Protocol #: CA224-070 / HCC 18-071

ClinicalTrials.gov Identifier: NCT03743766

Title: A Phase II Study of Anti-PD1 Monoclonal Antibody (Nivolumab, BMS-936558) Administered in Combination with Anti-LAG3 Monoclonal Antibody (Relatlimab, BMS-986016) in Patients with Metastatic Melanoma Naïve to Prior Immunotherapy in the Metastatic Setting

Revised Protocol Number: 03
Incorporates Amendment 03

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Protocol Type / Version # / Version Date: *[Revised / 03 / February 08, 2022]*

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 03	February 08, 2022	Incorporates Amendment 03
Amendment 03	February 08, 2022	The following changes were made • Assessment of pathological response (complete, major, partial, no response) on biopsy at 4-week assessment following lead-in treatment was updated in the exploratory endpoints
Revised Protocol 02	December 17, 2021	Incorporates Amendment 02
Amendment 02	December 17, 2021	The following changes were made • Increased number of immunologic analyses from 9 to 42 subjects
Revised Protocol 01	December 18, 2018	Incorporates Amendment 01
Amendment 01	December 18, 2018	The following changes were made • Added NCT number to title page • Revised agent administration guidance in Section 5.1
Original Protocol	September 26, 2018	Not applicable

SYNOPSIS

Title: A Phase II Study of Anti-PD1 Monoclonal Antibody (Nivolumab, BMS-936558) Administered in Combination with Anti-LAG3 Monoclonal Antibody (Relatlimab, BMS-986016) in Patients with Metastatic Melanoma Naïve to Prior Immunotherapy in the Metastatic Setting

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Concept and Rationale:
Melanoma is the most aggressive skin cancer, and patients with unresectable or metastatic melanoma have a poor prognosis. Tumors evade and develop resistance to the immune response by a variety of mechanisms. The goal of immunotherapy is to counteract these immune resistance mechanisms, and to allow the immune system to recognize and reject tumors. Despite recent advances in immunotherapy for patients with metastatic melanoma, the majority of patients still do not achieve a durable response.

With the advent of immune checkpoint blockade (ICB), overall survival has been improved in a subset of patients with unresectable and metastatic melanoma. Anti-PD1 therapy with nivolumab has improved objective response rate (RR), progression-free survival (PFS), and overall survival (OS) compared to chemotherapy in previously untreated patients [1]. The phase III trial CheckMate-067 evaluated previously untreated patients who were randomized to receive nivolumab, ipilimumab, or the combination[2]. In that trial, nivolumab demonstrated RR of 43% compared to RR of 19% with ipilimumab, and the combination demonstrated RR of 57%. PFS was also improved with the combination of nivolumab and ipilimumab compared to either agent alone. However, grade 3 or 4 treatment-related adverse events were seen in 55% of patients in the combination group, compared to 16% in the nivolumab group and 27% in the ipilimumab group. Although toxicity was increased with the anti-CTLA4 and anti-PD1 combination compared to either agent alone, these data suggest that combinations of immune-modulating agents may achieve more robust and prolonged responses than single-agent therapy in melanoma and warrant further exploration.

Lymphocyte activation gene-3 (LAG3; CD223) is a type I transmembrane protein that is expressed on the cell surface of activated CD4+ and CD8+ T cells. It requires binding to major histocompatibility complex (MHC) class II molecules and potentially other unknown ligands for its functional activity. LAG3 negatively regulates CD4+ and CD8+ T cell proliferation, activation, and homeostasis [3, 4], and also contributes to the development, homeostasis, and function of regulatory T cells (T_{regs}) [5].

Extensive co-expression of PD-1 and LAG3 has been demonstrated on tumor-infiltrating CD4+ and CD8+ T cells in melanoma [6]. While blockade of the interaction of PD-1/PD-L1 has

demonstrated restoration of antitumor immune response in both preclinical and clinical studies, LAG3-mediated T cell exhaustion may be a limiting factor in the antitumor immune response. Simultaneous blockade of PD-1 and LAG3 pathways on T cells may reverse this T cell exhaustion. In mouse models, tumor response in recurrent tumors can be achieved with combination treatment with anti-PD-L1 and anti-LAG3 antibodies[6], and dual anti-LAG3 and anti-PD1 antibody treatment has demonstrated responses in patients with tumors resistant to monotherapy [7].

LAG3-mediated T cell exhaustion contributes to inhibition of the antitumor immune response in patients treated with anti-PD-1 monotherapy. The preliminary results of the phase 1/2a dose escalation and cohort expansion study of anti-LAG3 with and without anti-PD1 therapy in patients with metastatic melanoma was recently reported [8]. These pre-treated patients, all of whom had progressed on anti-PD1 therapy, and 47% of whom had failed 3 or more prior therapies, were treated with the combination of nivolumab and anti-LAG3 therapy. Among 48 evaluable patients the objective response rate was 12.5%. Of note, patients with LAG3 expression >1% on tumor-infiltrating lymphocytes (TIL) had a response rate of 20%, compared to 7.1% among patients with <1% LAG3 expression. The combination of nivolumab and anti-LAG3 therapy was well-tolerated, with grade 3 or 4 treatment related adverse events seen in 9% of subjects, which is similar to the frequency seen with nivolumab alone, and no new toxicities were seen compared to nivolumab alone. In preliminary analysis of tumor specimens from first-line advanced melanoma subjects, LAG3 was evaluable by IHC in approximately 90% of cases. Among those evaluable, the rate of LAG-3 positivity, defined as the percentage of LAG3 immune cells ≥ 1% of tissue, was approximately 60%.

We hypothesize that the combination of anti-PD1 and anti-LAG3 treatment will demonstrate antitumor activity in subjects with unresectable melanoma who have not previously been treated with checkpoint blockade immunotherapy in the metastatic setting. This study will evaluate the antitumor activity of anti-LAG3 monoclonal antibody relatlimab and the anti-PD1 monoclonal antibody nivolumab in combination in subjects with unresectable or metastatic melanoma who have not received prior treatment with immunotherapy. The trial is designed with a 1 cycle (4 week) lead-in of anti-LAG3, anti-PD1, and combination anti-LAG3 + anti-PD1 treatment prior to all subjects proceeding to the combination of anti-LAG3+ anti-PD1 treatment. This lead-in design with accompanying tumor biopsies and peripheral blood analyses will enable mechanistic analyses of the effect of LAG3 and PD1 blockade alone and in combination to enhance understanding of mechanisms of response and resistance.

Objectives:
Primary Objective:

- Lead-in phase (4 weeks)
    - Assess change in immune biomarkers by analysis of peripheral blood and tumor biopsy samples taken serially from patients receiving treatment with relatlimab alone, nivolumab alone, and the combination of nivolumab + relatlimab
    - Estimate association between change in immune biomarkers and change in tumor size
- Combination phase
    - CT assessment of objective response rate relative to the beginning of the

combination phase by comparing CT measurements obtained 12 weeks after beginning of combination phase and subsequently at 12 week intervals with reference to CT measurements obtained at completion of initial 4 week lead-in phase

Secondary Objectives:

- To assess the potential clinical benefit of the combination therapy
- To assess the duration of response
- To assess progression-free survival and overall survival
- To assess the safety of the combination of nivolumab and relatlimab
- To evaluate for a correlation between LAG3 expression as assessed by immunohistochemistry (IHC) and/or multiplexed immunofluorescence (IF) at baseline and response to the study treatment
- To assess the change in immune biomarkers by analysis of peripheral blood and tumor biopsies obtained prior to initiating treatment, following 1 cycles (4 weeks) of lead-in treatment, and following 3 cycles of combination treatment in all three groups (12 weeks after initiating combination phase), and at the time of disease progression
- To estimate and compare tumor response profiles that combine both the lead-in and combination phases

Exploratory Objectives:

- Assessment of clinical response at 4 weeks following 1 cycle of assigned lead-in treatment with relatlimab, nivolumab, or the combination of nivolumab + relatlimab
- Assessment of matching peripheral blood lymphocytes and tumor biopsies by single cell RNAseq on 42 subjects
- Assessment of pathological response (complete, major, partial, no response) on biopsy at 4 weeks following 1 cycle of assigned lead-in treatment with relatlimab, nivolumab, or the combination of nivolumab+relatlimab

Primary endpoints:

- Lead-in phase (4 weeks)
    - Mechanistic analysis of immune infiltrate on tumor biopsy and peripheral blood on biopsy performed prior to the first dose of study drug, following 1 cycle (4 weeks) of the assigned treatment for lead-in phase
    - Evaluation of association between change in immune biomarkers and change in tumor size
- Combination phase
    - Antitumor activity of the combination of nivolumab and relatlimab as measured by overall response (defined as complete response + partial response) based on RECIST v1.1 criteria initially assessed at 12 weeks after initiation of combination phase and compared to baseline imaging obtained immediately prior to initiating combination, and subsequently at 12 week intervals until progression, with confirmation of progression determined by target lesion imaging no fewer than 28 days of the initial CT imaging

Secondary endpoints:

- Potential clinical benefit is defined as the combination of complete response, partial response, and stable disease as assessed by RECIST v1.1 initially assessed at 12 weeks after initiation of combination phase and compared to baseline imaging obtained immediately prior to initiating combination, and subsequently at 12 week intervals until progression, with confirmation of progression determined by target lesion imaging no fewer than 28 days of the initial CT imaging
- Duration of response is defined as the time measurement criteria are first met for complete response or partial response (whichever is first recorded) until the first date that progressive disease is objectively documented.
- Progression-free survival is defined as the time between the date of randomization and the first date of documented progression or death due to any cause, whichever occurs first.
- Overall survival is defined as the time between the date of randomization and the date of death due to any cause.
- Safety is measured by adverse events that will be graded using the Cancer Therapy Evaluation Program (CTEP) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Adverse events will be captured during treatment and up to 100 days after discontinuing treatment, with clinical follow-up as determined by treating physician. All subjects who receive at least one dose of relatlimab or nivolumab will be analyzed for safety.
- LAG3 expression will be assessed by IHC on biopsy taken at baseline and correlated with response
- Mechanistic analysis of immune infiltrate on tumor biopsy and peripheral blood performed prior to the first dose of study drug, following 1 cycle (4 weeks) of the assigned lead-in treatment, and following 3 cycles of combination treatment in all three groups (12 weeks after initiating combination phase) for mechanistic analysis of the effects of treatment of anti-LAG3 alone, anti-PD1 alone, and anti-LAG3/PD1 in combination.
- Subjects who achieve complete response, partial response, or stable disease will have an optional but strongly recommended tumor biopsy and peripheral blood draw performed at the time of disease progression for mechanistic analysis of the effects of anti-LAG3 and anti-PD1 treatment

