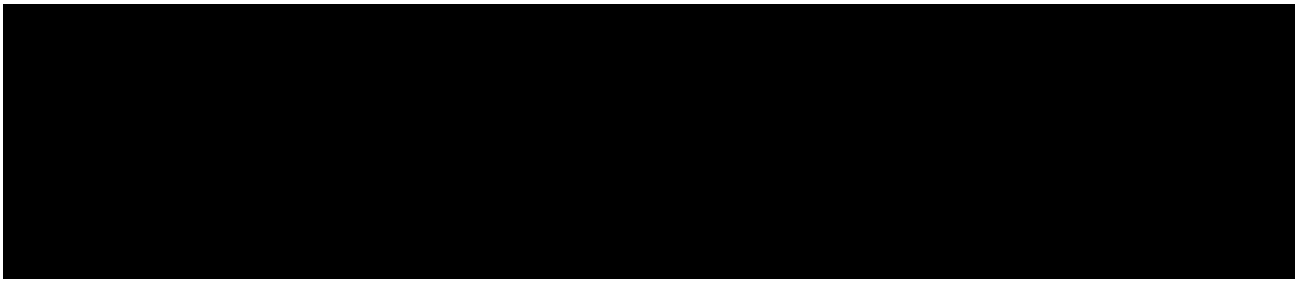
At the end of the study period, Bristol-Myers Squibb Company will not continue to supply study drug to subjects/investigators unless the Sponsor-Investigator chooses to extend their study. The investigator is responsible to ensure that the subject receives appropriate standard of care or other appropriate treatment in the independent medical judgement of the Investigator to treat the condition under study.

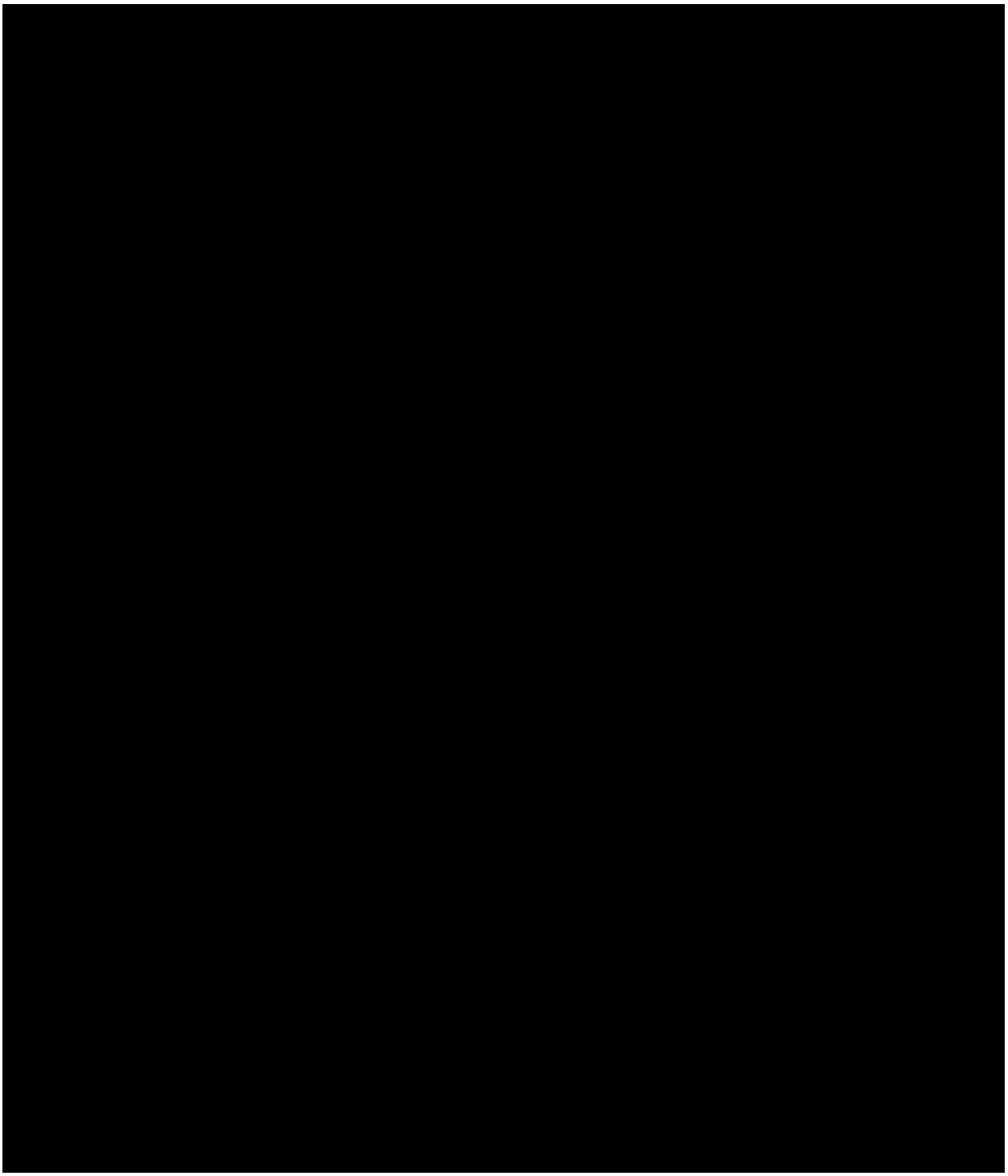
7.2. Mode of Action

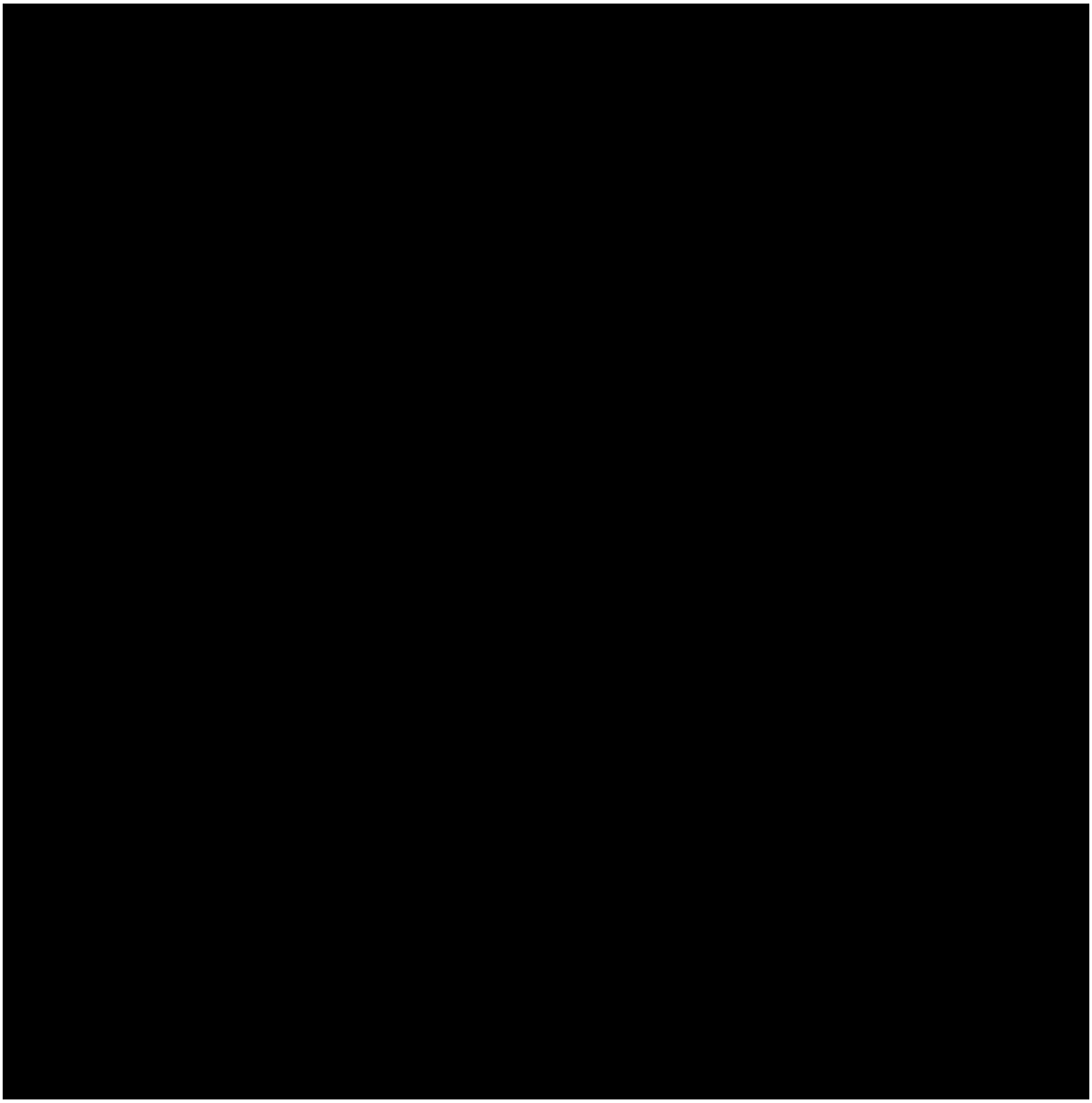
Nivolumab is a fully human monoclonal immunoglobulin (Ig) G4 antibody that binds to the PD-1 cell surface membrane receptor, a negative regulatory molecule expressed by activated T and B lymphocytes. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T cell responses to both foreign antigens as well as self-antigens.

Relatlimab is a fully human monoclonal immunoglobulin (Ig) G4 antibody that binds to the LAG-3 cell surface membrane receptor. LAG-3 is expressed on activated T cells and binds MHC class II with higher affinity than CD4, thereby downregulating the T-cell response. Relatlimab binds to a defined epitope on LAG-3 with high affinity and specificity and potently blocks the interaction of LAG-3 with its ligand, MHC class II, resulting in a reversal of LAG-3-mediated T-cell downregulation.









7.10. Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from BMS or designee, the amount dispensed to, and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. 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.

8. CORRELATIVE/SPECIAL STUDIES

Research samples will be collected at the discretion of the PI based on availability of supplies and safety of patient and staff. Sample collection, processing, storage, and shipment instructions will be provided in the Laboratory Manual.