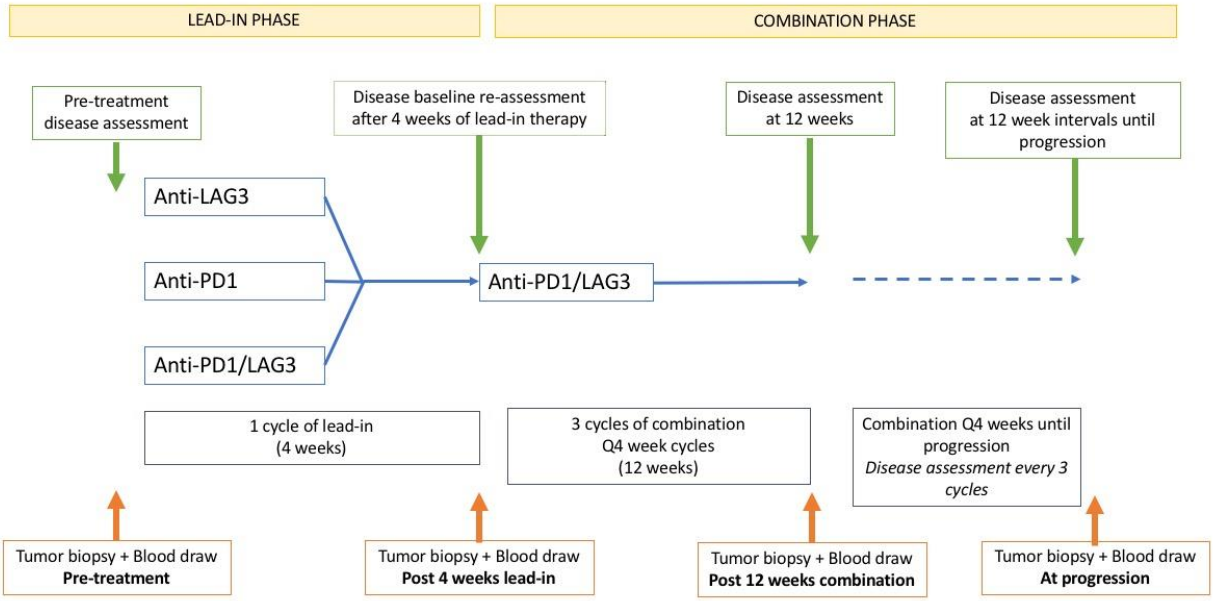
Exploratory Endpoints:

- Overall response as defined by complete response and partial response will be assessed following 1 cycle of assigned lead-in treatment and correlated with mechanistic analysis
- Matching peripheral blood lymphocyte and tumor biopsy samples assessed by single cell RNAseq obtained pre-treatment, following 1 cycle (4 weeks) of assigned lead-in treatment, following 3 cycles of combination treatment in all three groups (12 weeks after initiating treatment) and at disease progression
- Pathological response on biopsy as defined by major pathological response will be assessed following 1 cycle of assigned lead-in treatment and correlated with mechanistic analysis

Study Design:
This is a single center, phase 2 study to evaluate the change in immune biomarkers of treatment with relatlimab alone, nivolumab alone, and the combination of nivolumab/relatlimab and the objective response rate of the combination of nivolumab/relatlimab as compared to historical controls in patients with unresectable or metastatic melanoma who have not received prior treatment with immunotherapy in the metastatic setting.

- Subjects meeting AJCC 8th edition criteria for unresectable stage IIIB, stage IIIC, stage IIID, or stage IV melanoma who have not received prior immunotherapy in the metastatic setting will be eligible.
- In the 4-week lead-in phase, subjects will be randomized to one of three arms for 1 cycle (4 weeks) of lead-in treatment with nivolumab, relatlimab, or the combination of nivolumab and relatlimab. Randomization will be performed via the UPCI Biostatistics Facility randomization system (https://randomize.upci.pitt.edu/randomizer/home.seam).
- Following 1 cycle of lead-in treatment, all subjects will be treated with the combination of relatlimab and nivolumab every 4 weeks.
- Subjects will have tumor biopsies performed prior to initiating treatment, following 1 cycle (4 weeks) of the assigned lead-in treatment at the completion of the lead-in phase, following 3 cycles (12 weeks) of combination treatment in the combination phase, and if had prior response then also at disease progression.
- Clinical response will be assessed at initially at 12 weeks (+/- 1 week) following initiation of combination phase treatment using clinical measurement and CT imaging, and compared to clinical measurement and CT assessment obtained immediately prior to initiation of combination phase. Confirmation of disease progression by RECIST v1.1 criteria will be obtained with target lesion imaging no fewer than 28 days after initial imaging.
- Subjects who demonstrate clinical response or show potential clinical benefit (complete response + partial response + stable disease) will continue treatment every 4 weeks until disease progression, with assessment by CT imaging at 12-week intervals (+/- 1 week). Confirmation of disease progression by RECIST v1.1 criteria will be obtained with target lesion imaging no fewer than 28 days after initial imaging.

Study Schema:



Number of Patients: The study is designed to evaluate 42 subjects, but will allow for accrual of additional subjects if necessary to account for ineligible and untreated patients. Our institution is a major referral center for patients with melanoma, and has more than 500 new patient visits annually for evaluation for melanoma of which greater than one-third are newly diagnosed metastatic melanoma. Based on our institution's clinical volume and prior experience with melanoma clinical trials, we expect accrual of 42 patients to take between 12 to 18 months.

Main Inclusion Criteria:
Men or women 18 years of age or older meeting AJCC 8th edition criteria for unresectable stage IIIB, stage IIIC, stage IIID, or stage IV melanoma who have not received treatment with immunotherapy in the metastatic setting

Main Exclusion Criteria:

- Known or suspected CNS metastases, with the following exceptions:
    - Subjects with controlled brain metastases will be allowed to enroll. Controlled brain metastases are defined as no radiographic progression for at least 4 weeks following radiation and/or surgical treatment at the time of consent. Subjects must be off steroids for at least 2 weeks prior to randomization.
    - Subjects with signs or symptoms of brain metastases are not eligible unless brain metastases are ruled out by computed tomography or magnetic resonance imaging.
- Active autoimmune disease requiring treatment, with the exception of type 1 diabetes mellitus, vitiligo, resolved childhood asthma/atopy, controlled hyper/hypothyroidism, hypoadrenalism or hypopituitarism.
- Prior systemic treatment in the metastatic setting, including anti-PD1, anti-PDL1, anti-PDL2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell

costimulation or immune checkpoint pathways; or chemotherapy.
- Prior adjuvant treatment with anti-PD1, anti-PDL1, and/or anti-LAG3 antibody. Note that prior adjuvant treatment with targeted therapy (e.g. BRAF/MEK inhibition), anti-CTLA4, or treatment not otherwise specified above would be permitted.
- Ocular melanoma

Intervention and Mode of Delivery:
Relatlimab (BMS-986016) is supplied as a sterile 10mg/mL formulation to be administered as an intravenous (IV) infusion at 160 mg IV once every 4 weeks.

Nivolumab (BMS-936558) is supplied as a sterile 10-mg/mL formulation to be administered as an IV infusion at 480 mg IV once every 4 weeks.

Combination therapy will be administered by sequential infusion. Nivolumab administered at 480 mg IV followed by infusion of relatlimab at 160 mg IV once every 4 weeks.

Duration of Intervention and Evaluation: In the lead-in phase, subjects will be randomized 1:1:1 to one of three lead-in treatments: nivolumab alone, relatlimab alone, or the combination of nivolumab + relatlimab for 1 cycle (4 weeks). Following completion of 1 cycle of assigned lead-in treatment, all subjects will have staging CT imaging performed. All subjects will proceed to the combination phase and will be treated every 4 weeks with the combination of nivolumab + relatlimab until time of progression. CT imaging performed for disease assessment will be performed at 12 weeks (+/- 1 week) following initiation of combination phase, and then at subsequent 12 week (+/- 1 week) intervals, with confirmation of disease progression including target lesion measurement or imaging no fewer than 28 days following initial assessment. After trial discontinuation (whether due to subject withdrawal, disease progression, or toxicity), subjects will be evaluated as determined by treating physician. Patients may be contacted for survival follow-up for up to 5 years.

Statistical Methods: The expected clinical response rate with nivolumab in treatment naïve unresectable stage IIIB, stage IIIC, stage IIID, or stage IV melanoma patients is assumed to equal 40%[1, 2]. An increase to 60% due to the addition of relatlimab would be of sufficient interest to warrant further study of this combination in the presence of an acceptable safety profile. A single arm one stage design with $\alpha = \beta = .10$ has been selected that will require 41 patients to provide 90% power for a one sample one tailed exact binomial test. In that patients are to be randomly assigned to one of three lead-in regimens, 42 patients response-evaluable patients will be accrued and complete 12 weeks of treatment. Forty-two patients will permit exactly 14 patients per lead-in group. Additional accrual may be necessary to compensate for patients who do not complete 12 week response evaluation or are otherwise non-evaluable for response.

Patient Acceptability/Ethics and Consent Issues: We anticipate that this study will be favorable to patient accrual. Standard of care at our institution for this study population would be anti-PD1 therapy, and all patients in this single arm study would receive anti-PD1 therapy with nivolumab in addition to the anti-LAG3 monoclonal antibody relatlimab. A potential pitfall is that anti-LAG3 monotherapy may demonstrate efficacy inferior to anti-PD1 monotherapy or anti-PD1/LAG3 in combination, although our study is not powered to detect differences in

clinical response rate among lead-in arms. Due to the short duration of exposure we would expect any antitumor clinical differences between lead-in treatment arms to be not clinically significant. Conversely, if anti-LAG3 monotherapy were to have inferior clinical antitumor efficacy to anti-PD1, we would not expect this short 4-week delay in initiating the combination treatment to affect clinical outcomes, as subjects entering other clinical trials or standard of care therapy may anticipate insurance and other delays in initiating treatment that not infrequently reach 4 weeks. Phase 1/2a expansion cohort data demonstrated a frequency of grade 3 or 4 treatment-related adverse events with the combination therapy that was consistent with prior studies of nivolumab monotherapy. We do not anticipate increased toxicity with the combination, although safety monitoring of the combination is a secondary objective of the trial. The expansion cohort also demonstrated an efficacy signal in the pre-treated population. The requirement of tumor biopsy prior to initiating treatment, at the completion of 4 weeks of lead-in treatment, following 12 weeks of treatment in combination phase, and at the time of progression may be a barrier to patient acceptance, and will be clearly detailed in the consent documentation. This protocol has been reviewed and approved by the Melanoma and Skin Cancer SPORE patient advocates.

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1. OBJECTIVES

1.1 Primary Objectives

- Lead-in phase (4 weeks)
    - Assess change in immune biomarkers by analysis of peripheral blood and tumor biopsy between treatment with relatlimab alone, nivolumab alone, and combination of nivolumab + relatlimab
    - Estimate association between change in immune biomarkers and change in tumor size
- Combination phase
    - CT assessment of objective response rate relative to the beginning of the combination phase by comparing CT measurements obtained 12 weeks (+/- 1 week) after beginning of combination phase and subsequent 12 week (+/- 1 week) intervals to CT measurements obtained at initial 4 week completion of lead-in phase

1.2 Secondary Objectives

- To assess the potential clinical benefit of the combination therapy
- To assess the duration of response
- To assess progression-free survival and overall survival
- To assess the safety of the combination of nivolumab and relatlimab
- To evaluate for a correlation between LAG3 expression as assessed by immunohistochemistry (IHC) and/or multiplexed immunofluorescence (IF) at baseline and response to the study treatment
- To assess the change in immune biomarkers by analysis of peripheral blood and tumor biopsies obtained prior to initiating treatment, following 1 cycle (4 weeks) of lead-in treatment, and following 3 cycles of combination treatment in all three groups (12 weeks after initiating combination phase), and at the time of disease progression
- To estimate and compare tumor response profiles that combine both the lead-in and combination phases

1.3 Exploratory Objectives

- Overall response as defined by complete response and partial response will be assessed following 1 cycle of assigned lead-in treatment and correlated with mechanistic analysis
- Matching peripheral blood lymphocytes and tumor biopsies assessed by single cell RNAseq obtained pre-treatment, following 1 cycle (4 weeks) of assigned lead-in treatment, following 3 cycles of combination treatment in all three groups (12 weeks after initiating treatment) and at disease progression
- Assessment of pathological response (complete, major, partial, no response) on biopsy at 4 weeks following 1 cycle of assigned lead-in treatment with relatlimab, nivolumab, or the combination of nivolumab+relatlimab

2. BACKGROUND

2.1 Metastatic Melanoma

Melanoma is the most aggressive skin cancer, and patients with unresectable or metastatic melanoma have a poor prognosis, with 9,324 deaths attributed to melanoma in 2014 [9]. Immunotherapy with checkpoint blockade has revolutionized the treatment of metastatic melanoma.

Tumors evade and develop resistance to the immune response by a variety of mechanisms. The goal of immunotherapy is to counteract these immune resistance mechanisms, and to allow the immune system to recognize and reject tumors. Despite recent advances in immunotherapy for patients with metastatic melanoma, the majority of patients still do not achieve a durable response.

2.2 Study Agents

2.2.1 Relatlimab

Lymphocyte activation gene-3 (LAG3; CD223) is a type I transmembrane protein that is expressed on the cell surface of activated CD4+ and CD8+ T cells, and it requires binding to major histocompatibility complex (MHC) class II molecules and potentially other unknown ligands for its functional activity. LAG3 negatively regulates CD4+ and CD8+ T cell proliferation, activation, and homeostasis [3, 4], and also contributes to the development, homeostasis, and function of regulatory T cells (T_{regs}) [5].

LAG3 negatively regulates CD4+ and CD8+ T cell proliferation, activation, and homeostasis [4, 10-12], and also contributes to the development, homeostasis, and/or function of regulatory T cells (Tregs) [12, 13]. Natural and induced Treg demonstrate increased LAG-3 expression, which is required for maximal suppressive function [13, 14]. In murine models, LAG-3 maintained tolerance to self and tumor antigens via direct effects on CD8+ T cells [15].

LAG-3 has been validated in murine *in vivo* models as an immunotherapy target, using two antibodies specific for mouse LAG-3. Administration of anti-LAG-3 antibody resulted in overall tumor growth inhibition and an increase in the number of tumor-free mice in those treatment groups. Demonstration of synergistic pre-clinical benefit of dual anti-PD1/anti-LAG3 therapy has been demonstrated in several mouse models of cancer [7].

Relatlimab is a fully human antibody specific for human LAG-3, isolated from immunized transgenic mice expressing human immunoglobulin genes. It is expressed as an IgG4 isotype antibody that includes a stabilizing hinge mutation (S228P) for attenuated Fc receptor binding, in order to reduce or eliminate the possibility of antibody- or complement-mediated target cell killing. Relatlimab binds to a defined epitope on LAG-3 with high affinity (Kd, 0.25 – 0.5 nM) and specificity and potently blocks the interaction of LAG-3 with its only known ligand, MHC class II (IC50, 0.7 nM). The antibody demonstrates potent *in vitro* functional activity in reversing

LAG-3-mediated inhibition of antigen-specific murine T cell hybridoma overexpressing human LAG-3 (IC50, 1 nM). Relatlimab enhances activation of human T cells in superantigen stimulation studies when added alone or in combination with nivolumab.

Overall, the safety profile of relatlimab appears to be manageable as evaluated in the 2 ongoing studies with relatlimab monotherapy (clinical data cutoff date of June 15, 2017). The maximum tolerated dose (MTD) was not reached at any dose tested up to 800 mg flat dose, which was the maximum administered dose. There was no relationship between the incidence, severity, or causuality of adverse events (AEs) and relatlimab dose level. Most AEs were grade 1 to 2 in both studies, with only 2 drug-related grade 3 AEs reported (1 asymptomatic AE of lipase elevation and 1 AE of maculo-papular rash in Study CA224020). Infusion-related reactions of grade 1 to 2 were reported in 4 subjects and were manageable using updated protocol guidelines. There were 3 drug-related serious adverse events with relatlimab monotherapy: grade 2 pneumonitis and grade 3 shock reported in Part A1 monotherapy in Study CA224022 at a dose of 800mg relatlimab every 2 weeks and grade 3 aseptic meningitis with relatlimab monotherapy in Study CA224022 at a dose of 800mg relatlimab every 2 weeks. Further discussions with investigator have since clarified that the Grade 3 shock was a Grade 3 allergic reaction. The recommended phase 2 dose is relatlimab 160mg IV once every 4 weeks.

2.2.2 Nivolumab

Programmed cell death 1 (PD-1) is a cell surface signaling receptor that plays a critical role in T cell regulation [16]. It is a type 1 transmembrane protein of the CD28 family of T cell co-stimulatory receptors, along with BTLA, CTLA-4, ICOS, and CD28 [17] (5). PD-1 is also expressed on natural killer (NK) cells [18]. Binding of PD-1 by its ligands, PD-L1 and PD-L2, results in phosphorylation of the tyrosine residue in the proximal intracellular immune receptor tyrosine inhibitory domain, followed by recruitment of the phosphatase SHP-2, eventually resulting in downregulation of T cell activation. PD-1 has a role in limiting T cell activity in peripheral tissues during an inflammatory response to infection, thereby limiting the development of autoimmunity [19]. However, in the setting of malignancy, this can lead to the development of tumor resistance to the immune response.

PD-1 is highly expressed on tumor-infiltrating lymphocytes, and its ligands are upregulated on the cell surface of many different tumor types, including melanoma [17]. The binding of ligand to PD-1 results in immune evasion, and blockade of this interaction results in antitumor activity. This is the rationale for evaluation of the PD-1 pathway blockade for clinical efficacy.

Nivolumab is a fully human monoclonal antibody that binds to PD-1 with a high degree of specificity. Nivolumab does not bind to other related proteins in the CD28 family of T cell co-stimulatory receptors, such as BTLA, CTLA-4, ICOS, or CD28. Binding of nivolumab to PD-1 precludes the binding of PD-1 to its ligands PD-L1 and PD-L2.

In Checkmate-066, a phase 3, double-blind randomized controlled trial comparing nivolumab to dacarbazine in previously untreated patients with unresectable or metastatic melanoma, an overall survival benefit was seen with nivolumab [1]. In November 2015, nivolumab received FDA approval for the treatment of patients with unresectable or metastatic melanoma in the first line setting. Nivolumab is also approved by the FDA in combination with ipilimumab (anti-

CTLA-4). Further details regarding clinical pharmacodynamics and pharmacokinetics are detailed in the Investigator Brochure for nivolumab.

2.2.3 Sequential nivolumab and relatlimab dosage

Overall, the safety profile of relatlimab in combination with nivolumab is manageable in the 2 ongoing studies with combination therapy (clinical cutoff date of June 15, 2017), with no MTD reached at the tested doses up to 160 mg relatlimab/240 mg nivolumab administered every 2 weeks. Evaluation of 240 mg relatlimab/240 mg nivolumab Q2W combination dose is ongoing. There was no dose relationship between the incidence, severity, or causality of AEs and combination therapy, as referenced in further detail in Section 5.5 of the Investigator Brochure for relatlimab. Most AEs were of low grade (Grade 1 to 2). A total of 26 subjects out of the 322 subjects receiving combination therapy experienced a treatment-related SAE. Five Grade 1 and 13 Grade 2 infusion-related reactions were reported during infusion of study treatment and were manageable using the updated protocol guidelines.

In Studies CA224020 and CA224022, a total of 65 deaths occurred in subjects treated with combination therapy (19 deaths within 30 days, 55 deaths within 135 Days, and 10 deaths >135 days after last dose). Three subjects died for reasons other than disease progression. In Study CA224020 1 subject treated with 240 mg relatlimab/240 mg nivolumab Q2W died due to Grade 5 myocarditis, which was considered by the investigator to be related to study treatment, and 1 subject treated with 80 mg relatlimab/240 mg nivolumab Q2W died due to pneumonia, which was considered by the investigator to be not related to study treatment. In addition, since the clinical data cutoff date, the subject experiencing the Grade 4 treatment-related potential drug-induced liver injury in Study CA224020 experienced a Grade 5 respiratory failure, which was considered by the investigator to be not related to study treatment. In Study CA224022 1 subject died due to an unknown cause of death. All other deaths were due to disease progression and were considered by the investigator to be not related to study treatment.

The preliminary results of the phase 1/2a dose escalation and cohort expansion study of anti-LAG3 with and without anti-PD1 therapy in patients with metastatic melanoma was recently reported [8]. The combination was well-tolerated, with grade 3 or 4 treatment related adverse events seen in 9% of subjects, which is similar to the frequency seen with nivolumab alone.

Recent analyses of monoclonal antibodies have demonstrated that body weight-based dosing did not always offer advantages over flat dosing in reducing the degree of variability of exposure [20, 21]. The impact of body weight on the PK is small, and the dose-response relationship is relatively shallow near the 3-mg/kg dose level, indicating that nivolumab can also be administered in a flat dose in combination with relatlimab in his study.

Nivolumab will be administered at 480 mg every 4 weeks, which is the flat dose equivalent of the dose selected for the global Phase 3 program (3 mg/kg) which has been well tolerated in monotherapy. The recommended phase 2 dose for relatlimab is 160 mg IV every 4 weeks.

Sequential infusion of both drugs will start with nivolumab administration first followed by infusion of relatlimab. The study treatment will be administered every 4 weeks.

2.3 Rationale

The opportunity to improve upon anti-PD1 therapy to increase the anti-tumor immune response is a challenge in the treatment of patients with unresectable or metastatic melanoma.