8.1. Tumor Tissue Studies

Blocks or slides (twenty five unstained slides) will be collected from the surgical resection of each subject's primary tumor for CPM score determination as part of subject pre-screening (Cohort A and B only). CPM score determination for patients in Cohort C will be performed on archived samples at a later timepoint after enrollment. These slides will also be used for the evaluation of additional immune and tumor markers. Slides for CPM score determination will be stained with a hematoxylin and eosin (H&E) and PD-L1. See **Section 3.4** and the Laboratory Manual for additional details regarding tissue collection, processing, storage, and shipment.

Tumor biopsies will be collected (if the subject's tumor is thought reasonably safe and easy to biopsy) per **Section 9**. If a biopsy was done within 28 days before first dose, archived tissue from this biopsy may be used as a baseline sample. Fine needle aspiration samples do not contain sufficient tissue contextual information and will not be obtained. Additional biopsies may be obtained later in course of therapy.

To explore the association of the tumor microenvironment and clinical responses, archived tumor tissue and tumor tissue obtained at baseline and during treatment will be compared. PD-L1 expression may predict response to anti-PD-1 therapy[19]; however, PD-L1 is also upregulated in response to IFN-γ released by infiltrating T cells and could potentially be a predictor of response to any active immunotherapy. Pre- and post-treatment tumor biopsies will also be analyzed with immunohistochemistry and gene expression analysis for expression of T cell subset markers (CD3, CD4, CD8, FoxP3, Granzyme A/B, CD69), immune regulation (PD-L1, PD-L2, CTLA4, LAG-3, IDO1, TIM-3), and immune cell population markers (NK, DC, B cell, MDSC, M1/M2 macrophages).

To explore genetic determinants of response, whole-exome sequencing will be performed on DNA from tumors and matched normal tissue. We will characterize the tumor mutational landscape through exomic sequencing for mutation analysis and MANA prediction.

TCR sequencing will be undertaken to evaluate the T cell repertoire through next-generation sequencing in the tumor tissue for MANAFEST assay and to characterize peripheral immune responses to MANA. Gene expression profiling will also be employed to identify gene signatures within the tumor microenvironment (TME) associated with response and survival.

8.2. Whole Blood

Whole blood will be collected to assess the baseline characteristic of the subjects enrolled and to correlate these molecular and clinicopathologic criteria with treatment response and toxicity. DNA

will be extracted from whole blood and used to evaluate for any germline mutations that may correlate with response or toxicity.

Detailed instructions for sample collection, processing, storage, and shipment are provided in the laboratory manual.

8.3. Peripheral Blood Mononuclear Cells (PBMCs)

PBMCs will be collected per the study calendar. Post-treatment changes in PBMCs including effector, helper, and regulatory T cells, NK cells and macrophages through cell phenotyping analysis and gene expression profiling will be measured. Post-treatment expression of PD-1 and other lymphocyte activation markers will be measured and correlated with OS.

T cells will be isolated and co-cultured with synthetic peptide neoantigens and will undergo TCR sequencing to assess for clonal expansion as previously described[39]. Gene expression will also be conducted on pre- and on-treatment PBMCs.

Detailed instructions for sample collection, processing, storage, and shipment are provided in the laboratory manual.

8.4. Serum and Plasma Marker Studies

Sera and plasma will be collected per the study calendar to identify potential therapeutic targets, biomarkers, and predictors of response (including sLAG-3) and autoimmune toxicity through proteomic approaches. DNA will be extracted from plasma samples and ctDNA levels commonly mutated genes will be assessed.

Detailed instructions for sample collection, processing, storage, and shipment are provided in the laboratory manual.

8.5. Diagnostic Tissue Samples

Tissue, fluid, or blood may be collected from standard of care procedures used to treat or diagnoses immune related toxicities. Detailed instructions for sample collection, processing, storage, and shipment are provided in the laboratory manual.

8.6. Microbiome Studies

Stool and oral wash (and/or buccal mucosal) samples will be collected per the study calendar. Additional samples may be obtained if the patient has any drug-related toxicity at any point during the trial.

Microbial DNA will be isolated from stool and oral wash (and/or buccal mucosal) samples and prepared for 16S rRNA V4 amplicon sequencing to profile microbial species represented in the gut pre- and post-treatment. In addition, microbial DNA will be subjected to whole genome metagenomics profiling of microbial species via shotgun sequencing for detailed functional and

pathway analysis to determine the change in the species and functions in response to treatment. Further bioinformatics analyses will be performed with these sequencing data to identify candidate microbial biomarkers, and predictors of response. Detailed instructions for sample collection, processing, storage, and shipment are provided in the laboratory manual.

8.7. Genomic Analysis

Genomic sequencing library construction, whole genome/exome sequencing, whole transcriptome sequencing, microbial sequencing, neoepitope prediction, mutation burden, and bioinformatic analysis will be performed either at an on-campus laboratory or at an off-campus sequencing service. All the samples will be de-identified before sending to any laboratory for sequencing. The FASTQ files, BAM files and VCF files will be generated and analyzed.

Genomic sequencing data will be stored and computations conducted using a JH IT managed subscription of Azure.

Clinical analysis

Several CLIA-certified laboratories now offer molecular profiling of cancer specimens in commercial and noncommercial settings and provide these results to patients and their physicians (e.g. Foundation Medicine, PGDx, Michigan Center for Translational Pathology, or JHU CLIA Laboratories). It is possible, therefore, that some of our research analyses will be conducted in these CLIA-certified environments. If tissue or cells are evaluated with next generation sequencing strategies to provide a molecular profile of individual cancer specimens in a CLIA-certified facility, these results will be made available to the patient and their physician. Patient confidentiality will be maintained, and the patient's identity will not be publicly linked to any study results. Researchers may use the data set generated in the CLIA assay setting to study genetic alterations across a large number of genes important in cancer. Germline mutations are only identified in punitive cancer genes. Researchers will use the data set for exploratory research to study cancer cell heterogeneity. Some of the sequencing data obtained from the NGS strategies will be uploaded to government sponsored databases, such as GEO and dbGAP. The results of the research studies may be published but subjects will not be identified in any publication.

If a germline alteration of clinical importance (as judged by the Investigator) to the subject and his or her family members is identified by a CLIA-certified test in the course of this analysis, attempts will be made in writing to contact the subject and/or family members for genetic counseling referral.

9. STUDY CALENDAR

9.1. Cohorts A and B

Study Procedures	Pre-screen	Screen	Cycle (28 days)[21]	EOT[22]	Safety FU[23]	Clinical FU[24]	Survival FU[25]
Visit Windows (days)[1]	N/A	-28 to D1	± 3	± 7	+14	± 14	± 14
Nivolumab/ Relatlimab			X				
Informed Consent		X					
Inclusion/Exclusion Criteria		X					
Demographics		X					
Medical, Cancer, & Con Med History[2]		X					
Mucin/PD-L1 CPM	X						
Con Meds, Adverse Events[3]			X	X	X	X	
Physical Exam, ECOG PS[3]		X	X	X		X	
Vitals[4]		X	X	X		X	
Height[5]		X					
Weight		X	X	X		X	
Oxygen Saturation		X	X	X			
Virology[6]		X					
Hematology, Chemistry[7, 12]		X	X	X		X	
Endocrine[8, 12]		X	X	X			
Cardiac Troponin[9, 12]		X	X				
Urinalysis[10, 12]		X					
Pregnancy Test[11, 12]		X	X				
CEA[12]		X	X	X		X	
ECG[13]		X					
Echocardiogram[14]		X					
CT/MRI, RECIST/iRECIST[15]		X	X	X		X	
Whole Blood (up to 10cc) [16, 26]			X				
PBMC[17, 18, 26]			X (see footnote for schedule)				
Plasma (up to 20cc)[17, 26]			X (see footnote for schedule)				
Serum (up to 5cc)[17, 26]			X (see footnote for schedule)				
Stool and Oral Wash Samples[19, 26]			X (see footnote for schedule)				
Microbiome Questionnaire[19]			X (see footnote for schedule)				
Tumor Biopsies[20, 26]		X	X				
Archival Tissue[26]	X						
Survival Follow-up							X

In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

1: If necessary, a scheduled cycle may be delayed for up to 1 week. Longer delays to be approved by the IND Sponsor.
2: Cancer history includes: primary site of cancer, gross location of primary tumor, secondary sites of cancer, histology, histologic grade, date of initial diagnosis, date of metastatic diagnosis, prior cancer therapy regimens, MSI testing, and tumor mutation testing.
3: Complete physical examination and assessment of ECOG PS will be completed at baseline; focused physical examinations and assessment of ECOG PS will be conducted thereafter. Exams, concomitant medication, AE assessments, and ECOG PS can be evaluated up to 3 days prior to infusion.
4: Blood pressure, pulse, and temperature. Vitals will be collected prior to and at the end of the nivolumab/relatlimab infusion (+ 15 minutes).
5: Height will be obtained at or prior to baseline only.
6: Virology screen: HIV antibody, hepatitis B surface antigen and hepatitis C antibody; additional virology may also be evaluated. Subjects who are hepatitis C antibody positive and confirmed negative viral load at screening will be allowed to enroll.
7: Clinical hematology: CBC with differential ANC, ALC, AEC, and platelet count; serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, amylase, lipase, total protein, albumin, calcium, magnesium, and phosphorus. LDH at baseline only.
8: TSH (Total T3 and free T4 if TSH abnormal and clinically indicated).
9: T (cTnt) or I (cTnI). To be obtained on C1D1, C2D1, and C3D1 only. Troponin elevations will require the participant to undergo a cardiac evaluation per **Section 5.2**. Following this evaluation, determination of further treatment will be based on the discussion with the IND Sponsor.
10: Bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, color, protein, RBC and WBC count, and specific gravity.
11: Pregnancy tests will be administered to WOCBP: serum pregnancy test is required at screening; serum or urine pregnancy tests are required before doses on Day 1 of dosing weeks.
12: Labs may be collected within a window of up to 3 days prior to dosing.
13: ECG should be performed at baseline (within 14 days prior to first dose on C1D1), if clinically indicated, or at elevation of troponin levels per **Section 5.2**.
14: LVEF assessment with documented LVEF $\geq$ 50% by either TTE or MUGA (TTE preferred test) within 6 months from first study drug administration.
15: Spiral CT of thorax, abdomen and pelvis (and other imaging studies as clinically indicated to evaluate suspected sites of metastatic disease). If a subject cannot have a CT scan (e.g., allergy to contrast dye), an MRI should be performed. On study radiologic evaluations and tumor measurements (RECIST/iRECIST per **Appendix C and D**) will be at baseline, 12 weeks (+/- 2 week), every 8 weeks (+/- 2 week) through week 52, and then every 12 weeks (+/- 2 week) thereafter including the EOT evaluation (± 4 weeks). The EOT scans do not need to be repeated if

one has been done within the past 6 weeks. Weeks are in reference to calendar week and should not be adjusted due to dosing delays.

16: Baseline only (any time prior to the first dose after eligibility is met)

17: Whole blood for PBMC, plasma, and serum will be collected at baseline (any time prior to the first dose after eligibility is met), 4 weeks (+/- 1 week), every 16 weeks (+/- 2 week) through week 52, and then every 24 weeks (+/- 2 week) thereafter including the EOT evaluation. Weeks are in reference to calendar week and should not be adjusted due to dosing delays.

18: Up to 120cc of whole blood for PBMC isolation will be collected at baseline (any time prior to the first dose after eligibility is met) and at week 4. Up to 150 cc will be collected at subsequent time points.

19: Stool, oral wash (and/or buccal mucosal) specimens, and microbiome questionnaire will be obtained when available. All stool specimens should be collected within 72 hours (and ideally within 24 hours) of the patient's appointment. Baseline specimens may be obtained any time prior to the first dose after eligibility is met. On study stool specimens will be obtained every 12 weeks (+/- 2 week) through week 52, and then annually thereafter including the EOT evaluation (± 4 weeks). Oral wash and/or buccal swab will be collected at baseline, once during treatment and annually thereafter including the EOT evaluation (± 4 weeks). Additional samples may be obtained if the patient has any drug-related toxicity at any point during the trial. Detailed instructions for stool and oral wash collection and shipment are provided in the Laboratory Manual.

20: Tumor biopsies to be taken (if a subject's tumor is thought to be reasonably safe and easy to biopsy) at baseline (any time prior to the first dose after eligibility is met) and at Cycle 2 (4-6 cores per time point). The Cycle 2 biopsy has a ± 1 week window. Additional optional biopsies may be obtained later in the course of study treatment. Fine needle aspiration will not be acceptable. Detailed instructions for tissue collection, processing and shipment are provided in the Laboratory Manual.

21: Cycle 1 Day 1 evaluations do not need to be repeated if they were conducted within 3 days of the pre-study evaluations. Window of +7 days is for cycle 2 and beyond.

22: EOT visit will occur 30 (±7) days after the final dose (or within 7 days prior to initiation of a new anti-cancer treatment, whichever comes first). NOTE: CT scan assessment at EOT will occur 30 days (± 4 weeks) after the final dose. If the EOT visit occurs early, an assessment for AEs should be made by telephone or email on day 30 (±1) after last study dose.

23: Subjects who discontinue treatment should be contacted by telephone or email at 100 days (+ 14 day reporting window) from their last dose of study drug or within 7 days before initiation of a new antineoplastic treatment (whichever comes first) to assess for treatment related toxicities. In addition, all SAEs occurring during this time should be reported as well.

24: Subjects who discontinue treatment without disease progression (**Section 4.12.2**) will enter the clinical follow-up portion of the trial. Clinical follow-up visits will occur every 12 weeks (± 2 weeks) until progression. After disease progression, subjects will enter the survival follow-up portion of the trial.

25: Subjects who discontinue treatment and have disease progression (**Section 4.12.3**) will enter the survival follow-up portion of the trial. Subjects should be contacted every 12 weeks (± 2 weeks) to monitor overall survival. Information of other cancer therapies after discontinuation from the study treatment will be collected as well.

26: Research samples will be collected at the discretion of the PI based on availability of supplies and safety of patient and staff.

9.2. Cohort C

Study Procedures	Screen	Cycle (28 days)[21]	EOT[22]	Safety FU[23]	Clinical FU[24]	Survival FU[25]
Visit Windows (days)[1]	-28 to D1	± 3	± 7	+14	± 14	± 14
Nivolumab/ Relatlimab		X[27]				
Informed Consent	X					
Inclusion/Exclusion Criteria	X					
Demographics	X					
Medical, Cancer, & Con Med History[2]	X					
Con Meds, Adverse Events[3]		X	X	X	X	
Physical Exam, ECOG PS[3]	X	X	X		X	
Vitals[4]	X	X	X		X	
Height[5]	X					
Weight	X	X	X		X	
Oxygen Saturation	X	X	X			
Virology[6]	X					
Hematology, Chemistry[7, 12]	X	X	X		X	
Endocrine[8, 12]	X	X	X			
Cardiac Troponin, CPK[9, 12]	X	X				
Urinalysis[10, 12]	X					
Pregnancy Test[11, 12]	X	X				
CEA[12]	X	X	X		X	
ECG[13]	X					
Echocardiogram[14]	X					
CT/MRI, RECIST/iRECIST[15]	X	X	X		X	
Whole Blood (up to 10cc) [16, 26]		X				
PBMC[17, 18, 26]		X (see footnote for schedule)				
Plasma (up to 20cc)[17, 26]		X (see footnote for schedule)				
Serum (up to 5cc)[17, 26]		X (see footnote for schedule)				
Stool and Oral Wash Samples[19, 26]		X (see footnote for schedule)				
Microbiome Questionnaire[19]		X (see footnote for schedule)				
Tumor Biopsies[20, 26]	X	X				
Archival Tissue[26]	X					
Survival Follow-up						X

In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

1: If necessary, a scheduled cycle may be delayed for up to 1 week. Longer delays to be approved by the IND Sponsor.
2: Cancer history includes: primary site of cancer, gross location of primary tumor, secondary sites of cancer, histology, histologic grade, date of initial diagnosis, date of metastatic diagnosis, prior cancer therapy regimens, MSI testing, and tumor mutation testing.
3: Complete physical examination and assessment of ECOG PS will be completed at baseline; focused physical examinations and assessment of ECOG PS will be conducted thereafter. Exams, concomitant medication, AE assessments, and ECOG PS can be evaluated up to 3 days prior to infusion. Additional weekly visits with AE assessment will occur through Week 8 (C3D1) for patients that received the 480mg or 960mg dose of relatlimab.
4: Blood pressure, pulse, and temperature. Vitals will be collected prior to and at the end of the nivolumab/relatlimab infusion (+ 15 minutes).
5: Height will be obtained at or prior to baseline only.
6: Virology screen: HIV antibody, hepatitis B surface antigen and hepatitis C antibody; additional virology may also be evaluated. Subjects who are hepatitis C antibody positive and confirmed negative viral load at screening will be allowed to enroll.
7: Clinical hematology: CBC with differential ANC, ALC, AEC, and platelet count; serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, amylase, lipase, total protein, albumin, calcium, magnesium, and phosphorus. LDH at baseline only.
8: TSH (Total T3 and free T4 if TSH abnormal and clinically indicated).
9: T (cTnt) or I (cTnI). To be obtained on C1D1, C2D1, and C3D1 only. For patients receiving 480mg or 960mg dose of Relatlimab, cTnt or cTnI AND CPK will also be obtained weekly (± 3 day window) through and including C3D1. Troponin elevations will require the participant to undergo a cardiac evaluation per **Section 5.2**. Following this evaluation, determination of further treatment will be based on the discussion with the IND Sponsor.
10: Bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, color, protein, RBC and WBC count, and specific gravity.
11: Pregnancy tests will be administered to WOCBP: serum pregnancy test is required at screening; serum or urine pregnancy tests are required before doses on Day 1 of dosing weeks.
12: Labs may be collected within a window of up to 3 days prior to dosing.
13: ECG should be performed at baseline (within 14 days prior to first dose on C1D1), if clinically indicated, or at elevation of troponin levels per **Section 5.2**.
14: LVEF assessment with documented LVEF $\geq$ 50% by either TTE or MUGA (TTE preferred test) within 6 months from first study drug administration.
15: Spiral CT of thorax, abdomen and pelvis (and other imaging studies as clinically indicated to evaluate suspected sites of metastatic disease). If a subject cannot have a CT scan (e.g., allergy to contrast dye), an MRI should be performed. On study radiologic evaluations and tumor measurements (RECIST/iRECIST per **Appendix C and D**) will be at baseline, 12 weeks (+/- 2 week), every 8 weeks (+/- 2 week) through week 52, and then every 12 weeks (+/- 2 week) thereafter including the EOT

evaluation (± 4 weeks). The EOT scans do not need to be repeated if one has been done within the past 6 weeks. Weeks are in reference to calendar week and should not be adjusted due to dosing delays.

16: Baseline only (any time prior to the first dose after eligibility is met)

17: Whole blood for PBMC, plasma, and serum will be collected at baseline (any time prior to the first dose after eligibility is met), 4 weeks (+/- 1 week), every 16 weeks (+/- 2 week) through week 52, and then every 24 weeks (+/- 2 week) thereafter including the EOT evaluation. Weeks are in reference to calendar week and should not be adjusted due to dosing delays.

18: Up to 120cc of whole blood for PBMC isolation will be collected at baseline (any time prior to the first dose after eligibility is met) and at weeks 2 and 4. Up to 150 cc will be collected at subsequent time points.

19: Stool, oral wash (and/or buccal mucosal) specimens, and microbiome questionnaire will be obtained when available. All stool specimens should be collected within 72 hours (and ideally within 24 hours) of the patient's appointment. Baseline specimens may be obtained any time prior to the first dose after eligibility is met. On study stool specimens will be obtained every 12 weeks (+/- 2 week) through week 52, and then annually thereafter including the EOT evaluation (± 4 weeks). Oral wash and/or buccal swab will be collected at baseline, once during treatment and annually thereafter including the EOT evaluation (± 4 weeks). Additional samples may be obtained if the patient has any drug-related toxicity at any point during the trial. Detailed instructions for stool and oral wash collection and shipment are provided in the Laboratory Manual.