Inhibitory mechanisms within the tumor microenvironment represent major barriers to effective anti-tumor immunity, and include cell intrinsic mechanisms, such as inhibitory receptors including PD1 and LAG3, and cell extrinsic mechanisms such as T regulatory cells (Tregs) which block anti-tumor immunity [4, 10-13, 22]. CD141+ dendritic cells also have a role in T cell activation [23].

With the advent of immune checkpoint blockade (ICB) therapy, overall survival has been improved in a subset of patients with unresectable and metastatic melanoma. Anti-PD1 therapy with nivolumab has improved objective response rate (RR), progression-free survival (PFS), and overall survival (OS) compared to chemotherapy in previously untreated patients [1]. The phase III trial CheckMate-067 evaluated previously untreated patients by randomization to nivolumab, ipilimumab, or the combination [2]. In that trial, nivolumab demonstrated RR of 43% compared to RR of 19% with ipilimumab, and the combination demonstrated RR of 57%. PFS was also improved with the combination of nivolumab and ipilimumab compared to either agent alone. However, grade 3 or 4 treatment-related adverse events were seen in 55% of patients in the combination group, compared to 16% in the nivolumab group and 27% in the ipilimumab group. Although toxicity was increased with the anti-CTLA4 and anti-PD1 combination compared to either agent alone, these data suggest that combinations of immune-modulating agents may achieve more robust and prolonged responses than single-agent therapy in melanoma and warrant further exploration.

Lymphocyte activation gene-3 (LAG3; CD223) is a type I transmembrane protein that is expressed on the cell surface of activated CD4+ and CD8+ T cells, and it requires binding to major histocompatibility complex (MHC) class II molecules and potentially other unknown ligands for its functional activity. LAG3 negatively regulates CD4+ and CD8+ T cell proliferation, activation, and homeostasis [3, 4], and also contributes to the development, homeostasis, and function of T_{regs} [5].

Extensive co-expression of PD-1 and LAG3 has been demonstrated on tumor-infiltrating CD4+ and CD8+ T cells in melanoma [3]. While blockade of the interaction of PD-1/PD-L1 has demonstrated restoration of antitumor immune response in both preclinical and clinical studies, LAG3-mediated T cell exhaustion may be a limiting factor in the antitumor immune response. Simultaneous blockade of PD-1 and LAG3 pathways on T cells may reverse this T cell exhaustion. In mouse models, tumor response in recurrent tumors can be achieved with combination treatment with anti-PD-L1 and anti-LAG3 antibodies, and dual anti-LAG3 and anti-PD1 antibody treatment has demonstrated responses in tumors resistant to monotherapy treatment [7].

LAG3-mediated T cell exhaustion is a contributing factor to antitumor immune response failure in patients treated with anti-PD-1 monotherapy. The preliminary results of the phase 1/2a dose

escalation and cohort expansion study of anti-LAG3 with and without anti-PD1 therapy in patients with metastatic melanoma was recently reported [8]. These pre-treated patients, all of whom had progressed on anti-PD1 therapy and 47% of whom had received 3 or more prior therapies, were treated with the combination of nivolumab and anti-LAG3 therapy. In the 48 evaluable patients the objective response rate was 12.5%. Of note, patients with LAG3 expression >1% on tumor-infiltrating lymphocytes (TIL) had a response rate of 20%, compared to 7.1% in patients with <1% LAG3 expression. The combination was well-tolerated, with grade 3 or 4 treatment related adverse events seen in 9% of subjects, which is similar to the frequency seen with nivolumab alone, and no new toxicities were seen compared to nivolumab alone. In preliminary analysis of tumor specimens from subjects with advanced melanoma in the first-line treatment setting, LAG3 was evaluable by IHC in approximately 90% of cases. Among those evaluable the rate of LAG3 positivity defined as the percentage of LAG3 immune cells ≥ 1% of tissue was approximately 60%.

We hypothesize that the combination of anti-PD1 and anti-LAG3 treatment will demonstrate improved antitumor activity in subjects with unresectable melanoma who have not previously been treated with immunotherapy. This study will evaluate the antitumor activity of anti-LAG3 monoclonal antibody relatlimab and the anti-PD1 monoclonal antibody nivolumab in combination in subjects with unresectable or metastatic melanoma who have not received prior treatment with immunotherapy. The trial is designed with a lead-in phase of 2 cycles (4 week) treatment of either nivolumab, relatlimab, or the combination of nivolumab/relatlimab, followed by a combination phase of nivolumab/relatlimab treatment in all subjects. This lead-in design with accompanying tumor biopsies and peripheral blood analyses will enable mechanistic analyses of the effect of LAG3 and PD1 blockade alone and in combination to enhance understanding of mechanisms of response and resistance. Duration of response, progression free survival, and safety will be assessed as secondary objectives.

Correlative Studies Background

Tumor biopsies to be performed prior to treatment, at the completion of the lead-in phase, following 12 weeks of the combination phase treatment, and at time of disease progression in subjects who previously demonstrated response will provide for assessment of changes in immune infiltrate in relationship to treatment with the study combination and potential differences between responders and non-responders. Further details provided in **Section 9.**

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 AJCC 8th edition criteria for unresectable stage IIIB, stage IIIC, stage IIID, or stage IV melanoma who have not received prior immunotherapy treatment in the metastatic setting (defined as prior treatment with anti-PD1, anti-PDL1, anti-PDL2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint); or chemotherapy

- Subjects who have received prior adjuvant treatment with anti-PD1, anti-PDL1, and/or anti-LAG3 antibody would be excluded. Note that prior adjuvant treatment with targeted therapy (e.g. BRAF/MEK inhibition), anti-CTLA4, or treatment not otherwise specified would be permitted.

3.1.2 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of relatlimab in patients <18 years of age, children are excluded from this study.

3.1.3 ECOG performance status ≤1 (Karnofsky ≥80%, see Appendix A).

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

– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL
– total bilirubin	≤1.5 × institutional upper limit of normal (except in subjects with Gilbert's syndrome who must have a normal direct bilirubin)
– AST(SGOT)/ALT(SGPT)	≤2.5 × institutional upper limit of normal
– creatinine	within normal institutional limits OR
– creatinine clearance	≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

3.1.5 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. If subjects have a single lesion, the lesion must be amenable to biopsy without interfering with radiographic assessment as determined by PI. See Section 11 for the evaluation of measurable disease.

3.1.6 The effects of relatlimab and nivolumab on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. 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 treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 24 weeks following last dose. See Appendix B for acceptable methods of contraception.

3.1.7 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Target Disease

Known or suspected CNS metastases, with the following exceptions:

a) Subjects with controlled brain metastases will be allowed to enroll. Controlled brain metastases are defined as no radiographic progression for at least 4 weeks following radiation and/or surgical treatment at the time of randomization.
b) Subjects must be off steroids for at least 2 weeks prior to randomization
c) Subjects with signs or symptoms of brain metastases are not eligible unless brain metastases are ruled out by computed tomography or magnetic resonance imaging.

Ocular melanoma

3.2.2 Medical History and Concurrent Diseases

- Patients who are receiving any other investigational agents.

- History of allergic reactions attributed to compounds of similar chemical or biologic composition to nivolumab or relatlimab.

- Subjects with 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.

- Uncontrolled or significant cardiovascular disease including, but not limited to, any of the following:
    - Myocardial infarction (MI) or stroke/transient ischemic attack (TIA) 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, torsades de pointes, or poorly controlled atrial fibrillation)
    - QTc prolongation > 480 msec
    - History of other clinically significant cardiovascular disease (i.e., cardiomyopathy, congestive heart failure with New York Heart Association [NYHA] functional classification III-IV, pericarditis, significant pericardial effusion, significant coronary stent occlusion, poorly controlled deep venous thrombosis, etc)
    - 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

- A confirmed history of encephalitis, meningitis, or uncontrolled seizures in the year prior to informed consent

- Subjects with history of life-threatening toxicity related to prior immune therapy (eg. anti-CTLA-4 or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (eg, hormone replacement after endocrinopathy).

- Troponin T (TnT) or I (TnI) > 2 × institutional ULN. Subjects with TnT or TnI levels between > 1 to 2 × ULN will be permitted if repeat levels within 24 hours are ≤1 x ULN. If TnT or TnI levels are >1 to 2 × ULN within 24 hours, the subject may undergo a cardiac evaluation and be considered for treatment based on the discretion of the PI. 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 a cardiac evaluation and be considered for treatment, based on the discretion of the PI.

- Prior treatment with LAG-3 targeted agents.

- Subject has been administered prior chemotherapy or immunotherapy for melanoma at any time, and any with radiation therapy within 4 weeks prior to time of consent or who has not recovered (ie, ≤ Grade 1 or at baseline) from adverse events due to previously administered agent.
    a) Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.
    b) If subject underwent major surgery, subject must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

- Subject has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or *in situ* cervical cancer.

- 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 therapy.

- Pregnant women are excluded from this study because relatlimab has the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother, breastfeeding should be discontinued if the mother is treated with relatlimab.

- Subjects who are unable to undergo venipuncture and/or tolerate venous access

- Evidence of active infection that requires systemic antibacterial, antiviral, or antifungal therapy ≤ 7 days prior to initiation of study drug therapy

3.2.3 Other Exclusion Criteria

Prisoners or subjects who are involuntarily incarcerated

Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness

Inability to comply with restrictions and prohibited activities and treatments

3.3 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

4. REGISTRATION PROCEDURES

4.1 Patient Registration

Registration will be conducted at UPMC Hillman Cancer Center in Pittsburgh, Pennsylvania.

4.2 General Guidelines

Eligible patients will be entered on study at the UPMC Hillman Cancer Center by the Study Staff.

Following registration, patients should begin protocol treatment within 5 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled.

5. TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in **Section 8**. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Regimen Description					
Agent	**Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Single agent					
Nivolumab	None	480 mg	IV infused over 30 minutes.	Day 1	28 days
Relatlimab	None	160 mg	IV infused over 60 minutes.	Day 1	28 days
Combination					
Nivolumab	None	480 mg	IV before relatlimab infusion. Infused over 30 minutes.	Day 1	28 days
Relatlimab	None	160 mg	IV 30 minutes following nivolumab infusion. Infused over 60 minutes.	Day 1	28 days

5.2 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of relatlimab and nivolumab with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions.

5.2.1 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 Section 5.2.4
- 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
- Use of allergen hyposensitization therapy
- Use of cannabis or other recreational drugs other than alchohol or tobacco. Medical

marijuana prescribed under the care of a physician is permitted.

5.2.2 Other Restrictions and Precautions

Any vaccination containing attenuated or inactivated virus may be permitted if clinically indicated. However, this 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.

5.2.3 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 for infusion reactions. A brief course of corticosteroids for prophylaxis (e.g., contrast dye allergy) is permitted.

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 and nivolumab in combination is currently not fully 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 not clearly related to disease progression, then drug administration should be withheld, if possible, for at least 1 week before radiation and for at least 2 weeks 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 Investigator.