20: Tumor biopsies to be taken (if a subject's tumor is thought to be reasonably safe and easy to biopsy) at baseline (any time prior to the first dose after eligibility is met) and at Cycle 2 (4-6 cores per time point). The Cycle 2 biopsy has a ± 1 week window. Additional optional biopsies may be obtained later in the course of study treatment. Fine needle aspiration will not be acceptable. Detailed instructions for tissue collection, processing and shipment are provided in the Laboratory Manual.

21: Cycle 1 Day 1 evaluations do not need to be repeated if they were conducted within 3 days of the pre-study evaluations. Window of +7 days is for cycle 2 and beyond.

22: EOT visit will occur 30 (±7) days after the final dose (or within 7 days prior to initiation of a new anti-cancer treatment, whichever comes first). NOTE: CT scan assessment at EOT will occur 30 days (± 4 weeks) after the final dose. If the EOT visit occurs early, an assessment for AEs should be made by telephone or email on day 30 (±1) after last study dose.

23: Subjects who discontinue treatment should be contacted by telephone or email at 100 days (+ 14 day reporting window) from their last dose of study drug or within 7 days before initiation of a new antineoplastic treatment (whichever comes first) to assess for treatment related toxicities. In addition, all SAEs occurring during this time should be reported as well.

24: Subjects who discontinue treatment without disease progression (**Section 4.12.2**) will enter the clinical follow-up portion of the trial. Clinical follow-up visits will occur every 12 weeks (± 2 weeks) until progression. After disease progression, subjects will enter the survival follow-up portion of the trial.

25: Subjects who discontinue treatment and have disease progression (**Section 4.12.3**) will enter the survival follow-up portion of the trial. Subjects should be contacted every 12 weeks (± 2 weeks) to monitor overall survival. Information of other cancer therapies after discontinuation from the study treatment will be collected as well.

26: Research samples will be collected at the discretion of the PI based on availability of supplies and safety of patient and staff.

27: If nivolumab and relatlimab are being administered sequentially (due to Relatlimab 480 or 960mg dose), the order of administration is nivolumab followed by relatlimab. Subjects should be observed for a minimum of 30 minutes between each infusion.

10. STUDY ENDPOINTS

10.1. Primary Endpoint

The primary endpoint is ORR, which is defined as the proportion of subjects with PR or CR according to RECIST 1.1. Subjects who discontinue due to toxicity or clinical progression prior to post-baseline tumor assessments will be considered as non-responders. Subjects who discontinue for reasons other than toxicity or clinical progression prior to the post-baseline tumor assessments or for other reasons prior to their first dose of study drug will be replaced and not included in the primary efficacy analysis.

10.2. Secondary Endpoint

The secondary endpoint is as follows:

Safety assessed by the following measures:

- Number of patients who have grade 3 or higher drug-related toxicities
- Frequency of drug-related toxicity by grade
- Nivolumab- and relatlimab-related infusion reactions
- Immune-related AEs
- Unacceptable toxicities
- Vital signs: BP, pulse, respiratory rate, temperature
- Physical examination
- Changes in ECG readings
- Clinical hematology: complete blood count (CBC) with differential ANC, ALC, AEC, and platelet count
- Clinical serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, LDH, ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, amylase, lipase, total protein, albumin, calcium, magnesium, and phosphorus
- TSH, T3, Free T4
- Cardiac troponin

10.3. Exploratory Endpoints

Exploratory endpoints are as follows:

- Overall survival (OS), progression free survival (PFS), time to-progression (TTP), disease control rate (DCR), best overall response (BOR), duration of response (DOR), duration of clinical benefit (DCB), and time to objective response (TTOR) measured by RECIST 1.1 (**Appendix C**).
  - Overall survival (OS) is defined as the number of months from the date of first treatment until death or end of follow-up (OS will be censored on the date the subject was last known to be alive for subjects without documentation of death at the time of analysis).
  - Progression-free survival (PFS) is defined as the number of months from the date of first treatment to disease progression (PD or relapse from CR as assessed using

RECIST 1.1 criteria) or death due to any cause. PFS will be censored at the date of the last scan for subjects without documentation of disease progression at the time of analysis. iPFS is defined as the time to iUPD if the next scan (4-8 weeks later) confirms PD (state change from iUPD to iCPD, time to progression defined in this instance as iUPD).
  - Disease Control Rate (DCR) is defined as the percentage of subjects achieving stable disease or better (SD + PR + CR).
  - Best Overall Response (BOR) is defined in **Appendix C.**
  - Duration of Response (DOR) is defined as the number of months from the first documentation of a response to date of disease progression.
  - Duration of Clinical Benefit (DCB) is defined as the number of months from the date of first treatment to date of disease progression in those achieving a PR or CR.
  - Time to Objective Response (TTOR) is defined as the number of months from the date of first treatment to the date of documented partial or complete response.
  - Time to-progression (TTP) is defined as the number of months from the date of first treatment to the date of documented disease progression (PD or relapse from CR as assessed using RECIST 1.1 criteria). It differs from PFS in that it does not include death in the definition of an event. TTP will be censored at the date of the last scan for subjects without documentation of disease progression at the time of analysis.
- iORR by immune-related RECIST criteria (iRECIST).
- Immune subset analysis by IHC and gene expression profiling of the tumor
  - Sequencing of tumor
  - Assessment of tumor burden dynamics using standard protein biomarkers when available as well as circulating biomarkers (i.e. ctDNA).
  - Immune subset analyses by FACS in PBMCs including effector, helper, and regulatory T cells, NK cells and macrophages
  - T cell receptor (TCR) repertoire analysis in PBMCs and tumors
  - Gene expression analysis of PBMCs
  - Microbial community analysis and whole metagenome functional profiling analysis of stool and oral wash samples.

11. DATA REPORTING/ REGULATORY REQUIREMENTS

AE guidelines and instructions for AE reporting can be found in **Section 6 (Adverse Events: List and Reporting Requirements)**.

Dr. Dung Le will be holding the IND for this study. She will comply with all regulated reporting requirements to the FDA.

11.1. Data Collection and Processing

All information will be collected on study-specific CRFs by study staff. These data will be reviewed for completeness and accuracy by the Principal Investigator at each site.

CRFs will be used to capture study results and data. The study coordinator or other authorized study personnel will transcribe data from source documents onto eCRFs. Before or between visits, the IND Sponsor, or designee may request copies of the CRFs for preliminary medical review. Once the CRFs are complete and source-verified, the investigator must sign and date all required pages, verifying the accuracy of all data contained within the CRF.

11.2. Safety Meetings

Scheduled meetings will take place weekly and will include the protocol principal investigator, study coordinator(s), data manager(s), sub-investigators (as appropriate), collaborators (as appropriate), and biostatisticians (as appropriate) involved with the conduct of the protocol. During these meetings matters related to the following will be discussed: safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for objectives.

11.3. Monitoring

The SKCCC Compliance Monitoring Program will provide external monitoring for JHU-affiliated sites in accordance with SKCCC DSMP (Version 6.0, 02/21/2019). The SMC Subcommittee will determine the level of patient safety risk and level/frequency of monitoring. The PI shall internally monitor the progress of the trial, including review and confirmation of all safety/treatment-related outcomes, response assessments, safety reports and/or any related source documentation. The protocol will be monitored externally by the SKCCC CRO QA Office. Additional data and safety monitoring oversight will also be performed by the SKCCC Safety Monitoring Committee (SMC - as defined in the DSMP).

Dr. Le is holding the IND for this study. She will comply with all regulated reporting requirements to the FDA.

11.4. Study Documentation

11.4.1 Informed Consent and Authorization for use and Disclosure of Protected Health Information

Written informed consent and authorization of use and disclosure of protected health information (PHI) must be obtained from each subject (or the subject's legally authorized representative) before performing any study-specific screening/baseline period evaluations. The ICF and authorization for use and disclosure of PHI, which is prepared by the investigator or the site, must be reviewed and approved by the IND Sponsor, the study monitor (if applicable), and the site's IRB before the initiation of the study.

11.4.2 Investigator Study Files

Documentation about the investigator and study staff, the IRB and the institution, is required before study site initiation. A list of required documents will be provided by the

IND Sponsor or designee to each participating investigator. Copies of these documents as well as supplemental information, such as the investigator's obligations, IB, clinical study protocol and amendments, safety information, investigational agent information, biological samples and laboratory procedures, SRM, study logs and IND Sponsor/investigator/study monitor correspondence will be kept on-site in study site-specific binders.

The IND Sponsor or designee will be responsible for maintaining original and backup of all CRF data. The investigator is responsible for maintaining backup of all electronic data systems used for primary documentation or source documentation. Backup of electronic data will be performed periodically as described in the site-specific SOPs. Backup records must be stored at a secure location on site and backup and recovery logs must be maintained to facilitate data recovery. If an electronic medical records system that is not supported by the IND Sponsor or designee (or is discontinued or decommissioned) is used, the investigator must maintain a system to retrieve these records or arrange for the transfer of these records to an alternate electronic format or to paper.

Changes to any electronic records require an audit trail, in accordance with 21 CFR 11.10(e), and should include who made the changes and when and why the changes were made. An audit trail is defined as a secure, computer-generated, time-stamped electronic record that will allow reconstruction of the course of events relating to the creation, modification and deletion of an electronic record. Audit trails must be created incrementally, in chronological order and in a manner that does not allow new audit trail information to overwrite existing data. Audit trails should be in a readable format and readily available at the study site and any other location where electronic study records are maintained.

Audit trails are generated automatically for eCRFs. The investigator is responsible for maintaining audit trails of all electronic data systems used for primary documentation or source documentation.

11.4.3 Case Report Forms and Source Documentation

The investigator must make study data accessible to the site monitor, to other authorized representatives of the IND Sponsor (or designee) and to the appropriate regulatory authority inspectors. The original CRF for each subject will be checked against source documents at the study site by the site monitor.

11.4.4 Retention of Study Documents

According to ICH E6, Section 4.9, all CRFs, as well as supporting paper and electronic documentation and administrative records, must be retained for at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications, or at least 2 years have elapsed since the formal discontinuation of clinical development of an individual product. Longer retention periods may apply. The IND Sponsor will notify investigators as to when documents no longer need to be retained. No study documents will be destroyed or moved to a new location without prior written

approval from the IND Sponsor. If the investigator relocates, retires or withdraws from the clinical study for any reason, all records required to be maintained for the study should be transferred to an agreed-upon designee, such as another investigator at the institution where the study was conducted.

Audit trails for electronic documents must be retained for a period at least as long as that required for the subject electronic records to which they pertain. The investigator must retain either the original or a certified copy of audit trails.

11.4.5 Data Confidentiality and Subject Anonymity

All information about the nature of the proposed investigation provided by the IND Sponsor or their representative to the investigator (with the exception of information required by law or regulations to be disclosed to the IRB, the subject or the appropriate regulatory authority) must be kept in confidence by the investigator.

The anonymity of participating subjects must be maintained. Subjects will be identified by their assigned subject number on CRFs and other documents retrieved from the site or sent to the IND Sponsor, study monitor, BMS, regulatory agencies, or central laboratories/reviewers. Documents that identify the subject (e.g., the signed ICF) must be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing by the appropriate regulatory authority, the study monitor, IND Sponsor or their representative.

12. STATISTICAL CONSIDERATIONS

12.1. Study Design/Endpoints

Sample Size

This is an open-label, two stage, phase 2 study to evaluate the safety and clinical activity of nivolumab and relatlimab in patients with metastatic or locally advanced microsatellite stable (MSS) colorectal cancer that have a positive and negative composite PD-L1/Mucin (CPM). The primary endpoint is objective response rate (ORR) assessed using RECIST 1.1.

The trial will enroll two cohorts of MSS mCRC patients receiving 480mg nivolumab/160mg relatlimab: patients with MSS colorectal adenocarcinomas who have a positive CPM score (Cohort A); and patients with MSS colorectal adenocarcinomas who have a negative CPM score (Cohort B). The cut-off threshold $\geq$ 15% of CPM will be used to determine CPM positivity. An additional cohort of MSS mCRC patients without biomarker selection will be enrolled to receive 480mg nivolumab/960mg relatlimab or 480mg nivolumab/480mg relatlimab (Cohort C).

Each cohort will enroll up to 32 evaluable patients. The primary endpoint is objective response rate (ORR) per RECIST 1.1, and the three cohorts will be analyzed separately for the primary analysis of rate of ORR. For each cohort, the treatment will be considered inactive and of no interest for further evaluation if the ORR is 5% or less and considered active if the ORR is 20% or

greater. This design allows for evaluating the efficacy of the treatment and CPM as a predictive marker simultaneously.

Simon two-stage minimax design is planned for each cohort. Initially, 18 patients per cohort will be treated in stage 1. Patients will be considered evaluable if they receive at least one dose of study treatment. If there is at least 1 response in that cohort then an additional 14 patients will be enrolled in stage 2 for a total of 32 patients in that cohort. If a total of 4 or more responses are observed in stage 1 and 2 combined, we conclude the regimen is promising and warrant further study. This design has 90% power to reject the null response rate of 5% in favor of 20% response rate, with one-sided type 1 error 0.1.

We expect that the prevalence of a positive CPM score is 10-15% among MSS CRC patients. Therefore, we will need to screen 220-320 MSS CRC patients in order to identify 32 marker positive MSS CRC patients. Assuming 95% of CRC patients are MSS, we will screen a total of 235-340 CRC patients.

Statistical Analyses

The primary endpoint is objective response rate, defined as complete response (CR) or partial response (PR) per RECIST 1.1. Objective response rate (ORR) will be estimated as the proportion of subjects whose best overall response is either a CR or PR with corresponding 95% CI. The primary population for the analysis is all subjects who receive at least one dose of study drug, and have at least one post-baseline tumor assessments or discontinue due to toxicity or clinical progression prior to post-baseline tumor assessments.

Exploratory endpoints include progression-free survival (PFS), overall survival (OS), and duration of response (DOR). PFS is defined as the time from the first day of study treatment to the date of the first documented tumor progression or death due to any cause, whichever occurs first. Subjects who did not progress or die will be censored on the date of their last tumor assessment. Kaplan-Meier curves will be used to summarize PFS. Overall survival (OS) is the time from the first day of study treatment to the date of death due to any cause. A subject who has not died will be censored at last known date alive. Kaplan-Meier curves will be used to summarize OS. Among patients with an objective response, DOR is defined as the time between the date of initial complete or partial response to the date of the first documented tumor progression or death due to any cause. Subjects who neither progress nor die will be censored on the date of their last tumor assessment. Summary statistics will be presented for DOR.

For biomarkers, potential relationships between biomarker data and efficacy or safety endpoints will be investigated aimed at identifying baseline biomarkers that may be used to prospectively identify subjects likely (or not likely) to respond to the treatment and to identify subjects who may be predisposed to having adverse reactions to treatment. These exploratory biomarker analyses will be completed with biomarkers measured in blood and in tumor samples.

The performance of the PD-L1/mucin composite score (CPM) in predicting treatment response will be further evaluated. ROC analysis based on logistic regression will be used to assess the

prediction accuracy, and the cutoff threshold for identifying patients who may benefit the therapy will be validated.

Genomic sequencing library construction, whole genome/exome sequencing, whole transcriptome sequencing, microbial sequencing, neoepitope prediction, mutation burden, and bioinformatic analysis will be performed either at an on-campus laboratory or at an off-campus sequencing service. All the samples will be de-identified before sending to any laboratory for sequencing. The FASTQ files, BAM files and VCF files will be generated and analyzed.

Genomic sequencing data will be stored and computations conducted using a JH IT managed subscription of Azure.

12.2. Safety Analysis

The safety analysis will be performed in all treated subjects. AE data will be listed individually and incidence of AEs summarized by system organ class and preferred terms within a system organ class for each cohort. When calculating the incidence of AEs, each AE (based on preferred terminology defined by CTCAE version 5.0) will be counted only once for a given subject. In analyses of grade and causality, if the same AE occurs on multiple occasions, the highest grade and strongest relationship to study drug will be assumed. If 2 or more AEs are reported as a unit, the individual terms will be reported as separate experiences.

Changes in vital signs, hematology and clinical chemistry parameters from baseline to the end of the study will be examined. Toxicity will be tabulated by type and grade. Toxicities will be characterized according to the CTCAE version 5.0. Treatment-emergent changes from normal to abnormal values in key laboratory parameters will be identified.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B: MANAGEMENT ALGORITHMS

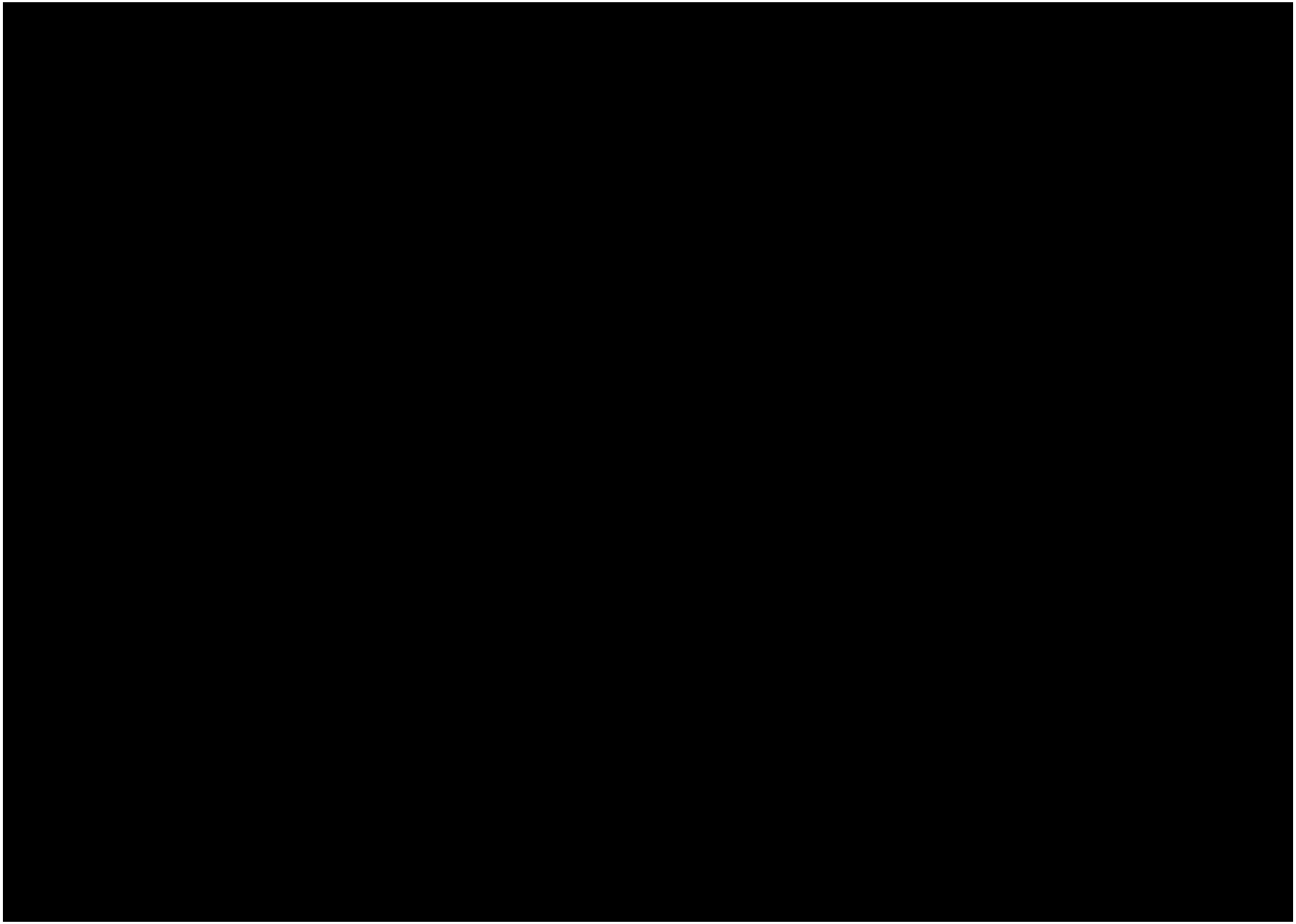
These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the IND Sponsor. The guidance applies to all immuno-oncology (I-O) agents and regimens.