Details of palliative radiotherapy should be documented in the source records. Details in the source records should include: dates of treatment, anatomical site, dose administered and fractionation schedule, and AEs. Symptoms requiring palliative radiotherapy should be evaluated for objective evidence of disease progression. 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 investigator.

5.2.4 Treatment of Relatlimab or Nivolumab-Related Infusion Reactions

Since relatlimab and nivolumab contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it may manifest with fever, chills, rigors, headache, rash, pruritus,

arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported as a SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE version 5.0 guidelines.

If a subject has an infusion reaction with nivolumab, the relatlimab infusion can be given (without prophylactic medications) if the infusion reaction resolves within 3 hours. For scheduling purposes after a nivolumab infusion reaction, the RELATLIMAB infusion may be given the next day. Prophylactic pre-infusion medications should be given prior to all subsequent nivolumab infusions.

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

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

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

For Grade 2 symptoms (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [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/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further study drug will be administered at that visit.

For future infusions, the following prophylactic premedications are recommended:

- Diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 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 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]. Life-threatening, Grade 4: pressor or ventilatory support indicated).

- Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous (SC) 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 drug(s) will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

In 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).

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression of melanoma
- Patient non-compliance
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify the IRB in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent
- Maximum planned duration of treatment for 24 months (48 cycles) has been completed.
- At the end of the study period, Bristol-Myers Squibb Company will not continue to supply study drug to subjects/investigators unless an agreement is made to extend the 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.

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

5.4 Duration of Follow Up and Retreatment

After trial discontinuation (whether due to subject withdrawal, disease progression, or toxicity), subjects will be evaluated as determined by the treating physician. Patients may be contacted for survival follow-up for up to 5 years. Survival follow-up will be performed at approximately 3

month intervals. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.5 Withdrawal of Consent

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

5.6 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 3 documented phone calls, faxes, or emails, as well as lack of response by subject to one registered mail letter over the course of a 3 month period. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Dose Delay Criteria

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 will be provided in the current BMS-986016 (relatlimab) and BMS-936558 (nivolumab) Investigator's Brochures. Additionally, management algorithms have been developed to assist Investigators with select toxicities and can be found in the current BMS-936558 (nivolumab) Investigator's Brochure; toxicities for which management algorithms have been developed include:

- Pulmonary
- Gastrointestinal
- Hepatic
- Endocrine
- Renal
- Dermatologic

- Neurologic (see Table "Neurological Exam" for criteria for protocol-required neurologic exams)

Subjects who experience the following must have all study drug(s) held:

- Potential DLTs (per definition, are related to study drug) until DLT relatedness is defined.
- Select drug-related AEs and drug-related laboratory abnormalities:
    - Myocarditis (any grade)
    - All troponin elevations require a dose delay to allow for prompt cardiac evaluation. Following this evaluation, determination of further treatment will be based on the discretion of the PI.
    - Grade 1 pneumonitis
    - Single grade increase shift in abnormality in AST, ALT, or total bilirubin
    - Grade 2 creatinine
    - Grade 2 diarrhea or colitis
    - Grade 2 neurological AE
    - Grade 4 amylase and/or lipase abnormalities regardless of symptoms or clinical manifestations
- AE, laboratory abnormality, or concurrent illness that, in the judgment of the Investigator, warrants delaying the dose of study drug.

Dose delays > 7 days will be considered missed and will not be replaced. Subjects who meet criteria listed in Section 6.4 are required to permanently discontinue all study drug(s). All other subjects will be permitted to resume therapy with study drug(s) at the same dose level(s) following resolution of the AE as described in Section 6.2.

6.2 Criteria to Resume Treatment After Dose Delay

Subjects will be permitted to resume therapy at the same dose level(s) following resolution of the AE to ≤ Grade 1 or to baseline within 6 weeks after last dose, with the exception of subjects who meet criteria for permanent discontinuation. Subjects who meet criteria for permanent discontinuation should receive no further study therapy. The following exceptions apply:

- If the toxicity resolves to ≤ Grade 1 or baseline > 6 weeks after last dose, but the subject does not otherwise meet the 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 drug(s) following the approval of the PI.
- Subjects with a 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, and after consultation with the PI.
- Subjects with baseline Grade 1 AST, ALT, or total bilirubin who require dose delays for reasons other than a drug-related hepatic event may resume treatment in the presence of Grade 2 AST, ALT, or total bilirubin.
- 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.

- All troponin elevations require a dose delay to allow for prompt cardiac evaluation. Following this evaluation, determination of further treatment will be based on the discretion of the PI.
- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.

6.3 Treatment beyond Disease Progression

Accumulating evidence indicates that a subset of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD. Per RECIST v1.1, PD is defined as ≥ 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an **absolute increase of at least 5 mm**. NOTE: Either the appearance of new lesions or the unequivocal progression of existing non-target lesions is also considered progression. Subjects with initial RECIST v1.1-defined PD may be permitted to continue study therapy provided the following criteria are met:

- Disease progression is not rapid as assessed by the Investigator
- Subject continues to meet relevant eligibility criteria as determined by the Investigator
- Subject tolerates study drug
- Subject has stable performance status (ECOG PS 0 – 1 as per entry criteria)
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases)
- Subjects have provided written informed consent prior to receiving additional study drug

A follow-up scan should be performed at the next scheduled imaging evaluation 8 weeks later (but no sooner than 4 weeks) to determine whether there has been a decrease in the tumor size or continued further PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment. If the investigator feels that the subject continues to achieve clinical benefit by continuing treatment, the subject should remain on the study and continue to receive monitoring according to the Time and Events Schedule. The decision to continue treatment should be discussed with the PI and documented in the study records.

For subjects who continue study therapy beyond initial RECIST v1.1-defined PD, further progression is defined as an additional 10% increase in tumor burden volume from time of initial PD assessment. This includes an increase in all target lesions and/or the development of new measurable lesions. Study therapy should be discontinued in any subject for whom these criteria are met and documented.

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

6.4 Guidelines for Permanent Discontinuation

Subjects meeting any of the following criteria will be required to permanently discontinue all study drug(s) relatlimab (BMS-986016) and nivolumab (BMS-936558)

- Progressive disease
- Clinical deterioration as assessed by the Investigator
- Grade 3 infusion reaction
- Grade 3 pneumonitis
- Grade 3 uveitis
- Grade 3 myocarditis
- Any Grade 4 AE; however, an exception may be made for the following upon consultation with the PI:
    - Grade 4 electrolyte abnormalities < 72 hours in duration
    - Grade 4 neutropenia < 7 days in duration
    - Grade 4 lipase and/or amylase elevation that recovers to at least grade 3, remains asymptomatic, and is not associated with clinical manifestations of pancreatitis
- Any toxicity that meets DLT criteria as previously defined however, an exception may be made for the following upon consultation with the PI:
    - Grade 3 diarrhea, nausea, vomiting, or abdominal pain that returns to Grade 1 or baseline within 3 days with medical intervention
    - AST or ALT >5 and <8 × ULN for < 2 weeks
- Any dosing interruption lasting > 6 weeks after last dose with the following exceptions:
    - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related AEs are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks after last dose and with no more than 3 missed doses, the PI must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
    - Dosing interruptions > 6 weeks after last dose that occur for non−drug-related reasons may be allowed if approved by the PI. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks after last dose and with no more than 3 missed doses, the PI must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted and subjects must otherwise meet the criteria for continued treatment at the time re-initiation of study therapy is considered.

6.5 Dose Modifications

Dose reductions or dose modifications are not permitted. Treatment doses may be delayed or discontinued as per the guidance in Section 6.

7. STUDY ASSESSMENTS AND PROCEDURES

7.1 Time and Events Schedule

Table 7.1-1 Screening Procedural Outline

Procedure	Screening Visit (Day -56 to -29)	Day -42 to -29 Visit	Day -31 to -29 Visit	Notes
Eligibility Assessments				
Informed consent	X See Notes			A subject is considered enrolled only when an IRB/IEC-approved informed consent is signed and dated. Obtain subject number from IVRS.
Inclusion/exclusion criteria	X			
Medical history	X			May include more detailed medical history of risk factors for potential events such as pulmonary or cardiac related events. Include any toxicities or allergy related to previous treatments.
Fresh pre-treatment tumor biopsy		X See Notes		See Laboratory Manual for delivery and processing indications.
Biomarker assessments		X		

Procedure	Screening Visit (Day -	Day -42 to -29	Day -31 to -29	Notes

	56 to -29)	**Visit**	**Visit**	
Safety Assessments				
Physical examination (PE)	X			If the screening PE is performed within 1 day of dosing on in lead-in phase then a single exam may count as both the screening and pre- dose evaluation.
Performance status	X			ECOG Performance Status
Physical measurements	X			Includes height, weight.
Vital signs	X See Notes			Includes body temperature, seated blood pressure, and heart rate.
Oxygen saturation	X See Notes			Collected at rest via pulse oximetry to establish baseline. If subject has oxygen saturation ≤ 90%, consult PI prior to enrollment.
Electrocardiogram (ECG)	X			12-lead ECG

Procedure	**Screening Visit (Day -56 to -29)**	**Day -42 to -29 Visit**	**Day -31 to -29 Visit**	**Notes**
Echocardiogram	X See Note			Echo assessment with documented LVEF ≥ 50% by either TTE or MUGA (TTE preferred test) within 6 months from first study drug administration

Laboratory tests	X See Notes			Blood and Urine Tests: To include hematology, serum chemistry, endocrine panel, serology, urinalysis, and CARDIAC TROPONIN LEVELS. See Section 7 for panel requirements. (Subjects with controlled hyperthyroidism must be negative for thyroglobulin and thyroid peroxidase antibodies and thyroid-stimulating immunoglobulin.) (Subjects with type 2 diabetes must have HbA1c to establish baseline.) If tests are performed within 3 days of dosing in lead-in phase, then lead-in phase laboratories are not required.
Pregnancy test (WOCBP)			X See Notes	Pregnancy test should be performed in all WOCBP prior to first study drug administration. Serum or urine pregnancy test (minimum sensitivity of urine pregnancy test of 25 IU/L of either total hCG or the beta fraction). If performed within 24 hours of dosing on lead-in phase then lead-in phase pregnancy test is not required.

Procedure	**Screening Visit (Day -56 to -29)**	**Day -42 to -29 Visit**	**Day -31 to -29 Visit**	**Notes**
Concomitant medications		X		Collected during the 2-week period prior to start of lead-in phase (day -28)
Assessment of		X		Collected during the 2-week period prior

signs and symptoms				to start of lead-in phase (day -28)
Adverse Event Reporting				
Monitor for serious adverse events	X			All SAEs must be collected from the start of treatment
Efficacy Assessments				
Diagnostic Imaging	X See Notes			CT with contrast is the preferred modality (CT chest without contrast or MRI if CT is not feasible or appropriate given location of the disease). Assessment should include the chest/abdomen/pelvis at a minimum, and should include other anatomic regions as indicated based on the subject's tumor type and/or disease history.
Brain imaging	X See Notes			Applicable Subjects: Brain imaging (MRI) for subjects with history or symptoms of brain metastases who have not had brain imaging within 30 days of anticipated first study drug administration. CT imaging is permitted, but brain MRI is preferred.