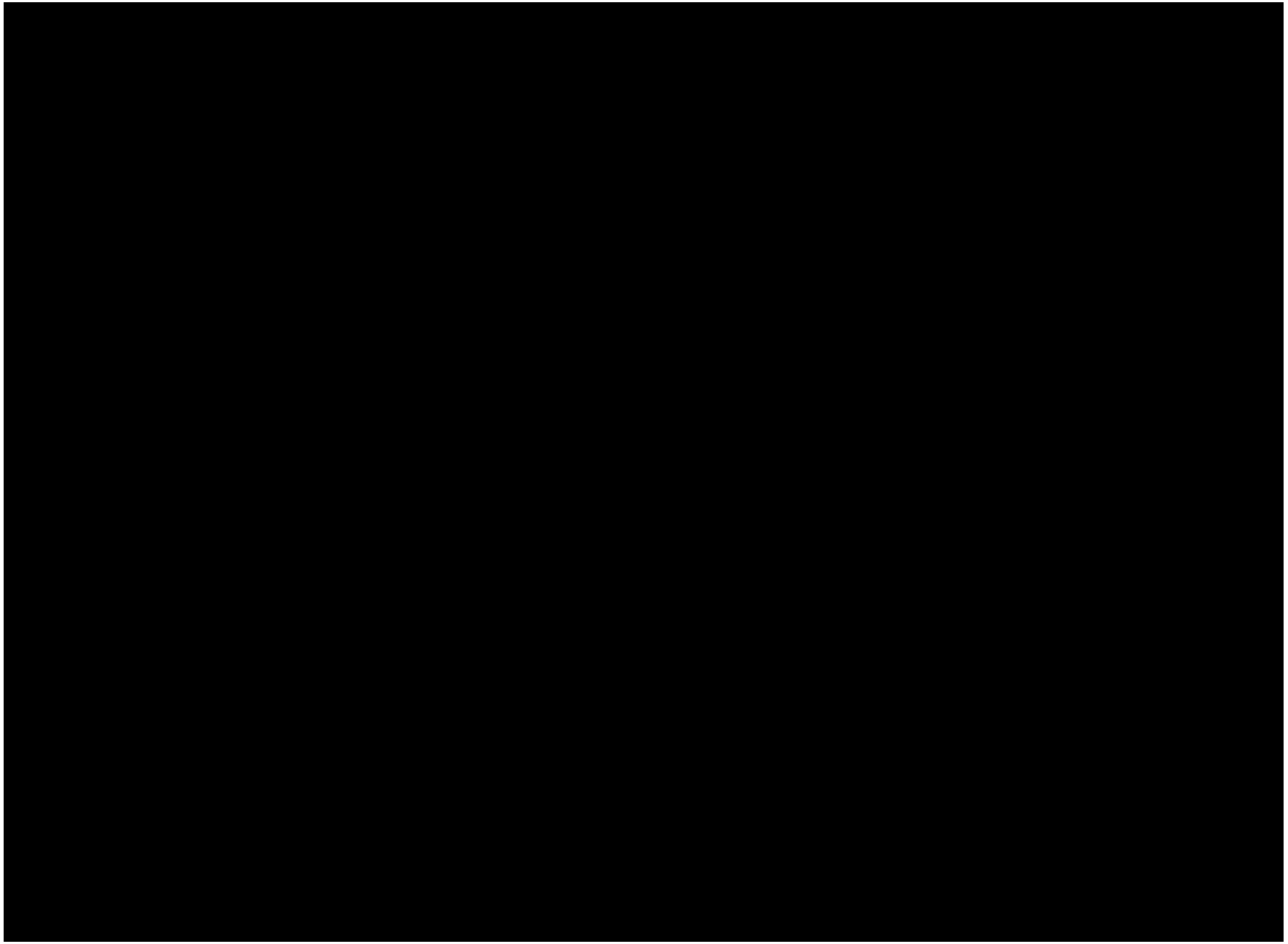
A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

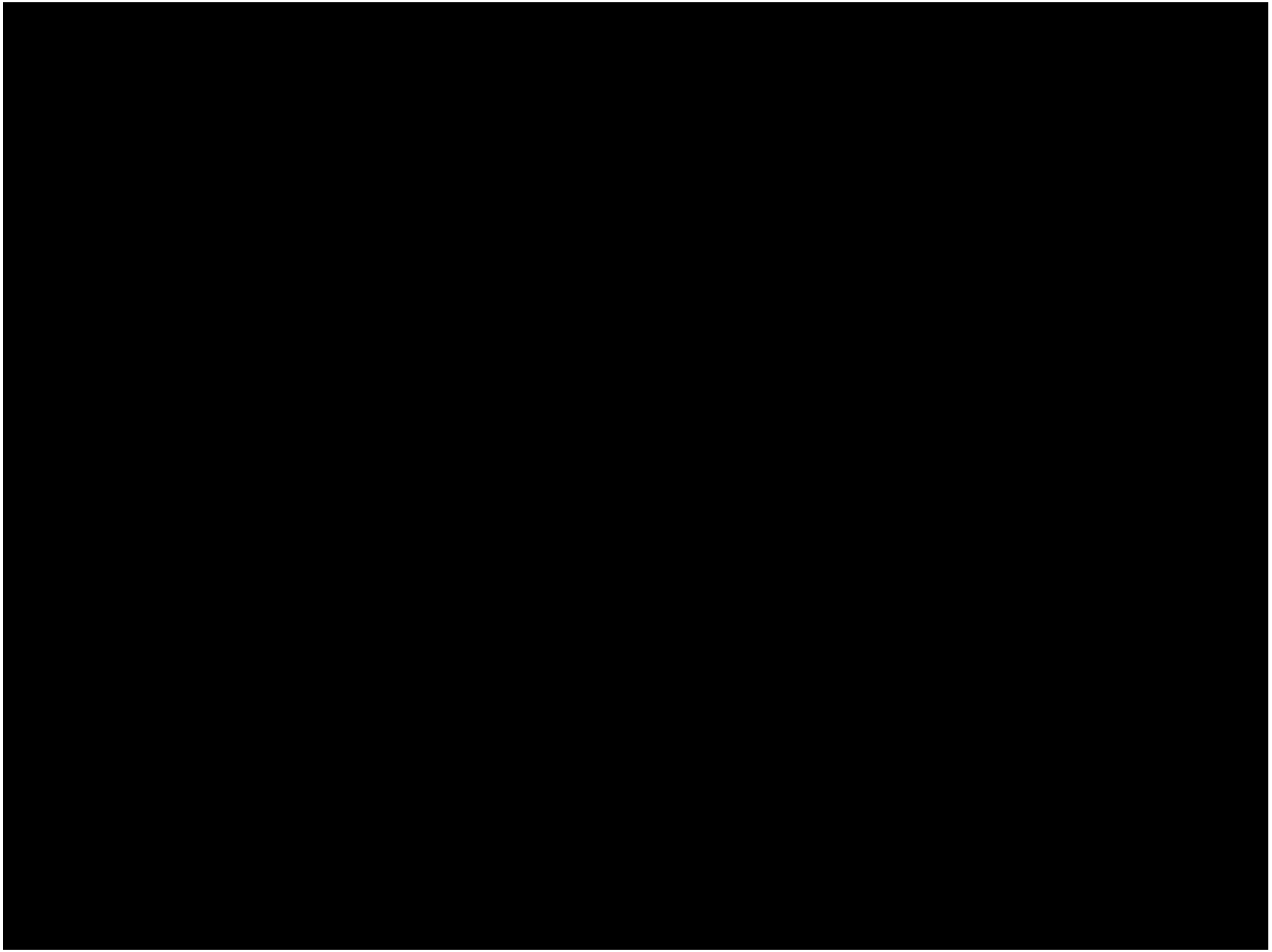
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory subjects with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

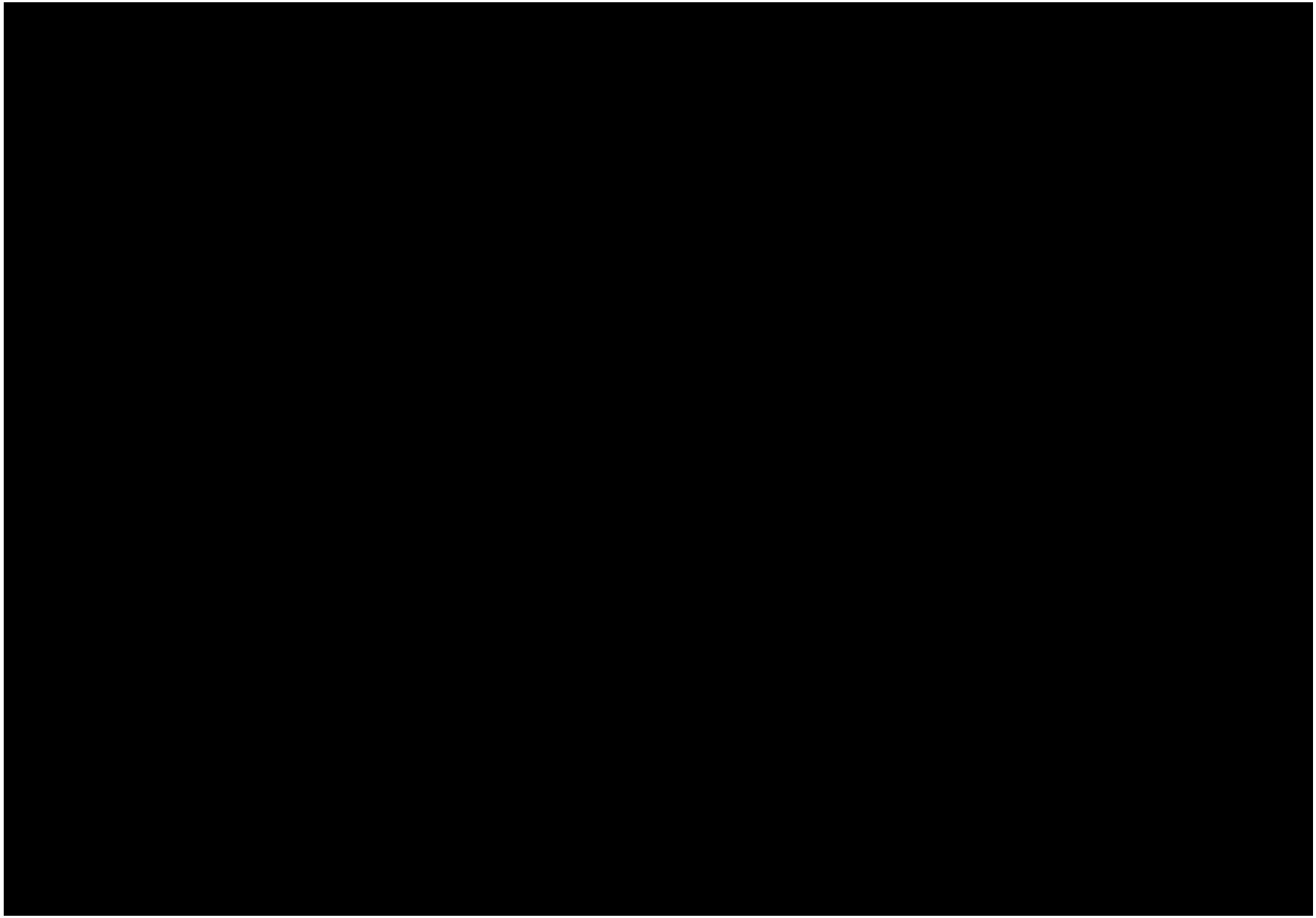
Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

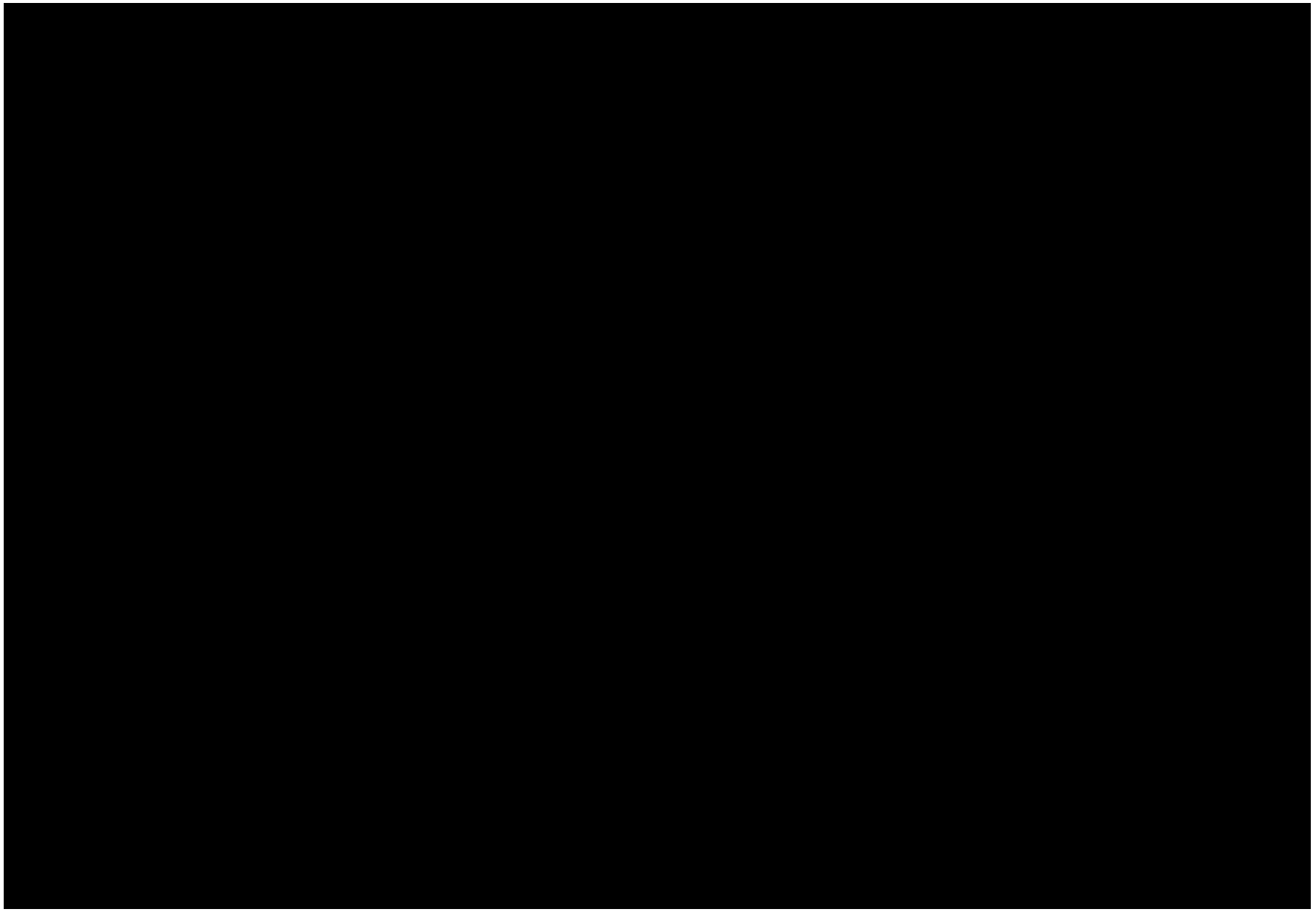
The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