Table 7.1-2 Lead-in Phase Outline

Procedure	**Day -28 (± 2 days)**	**Day - 14 (± 2 days)**	**Days -7 - -1**	**Notes**
Physical Examination	X			
Performance status	X			
Weight	X			
Vital signs	X			Includes temperature, seated blood pressure, and heart rate.

Oxygen saturation	X			
Laboratory tests	X			Labs are performed locally and may be collected within 3 days prior to dosing. To include serum chemistry and hematology; see section 7 for panel requirements. Results must be reviewed by the Investigator or appropriate designee prior to dose administration
Endocrine panel	X			Labs are performed locally and may be collected within 3 days prior to dosing. To include serum chemistry and hematology; see section 7 for panel requirements. Results must be reviewed by the Investigator or appropriate designee prior to dose administration
Cardiac troponin	X	X		Labs are performed locally and may be collected within 3 days prior to dosing. To include serum chemistry and hematology; see section 7 for panel requirements. Results must be reviewed by the Investigator or appropriate designee prior to dose administration
EKG	X	X		
Assess adequate contraceptive use	X			For WOCBP and male subjects able to reproduce and sexually active with WOCBP: Assess for continued use of acceptable methods of contraception; see Appendix B
Monitor for non-serious adverse events	X			
Monitor for serious adverse events	X			
Biomarker assessments			X	
Tumor biopsy performed at conclusion of lead-in phase			X	See Lab Manual.
Diagnostic imaging			X	
Assigned lead-in treatment	X			

Table 7.1-3 Combination Phase 12 Week Interval Outline

	To be repeated every 12 weeks until criteria for discontinuation met as per Section 6.4	

Procedure	Day 1 (± 2 days) Cycle 1, Day 1	Day 15 (± 2 days)	Day 29 (± 2 days) Cycle 2, Day 1	Day 43 (± 2 days)	Day 57 (± 2 days) Cycle 3, Day 1	Day 78 - 84	Notes
Physical Examination	X		X		X		
Performance status	X		X		X		
Weight	X		X		X		
Vital signs	X		X		X		Includes temperature, seated blood pressure, and heart rate.
Oxygen saturation	X		X		X		
Laboratory tests	X		X		X		Labs are performed locally and may be collected within 3 days prior to dosing. To include serum chemistry and hematology; see section 7 for panel requirements. Results must be reviewed by the Investigato or appropriate designee prior to dose administration
Endocrine panel	X		X		X		Labs are performed locally and may be collected within 3 days prior to dosing. To include serum chemistry and hematology; see section 7 for panel requirements. Results must be reviewed by the Investigato or appropriate designee prior to dose administration
Cardiac troponin	X	X	X	X	X		Troponin monitored every 2 weeks for first months (through cycle 3, day 1) Labs are performed locally and may be

							collected within 3 days prior to dosing. To include serum chemistry and hematology; see section 7 for panel requirements. Results must be reviewed by the Investigato or appropriate designee prior to dose administration
EKG	X	X	X	X	X		EKG monitored every 2 weeks for first 2 months (through cycle 3, day 1)
Assess adequate contraceptive use	X						For WOCBP and male subjects able to reproduce and sexually active with WOCBP: Assess for continued use of acceptable methods of contraception; see Appendix B
Monitor for non-serious adverse events	X		X		X		
Monitor for serious adverse events	X		X		X		
Biomarker assessments						X See Notes	Following initial 3 cycles of treatment on combination phase
Tumor biopsy following 12 weeks combination phase						X See Notes	Following initial 3 cycles of treatment on combination phase
Diagnostic imaging						X	Every 3 cycles (12 weeks) of combination phase treatment.
Relatlimab and nivolumab	X		X		X		
Biomarker assessments on progression	See Notes						Optional but strongly recommended peripheral blood biomarker assessment performed at progression in patients with

		prior CR, PR, or SD
Tumor biopsy on progression	See Notes	Optional but strongly recommended tumor biopsy performed at progression in patient with prior CR, PR, or SD

7.2 Laboratory Test Assessments

A local laboratory will perform the analyses and will provide reference ranges for these tests.

Clinical laboratories will be assessed at the timepoints indicated in Table 7.1-1, Table 7.1-2, Table 7.1-3, and Table 7.1-4.

At screening, sites should collect samples during the timeframe indicated in Table 7.1-1 and ensure that results required for eligibility are verified prior to registration. During treatment, unless otherwise indicated, results of clinical laboratory tests must be reviewed prior to dosing.

The following clinical laboratory tests will be performed:

Hematology

Hemoglobin
Hematocrit
Total leukocyte count, including differential
Platelet count

Serum Chemistry

Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin
Alkaline phosphatase
Lactate dehydrogenase (LDH) Creatinine
Creatinine clearance by the Cockcroft-Gault formula (screening only)
Blood urea nitrogen (BUN) Glucose
Amylase
Lipase
Albumin
Sodium
Potassium

Chloride
CO_2
Calcium
Magnesium
Phosphorus

Endocrine Panel

Thyroid-stimulating hormone (TSH) with reflex to free T3 and free T4 as applicable for elevated TSH

Subjects with controlled hyperthyroidism must be negative for thyroglobulin and thyroid peroxidase antibodies and thyroid stimulating immunoglobulin (screening only)

Cardiac Troponin

T (cTnt) or I (cTnI)

Reproductive Analyses

Pregnancy test: serum or urine (minimum sensitivity of urine pregnancy test of 25 IU/L of either total human chorionic gonadotropin (hCG) or the beta fraction)

8. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

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

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

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

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

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject.

8.1 List of adverse events associated with study agents

The following are a list of adverse events that have been identified in prior clinical trials of nivolumab and relatlimab.

8.1.1 NIVOLUMAB

Very common adverse events associated with nivolumab: [≥ 10 %]

- Diarrhea
- Fatigue
- Itching
- Rash

Common adverse events associated with nivolumab: [≥1% to <10%]

- Abdominal pain
- Alkaline phosphatase increased
- ALT increased
- Amylase increased
- AST increased
- Chills
- Constipation
- Cough
- Creatinine increased
- Decreased appetite
- Dizziness
- Dry mouth
- Dry skin
- Fever
- Headache
- Increased blood sugar
- Inflammation of the colon
- Inflammation of the mouth
- Infusion related reaction
- Joint pain or stiffness
- Lipase increased
- Loss of color (pigment) from areas of skin
- Lung inflammation (pneumonitis)
- Musculoskeletal pain
- Nausea
- Redness

- Shortness of breath
- Hyponatremia
- Swelling, including face, arms, and legs
- Thyroid gland function decreased
- Thyroid gland function increased
- Thyroid stimulating hormone increased
- Tingling, burning, numbness or weakness, possibly in arms, legs, hands and feet
- Vomiting

Uncommon adverse events associated with nivolumab: [≥0.1% to <1%]

- Adrenal gland function decreased
- Allergic reaction/hypersensitivity
- Bilirubin increased
- Bronchitis
- Cranial nerve disorder
- Diabetes
- Dry eye
- Hair loss
- Heart rate increased
- Heart rhythm abnormal
- High blood pressure
- Hives
- Inflammation of the eye
- Inflammation of the kidney
- Inflammation of the pancreas
- Inflammation of the pituitary gland
- Inflammation of the stomach
- Inflammation of the thyroid gland
- Liver inflammation
- Low blood pressure
- Lung infiltrates, associated with infection or inflammation
- Pituitary gland function decreased
- Psoriasis: characterized by patches of abnormal, scaly skin
- Renal failure or renal injury
- Respiratory failure
- Upper respiratory tract infection
- Vertigo (feeling off balance which can lead to dizziness)
- Vision blurred

Rare adverse events associated with nivolumab: [≥0.01% to < 0.1%]

- Anaphylactic reaction (severe allergic reaction)
- Damage to the protective covering of the nerves in the brain and spinal cord
- Diabetes complications resulting in excess blood acids and diabetic coma
- Erythema multiforme: skin inflammatory reaction
- Guillain-Barre syndrome, an autoimmune disorder associated with progressive muscle weakness or paralysis
- Inflammation of blood vessels
- Inflammation of the brain, potentially life-threatening or fatal

- Inflammation of the heart
- Muscle inflammation
- Myasthenic syndrome (neurologic syndrome characterized by muscle weakness) including myasthenia gravis, a nerve disease that may cause weakness of eye, face, breathing, and swallowing muscles.
- Polymyalgia rheumatica, an inflammatory disorder causing muscle pain and stiffness
- Rhabdomyolysis: muscle fiber released into the blood stream which could damage your kidneys
- Rosacea: acne-like skin condition resulting in redness of face
- Sarcoidosis, a disease involving abnormal collections of inflammatory cells (granulomas) in organs such as lungs, skin, and lymph nodes
- Stevens Johnson syndrome: inflammatory disorder of skin and mucous membranes, resulting in blistering and shedding of skin
- Toxic epidermal necrolysis: a potentially fatal disease characterized by blistering and peeling of the top layer of skin resembling a severe burn
- Histiocytic necrotizing lymphadenitis or Kikuchi lymphadenitis: disorder of the lymph nodes which causes the lymph nodes to become enlarged, inflamed and painful, commonly affecting lymph nodes of the neck and possibly associated with fever or muscle and joint pains.
- Vogt Koyanagi Harada syndrome; a disease that affects the pigmented tissue; this may affect the eye leading to swelling, pain and/or blurred vision; the ear leading to hearing loss, ringing in the ears and/or the skin leading to loss of skin color

8.1.2 RELATLIMAB

As of June 15, 2017, approximately 385 subjects have been treated with relatlimab therapy either as single agent (63 patients) or in combination with nivolumab (322 patients). This includes 329 subjects with solid tumors and 56 subjects with cancers that affect the blood or lymph system.

Very common adverse events associated with relatlimab: [≥ 10 %]

- Decreased appetite
- Fatigue
- Nausea
- Anemia
- Cough
- Diarrhea
- Fever
- Headache
- Muscle pain (myalgia)
- Weight loss
- Rash

Common adverse events associated with relatlimab: [≥0.5 to >10%]

- Difficulty in swallowing (Dysphagia)
- Infusion related reaction e.g., rash & chills
- Joint Pain (arthralgia)
- Mouth and/or throat (Oropharyngeal) pain
- Swelling in arms, legs

- Thyroid function test abnormalities

8.1.3 NIVOLUMAB AND RELATLIMAB

As of June 15, 2017, the combination of study drugs has been tested in 322 humans and two life-threatening events occurred, one of which contributed to a subject's death. One subject experienced an episode of ventricular fibrillation. This event was not associated with known side effects of either drug but it was considered as possibly caused by either relatlimab or the combination therapy with nivolumab. At present time, there is not enough information to determine whether ventricular fibrillation might occur in subjects treated in this protocol with relatlimab alone or in combination with nivolumab. The second subject developed myocarditis. Biopsy of the heart muscle showed that the combination of BMS-986016 (anti-LAG-3) and nivolumab (BMS-936558) resulted in the immune system attacking the heart muscle. Due to these events, EKG and troponin monitoring are performed as described in the protocol.

Very common adverse events associated with the combination of relatlimab and nivolumab: [≥10%]

- Constipation
- Cough
- Decreased appetite
- Diarrhea
- Fatigue
- Fever
- Joint Pain
- Nausea
- Shortness of breath

Common adverse events associated with the combination of relatlimab and nivolumab: [≥5% to <10%]

- Abdominal pain and discomfort
- Anemia
- ALT increased
- AST increased
- Back pain
- Headache
- Infusion related reactions e.g., rash & chills
- Itching
- Muscle pain
- Rash
- Vomiting

8.1.4 ALLERGIC REACTIONS

Nivolumab and relatlimab are monoclonal antibodies which may very rarely be associated with allergic reactions occurring 10 minutes to 4 hours after infusion of antibodies. Mild symptoms may include mild to moderate swelling and itching at infusion site, mild headache, flushing, dizziness and/or nausea. Moderate symptoms may include chest pain, shortness of breath, fever, and/or change in blood pressure. Severe symptoms may include partial obstruction of airways, severe flushing, and/or joint stiffness. Delayed symptoms may occur 24 hours to 14 days after study drug treatment, and include rash, flu-like symptoms, joint stiffness, headache, and/or muscle pain.

8.1.5 IMMUNE RELATED ADVERSE EVENTS

Nivolumab and relatlimab are immune checkpoint blockade agents which may be associated with autoimmune adverse events. A list of adverse events that may be seen with the study agents is detailed above in sections 8.1.1, 8.1.2, and 8.1.3. Immune related adverse events that have been seen with nivolumab and/or relatlimab include uveitis, hypophysitis, hyperthyroidism, hepatitis, pancreatitis, colitis, arthritis, myocarditis, aseptic meningitis, nephritis, and pneumonitis.

8.2 Serious Adverse Events

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

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

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

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

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

NOTE: The following hospitalizations will not be considered SAEs in this study:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg,

routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

8.2.1 Serious Adverse Event Collection and Reporting

- All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 100 days of discontinuation of dosing must be reported to BMS Worldwide Safety, whether related or not related to study drug. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).
- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these aforementioned time periods, which is believed to be related to study drug or protocol-specified procedure.
- An SAE report should be completed for any event where doubt exists regarding its seriousness;
- If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

REPORTING OF SERIOUS ADVERSE EVENTS

All events meeting the definition of a serious adverse event should be reported according to the departmental SAE checklist and SAE form. The initial SAE form should be sent to the following within 2 business days of the Principal Investigator becoming aware:

- Investigator
- crssafetysubmissions@upmc.edu
- Local Institutional Review Board when reporting requirements are met
- Worldwide.Safety@BMS.com or Fax to +1 609-818-3804

In addition to completing appropriate patient demographic and suspect medication information, the report should include as applicable the following information that is available at the time of report within the Sections B and C of the departmental SAE form:

- CTCAE term(s) and grade(s)
- current status of study drug
- all interventions to address the AE (testing and result, treatment and response)
- hospitalization and/or discharge dates
- event relationship to study drug

Follow-up reports:

Additional information may be added to a previously submitted report by adding to the original departmental SAE form and submitting it as follow-up or creating supplemental summary information and submitting it as follow-up with the original departmental SAE form.

8.3 Nonserious Adverse Events

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

8.3.1 Nonserious Adverse Event Collection and Reporting

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

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.

8.4 Laboratory Test Result Abnormalities

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

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

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

8.5 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant).

The investigator must immediately notify Worldwide.Safety@bms.com of this event via either the CIOMS, MedWatch or appropriate Pregnancy Surveillance Form in accordance with SAE reporting procedures.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the departmental SAE form. A BMS Pregnancy Surveillance Form may be provided upon request.

Any pregnancy that occurs in a female partner of a male study participant should be reported on the departmental SAE form and sent to BMS. Information on this pregnancy may also be collected on the BMS Pregnancy Surveillance Form. In order for PI or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

8.6 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 an SAE (see Section 8.1.1 for reporting details.).

8.7 Potential Drug Induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential drug-induced liver injury (DILI) event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 8.1.1 for reporting details).
Potential drug induced liver injury is defined as:

- AT (ALT or AST) elevation > 3 times upper limit of normal (ULN) AND
- Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase), AND
- No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

8.8 Review of Safety Information: Sponsor Responsibilities

The sponsor must promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States.

8.9 IND safety reports

The sponsor must notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting under Sections 1.5.1 to 1.5.4 below. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected

adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.

8.9.1 Serious and unexpected suspected adverse reaction

The sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

8.9.2 Findings from other studies

The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies (other than those reported under section 1.5.1), whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug. Ordinarily, such a finding would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

8.9.3 Findings from animal or in vitro testing

The sponsor must report any findings from animal or in vitro testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure. Ordinarily, any such findings would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

8.9.4 Increased rate of occurrence of serious suspected adverse reactions

The sponsor must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.

8.10 Submission of IND safety reports

The sponsor must submit each IND safety report in a narrative format or on Form FDA 3500A or in an electronic format that FDA can process, review, and archive. FDA will periodically issue

guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files). The sponsor may submit foreign suspected adverse reactions on a Council for International Organizations of Medical Sciences (CIOMS) I Form instead of a Form FDA 3500A. Reports of overall findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies must be submitted in a narrative format. Each notification to FDA must bear prominent identification of its contents, i.e., "IND Safety Report," and must be transmitted to the review division in the Center for Drug Evaluation and Research or in the Center for Biologics Evaluation and Research that has responsibility for review of the IND. Upon request from FDA, the sponsor must submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

8.10.1 Unexpected fatal or life-threatening suspected adverse reaction reports

The sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

8.10.2 Reporting format or frequency

FDA may require a sponsor to submit IND safety reports in a format or at a frequency different than that required under this paragraph. The sponsor may also propose and adopt a different reporting format or frequency if the change is agreed to in advance by the director of the FDA review division that has responsibility for review of the IND.

8.10.3 Investigations of marketed drugs

A sponsor of a clinical study of a drug marketed or approved in the United States that is conducted under an IND is required to submit IND safety reports for suspected adverse reactions that are observed in the clinical study, at domestic or foreign study sites. The sponsor must also submit safety information from the clinical study as prescribed by the post marketing safety reporting requirements.

8.10.4 Reporting study endpoints

Study endpoints (e.g., mortality or major morbidity) must be reported to FDA by the sponsor as described in the protocol and ordinarily would not be reported under Section 1.7 third bullet of this section. However, if a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis), the event must be reported under Serious and unexpected suspected adverse reaction as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (e.g., all-cause mortality).

8.11 Follow-up

- The sponsor must promptly investigate all safety information it receives.

- Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such, i.e., "Follow-up IND Safety Report."
- If the results of a sponsor's investigation show that an adverse event not initially determined to be reportable under section IND safety reports of this section is so reportable, the sponsor must report such suspected adverse reaction in an IND safety report as soon as possible, but in no case later than 15 calendar days after the determination is made.

8.12 Disclaimer

A safety report or other information submitted by a sponsor under this part (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the sponsor or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse event. A sponsor need not admit, and may deny, that the report or information submitted by the sponsor constitutes an admission that the drug caused or contributed to an adverse event.

The principal investigator must promptly review all information relevant to the safety of the drug obtained or otherwise received from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States. The study sponsor must notify all participating investigators of potential serious risks, from clinical trials or any other source, as soon as possible.

8.13 Reporting adverse events to the responsible IRB

In accordance with applicable policies of the University of Pittsburgh Institutional Review Board (IRB), the Sponsor-Investigator will report, to the IRB, any observed or volunteered adverse event that is determined to be 1) *associated with the investigational drug or study treatment(s)*; 2) *serious*; and 3) *unexpected*. Adverse event reports will be submitted to the IRB in accordance with the respective IRB procedures.

Applicable adverse events will be reported to the IRB as soon as possible and, in no event, later than 10 calendar days following the sponsor-investigator's receipt of the respective information. Adverse events which are 1) *associated with the investigational drug or study treatment(s)*; 2) *fatal or life-threatening*; and 3) *unexpected* will be reported to the IRB within 24 hours of the Sponsor-Investigator's receipt of the respective information.

Follow-up information to a reported adverse event will be submitted to the IRB as soon as the relevant information is available. If the results of the Sponsor-Investigator's follow-up investigation show that an adverse event that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting; the Sponsor-Investigator will report the adverse event to the IRB as soon as possible, but in no event later than 10 calendar days, after the determination was made.

8.14 Other Safety Considerations

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

9. DATA SAFETY MONITORING PLAN

Investigator/Sub-investigators, regulatory, CRS management, clinical research coordinators, clinical research associates, data managers, and clinic staff meet regularly in disease center Data Safety Monitoring Boards (DSMB) to review and discuss study data to include, but not limited to, the following:

- serious adverse events
- subject safety issues
- recruitment issues
- accrual
- protocol deviations
- unanticipated problems
- breaches of confidentiality

Minutes from the disease center DSMB meetings are available to those who are unable to attend in person.

All toxicities encountered during the study will be evaluated on an ongoing basis according to the NCI Common Toxicity Criteria Version 5.0. All study treatment associated adverse events that are serious, at least possibly related and unexpected will be reported to the IRB. Any modifications necessary to ensure subject safety and decisions to continue, or close the trial to accrual are also discussed during these meetings. If any literature becomes available which changes the risk/benefit ratio or suggests that conducting the trial is no longer ethical, the IRB will be notified in the form of an Unanticipated Problem submission and the study may be terminated.

All study data reviewed and discussed during these meetings will be kept confidential. Any breach in subject confidentiality will be reported to the IRB in the form of an Unanticipated Problem submission. The summaries of these meetings are forwarded to the UPMC Hillman Cancer Center DSMC which also meets monthly following a designated format.

For all research protocols, there will be a commitment to comply with the IRB's policies for reporting unanticipated problems involving risk to subjects or others (including adverse events). DSMC progress reports, to include a summary of all serious adverse events and modifications, and approval will be submitted to the IRB at the time of renewal.
Protocols with subjects in long-term (survival) follow-up or protocols in data analysis only, will be reviewed bi-annually.

Both the UPMC Hillman Cancer Center DSMC as well as the individual disease center DSMB have the authority to suspend accrual or further investigate treatment on any trial based on information discussed at these meetings.