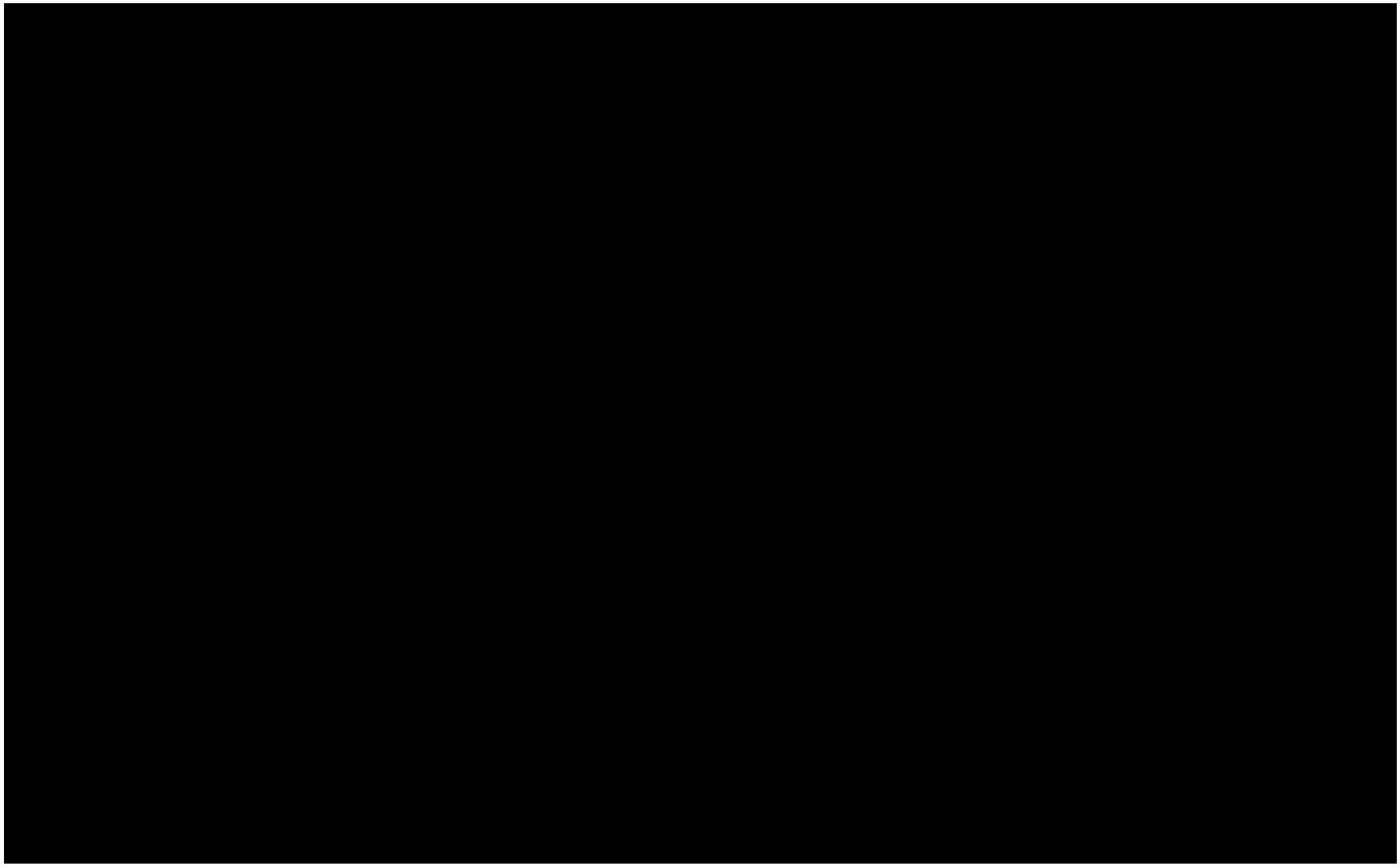


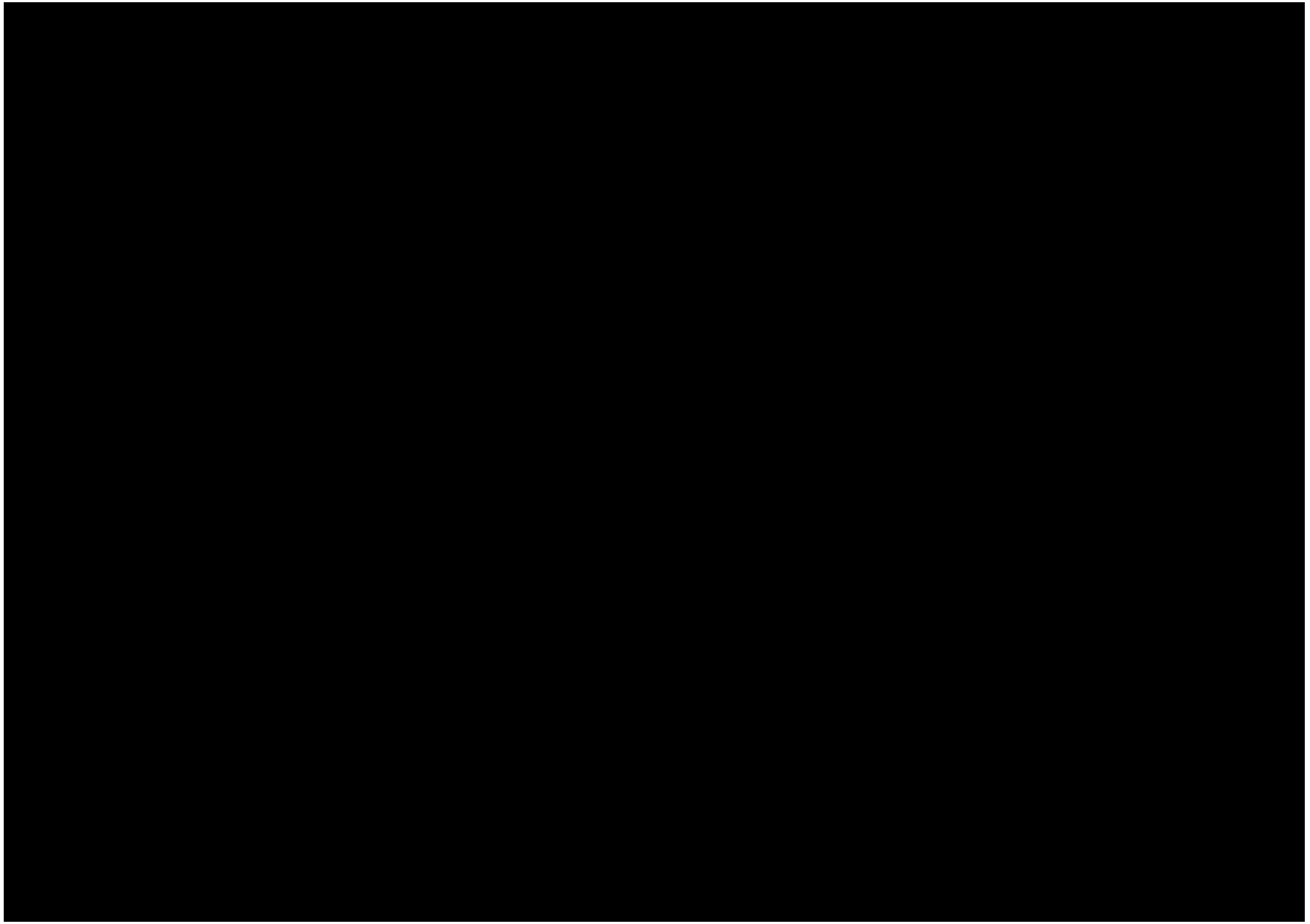












APPENDIX C: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST)
1.1 CRITERIA FOR EVALUATING RESPONSE IN SOLID TUMORS

RECIST version 1.1 will be used in this study for assessment of tumor response. While either CT or MRI may be used utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

> Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable unless there is evidence of progression in the irradiated site. 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). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

> Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
>
> 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. 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 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.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

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 the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the 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 progressions).

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.

Evaluation of Non-Target Lesions

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

Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.

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):Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements

recorded since the treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Subjects with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

Reference

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

APPENDIX D: DESCRIPTION OF THE IRECIST PROCESS FOR ASSESSMENT OF DISEASE PROGRESSION

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

In participants who show evidence of radiological PD by RECIST 1.1 the Investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained using the criteria outlined in **Section 4.10.1**.

If the Investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment.

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥ 20% and ≥ 5 mm from nadir
    - Please note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including **iUPD** (unconfirmed progressive disease) and **iCPD** (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
  - For target lesions, worsening is a further increase in the sum of diameters of ≥ 5 mm, compared to any prior iUPD time point
  - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
  - For new lesions, worsening is any of these:
    - An increase in the new lesion sum of diameters by ≥ 5 mm from a prior iUPD time point
    - Visible growth of new non-target lesions
    - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the scan on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation scan proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression,

whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Detection of Progression at Visits After Pseudo-progression Resolves

After resolution of pseudo-progression (ie, achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the PD threshold (≥ 20% and ≥ 5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions
  - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
  - If non-target lesions had shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.
- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, except in one respect. If new lesions occurred at a prior instance of iUPD, and at the confirmatory scan the burden of new lesions has increased from its smallest value (for new target lesions, their sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication[40].

Table 3: Comparison between RECIST 1.1 and iRECIST

	RECIST 1.1	iRECIST
Definitions of disease: numbers, sites and target or non	Measurable are diameters greater than 10 mm (15 for nodes maximum of 5 (2 per organ)	No change from RECIST 1.1
CR, PR or SD	Cannot have met criteria for progression	Can have had iUPD (more than once) but not iCPD before iCR, iPR or iSD
Confirmation of CR or PR	Only in non-randomized studies	As per RECIST 1.1
Confirmation of SD	Not required	As per RECIST 1.1
New lesions	Progression: recorded but not measured	iUPD but only becomes iCPD if on the next scan there are new lesions or the size increases by greater than 5 mm
Confirmation of progression	Not required	Required
Consideration of clinical status	Not required	Clinical stability considered at iUPD to decide treatment continuation

Table 4: Trajectory of progression in iRECIST

Target Lesions: iCR, Non-target: iCR, no new lesions	iCR	iCR
Target lesions: iCR, Non-target: non iCR/non iUPD, no new lesions	iPR	iPR
Target Lesions: iPR, Non-target: non iCR/non iUPD, no new lesions	iPR	iPR
Target lesions: iSD, Non-target: non iCR/non iUPD, no new lesions	iSD	iSD
Target lesions: iUPD with no change or with a decrease from the last time point, Non-target: iUPD with no change or decrease from last time point, new lesions	NA	New lesions confirm iCPD if new lesions previously identified and increased in size (≥ 5 mm in sum of measures for new lesions or any increase for new lesion non-target) or increase in number. If no change is seen in new lesions assignment remains iUPD

Target lesions: iSD, iPR, iCR, non-target: iUPD, no new lesions	iUPD	Remains iUPD unless iCPD is confirmed by increase in the size of non-targets (does not need to meet RECIST 1.1 criteria)
Target lesions: iUPD, non-target: non iCR/non iUPD, no new lesions	iUPD	Remains iUPD unless iCPD confirmed on the basis of further increase ≥ 5 mm; otherwise stays as iUPD
Target lesions: iUPD, non-target: iUPD, no new lesions	iUPD	Remains iUPD unless iCPD confirmed on previously identified targets iUPD ≥ 5 mm or non-target iUPD
Target lesions: iUPD, non-targets: iUPD, new lesions	iUPD	Remains iUPD unless iCPD confirmed by increase of ≥ 5 mm previously identified target, or non-target or an increase in size or number of new lesions
Target lesions non iUPD or progression, non-targets: non iUPD or progression, new lesions	iUPD	Remains iUPD unless iCPD confirmed by increase in size or number of new lesions previously identified.

Target lesions, non-target lesions and new lesions are defined according to RECIST 1.1 criteria: if no pseudoprogression occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD are the same. * Previously identified in the assessment prior to this time point. 'I' indicates immune responses assigned using iRECIST

APPENDIX E: SAE REPORTING FORM

[redacted]

FAX

TO:	BMS Worldwide Safety	FROM:	
FAX:	[redacted]	PAGES:	
PHONE:		DATE:	
RE:		CC:	

Study:

A Phase 2 study Evaluating Response and Biomarkers in Patients with Microsatellite Stable (MSS) Advanced Colorectal Cancer treated with Nivolumab in Combination with Relatlimab (J18119, CA224-068)

Comments:

Please confirm receipt to:

Serious Adverse Event Reporting Form

[redacted]

Protocol Title:	**A Phase 2 study Evaluating Response and Biomarkers in Patients with Microsatellite Stable (MSS) Advanced Colorectal Cancer treated with Nivolumab in Combination with Relatlimab**		
Protocol Number: CA224-068 J18119	**Signature of PI:**	**Principal Investigator:** Dr. Dung Le	**Date of Report:**
Report Type: ☐Initial ☐Follow-up ☐Final Follow-up ☐Death ☐Addendum to:	**Serious Criteria (check all that apply):** ☐Death ☐Life-threatening ☐ Hospitalization or Elongation of Existing Hospitalization ☐ Other Important Medical Event ☐ Cancer ☐ Overdose ☐ Other:_____	**Hospital Admission Date:** **Hospital Discharge Date:**	**Date Event Discovered:**

Section A: Subject Information		
Subject ID:	**Subject Gender:** ☐Male ☐Female	**Subject Age:**

Section B: Event Information			
Event diagnosis or symptoms:	**Event Grade:**	**Cause of death (if applicable):**	**Event Outcome:** ☐ Not Recovered ☐ Recovering ☐ Recovered ☐ Recovered with sequelae ☐ Death ☐ Unknown
Event Onset Date (or Date of Death):		**Event End Date:**	

Section C: Study Drug Information

Investigational Product: Nivolumab (480 mg) and Relatlimab (160 mg, 480 mg, or 960 mg) IV every 28 days

Indication: Metastatic or locally advanced microsatellite stable (MSS) colorectal adenocarcinoma

Relatlimab Formulation: ☐ With pentetic acid ☐ Without pentetic acid	**Number of Total Cycles:**	**Action taken with the study drug:** ☐ None ☐ Interrupted ☐ Delayed ☐ Discontinued
Relatlimab Dose: ☐ 160 mg (Cohort A/B) ☐ 480 mg (Cohort C) ☐ 960 mg (Cohort C)		
Date of First Dose:	**Date of Last Dose prior to Event:**	

Relationship to:	**Nivolumab**	**Relatlimab**	**Underlying Disease**
Unrelated	☐	☐	☐
Related	☐	☐	☐

Section D: Brief Description of the Event:

Section E: Relevant Tests/Laboratory Data

Section F: Relevant Medical History

Section G: Concomitant Drug (Not related to SAE)

Name of the Drug	**Start Date**	**Stop Date**	**Route**	**Dose**	**Frequency**

Section H: Comments

Additional Documents: ☐ Please specify