All records related to this research study will be stored in a locked environment. Only the researchers affiliated with the research study and their staff will have access to the research records.

10. PHARMACEUTICAL INFORMATION

Product description and storage information is described below in Table 9.1. Preparation and administration instructions will be provided separately via site training materials.

For study drugs not provided by BMS and obtained commercially by the site, storage should be in accordance with the package insert, summary of product characteristics (SmPC), or similar documentation.

Table 10.1 Product Description and Dosage Form

Product Description / Class and Dosage Form	Concentration	IP/Non-IMP	Blinded or Open Label	Packaging / Appearance
Relatlimab[a] Injection (10mg/mL)	10mg/mL	IP	Open Label 4 vials per carton/ 100mg/vial (10mL vial) or Open Label 4 vials per carton/ 80 mg /vial (8mL vial)	Colorless to pale yellow liquid, clear to opalescent, light (few) particulates (consistent in appearance to protein particulates) may be present
Nivolumab[a] Injection (10mg/mL)	10mg/mL	IP	Open Label 4 vials per carton/ 100mg/vial (10mL vial)	Clear to opalescent, colorless to pale yellow liquid. Light (few) particulates may be present.

10.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form. The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational products are: relatlimab (BMS-986016) and nivolumab (BMS-936558).

10.2 Non-investigational Product

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

In this protocol, non-investigational product(s) is/are: Not applicable for this study.

10.3 Handling and Dispensing

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration, and, as applicable, storage temperatures, reconstitution, and use of required processes (e.g., required diluents, administration sets).

For non-investigational product, if marketed product is utilized, it should be stored in accordance with the package insert, summary of product characteristics (SmPC), or similar.

Nivolumab will be administered first followed by relatlimab within 30 minutes after completion of the nivolumab infusion. Further details regarding preparation and administration will be provided separately in site/pharmacy training materials.

11. BIOMARKER STUDIES

Tumor biopsy and peripheral blood draw will be performed within 1 week prior to the first dose of study drug, at the completion of the 4-week lead-in phase (+/- 5 days), and 12 weeks after initiation of the combination phase (+/- 5 days). Subjects who achieve complete response or partial response will have a tumor biopsy and peripheral blood draw performed at the time of disease progression.

The following biomarker studies will be performed:

- Assessment of pathological response on biopsy at 4 weeks following 1 cycle of assigned lead-in treatment with relatlimab, nivolumab, or the combination of nivolumab+relatlimab. A semiquantitative scale of irPR will be generated based on the following features: tumor infiltrating lymphocytes, neovascularization, fibrosis, plasma cells, lymphoid aggregates. Residual viable tumor (RVT) % will be calculated. irPR score will be scaled from 0-3 based on study of Stein et al.[24], 0 no features of irPR; 1 <3 colocalized features of irPR (e.g. TIL and/or fibrosis), or if more features are present, they are not colocalized; 2 at least 3 colocalized features of irPR are present and there is >10% RVT; and 3 MPRbx; at least three features of irPR present and 10% RVT). The assessment of irPR will be reported among first 21 patients and at the time of completion of trial accrual.

- Expression of exhaustion markers and metalloproteases: Immune correlates from peripheral blood and tumor infiltrating lymphocytes obtained within 2 weeks prior to the first dose of study drug (days -42 to -29), at the completion of the 4-week lead-in phase (days -7 to -1), 12 weeks after initiation of the combination phase (days 78 - 84), and at the time of progression if previously demonstrated complete response, partial response,

or stable disease may include, but are not limited to assessment of inhibitory receptors (PD1, LAG3, CTLA4, TIM3, TIGIT, 2B4 [CD244], CD160, NRP1) and the metalloproteases ADAM10 and ADAM17. LAG3 assessment will be performed based on BMS 17B4 antibody LAG3 assay.

- Correlates of tumoricidal activity: Evaluation of peripheral blood and tumor infiltrating lymphocytes obtained within 2 weeks prior to the first dose of study drug (days -42 to -29), at the completion of the 4-week lead-in phase (days -7 to -1), 12 weeks after initiation of the combination phase (days 78 - 84), and at the time of progression if previously demonstrated complete response, partial response, or stable disease for known correlates of tumoricidal activity will be performed, including but not limited to measurement of percentage and number of CD8+ and CD4+ tumor infiltrating lymphocytes, along with CD8+:Treg and CD4+:Treg ratio, as well as markers of effector function (IFN-g, TNF-a-IL-2, granzyme B (CD8+ lytic capacity), CD107a (Lamp1, indicator of CTL granule exocytosis)), effector/memory status (CD44, CD62L, CD127, KLRG1), and activation and maturation of dendritic cells (MHC class II, CD80, CD86, CD40, CD83, PD-L1/CD274, PD-L2, CD273).
- T cell proliferation and/or survival: Evaluation of peripheral blood and tumor infiltrating lymphocytes obtained within 2 weeks prior to the first dose of study drug (days -42 to -29), at the completion of the 4-week lead-in phase (days -7 to -1), 12 weeks after initiation of the combination phase (days 78 - 84), and at the time of progression if previously demonstrated complete response, partial response, or stable disease with dye dilution-based in vitro proliferation assay and Ki67 staining (in G1-S-G2); cell death by active caspase (apoptosis marker) and Bcl-2 (survival factor).
- Increased soluble LAG3: Evaluation of peripheral blood obtained within 2 weeks prior to the first dose of study drug (days -42 to -29), at the completion of the 4-week lead-in phase (days -7 to -1), 12 weeks after initiation of the combination phase (days 78 - 84), and at the time of progression if previously demonstrated complete response, partial response, or stable disease to assay soluble LAG3.
- Treg: Tumor samples obtained within 2 weeks prior to the first dose of study drug (days -42 to -29), at the completion of the 4-week lead-in phase (days -7 to -1), 12 weeks after initiation of the combination phase (days 78 - 84), and at the time of progression if previously demonstrated complete response, partial response, or stable disease will be assessed for expression of known Treg markers and mediators (effectors of suppressive activity (TGFb, GARP, CD39, GrzB, CD107a), inhibitory receptors (CTLA4, PD1, LAG3, TIGIT, TIM3), mediators of inhibitory receptors i.e. metalloproteases ADAM 10/17, mediators of migration egress (CCR4, S1pr1), transcription factors (Foxp3, Eos), activation/maturation status (CD25, Klrg1), and IL10/IL35 expression. Proliferation will be determined by Ki67 staining. Staining for active caspase and Bcl-2 will assess survival profile. Markers previously shown to be associated with Treg stability will be assessed by flow cytometry (NRP1, Helios, ICOS, CXCR3).
- Single cell RNA sequencing: To be performed on matching peripheral blood lymphocytes and tumor biopsies from 14 subjects per treatment arm (BMS-986016 alone, nivolumab alone, and combination with BMS-986016 and nivolumab) obtained within 2 weeks prior to the first dose of study drug (days -42 to -29), at the completion of the 4-week lead-in phase (days -7 to -1), 12 weeks after initiation of the combination phase (days 78 - 84), and at the time of progression if previously demonstrated complete

response, partial response, or stable disease to assess the mechanistic effects of the individual and combined therapies.

Tumor samples will be processed by the UPCI Immunologic Monitoring and Cellular Products Laboratory. Immunohistological analysis will be performed using Perkin Elmer Vectra system using paraffin-embedded tissue.

Analysis of biomarker data will be performed as described in Section 13.

12. MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients will be re-evaluated for response every 12 weeks (+/- 1 week). In addition, confirmatory scans will be obtained no fewer than 28 days following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with the study treatment of nivolumab and/or relatlimab.

Evaluable for objective response. Only those patients who have measurable disease present at baseline as assessed following completion of lead-in phase, have received at least one cycle of therapy, and have had their disease re-evaluated following 12 weeks of combination phase will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

12.1.2 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 (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). 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 [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] 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 patient, 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.

12.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being

followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of sufficiently comparable diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor

types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

12.1.4 Response Criteria

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 (<1 cm).

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 (0.5 cm).

(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 [<1 cm] short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient 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 patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients 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	No	PR	

	evaluated			
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: Patients 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.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

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

12.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

12.1.6 Progression-Free Survival

Progression-free survival defined as the time between the date of randomization and the first date of documented progression or death due to any cause, whichever occurs first.

12.1.7 Overall Survival

Overall survival is defined as the time between the date of randomization and the date of death due to any cause. Patients who are alive will be censored at the time of the last follow-up

13. STUDY OVERSIGHT AND DATA HANDLING

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

13.1 Study Oversight

Investigator/Sub-investigators, regulatory, CRS management, clinical research coordinators, clinical research associates, data managers, and clinic staff meet monthly in disease center Data Safety Monitoring Boards (DSMB) to review and discuss study data to include, but not limited to, the following:

- Serious adverse events
- Subject safety issues
- Recruitment issues
- Accrual
- Protocol deviations
- Unanticipated problems
- Breaches of confidentiality

All study data reviewed and discussed during these meetings will be kept confidential. Any breach in subject confidentiality will be reported to the IRB in the form of an Unanticipated Problem submission. The summaries of these meetings are forwarded to the UPMC HCC DSMC which also meets monthly following a designated format.

For all research protocols, there will be a commitment to comply with the IRB's policies for reporting unanticipated problems involving risk to subjects or others (including adverse events). DSMC progress reports, to include a summary of all serious adverse events and modifications, and approval will be submitted to the IRB at the time of renewal.

Protocols with subjects in long-term (survival) follow-up or protocols in data analysis only, will be reviewed twice a year rather than monthly.

Both the UPMC HCC DSMC as well as the individual disease center DSMB have the authority to suspend accrual or further investigate treatment on any trial based on information discussed at these meetings.

All records related to this research study will be stored in a locked environment. Only the researchers affiliated with the research study and their staff will have access to the research records.

13.2 Data Handling and Record Keeping

A Case Report Form (CRF) will be completed for each subject enrolled into the clinical study. Source Data are the clinical findings and observations, laboratory and test data, and other information contained in Source Documents. Source Documents are the original records including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, etc. When applicable, information recorded on the CRF shall match the Source Data recorded on the Source Documents.

14. STATISTICAL CONSIDERATIONS

14.1 Study Design / Objectives

This is a single center, phase 2 study to evaluate the change in immune biomarkers of treatment with relatlimab alone, nivolumab alone, and the combination of nivolumab + relatlimab and the objective response rate of the combination of nivolumab + relatlimab as compared to historical controls in patients with unresectable or metastatic melanoma who have not received prior treatment in the metastatic setting.

Primary Objectives:

- Lead-in phase (4 weeks)
    - Compare immune biomarkers from tumor biopsy and peripheral blood performed prior to the first dose of study drug to samples obtained following 1 cycle (4 weeks) of the assigned treatment for lead-in phase. Pre-treatment immune markers will be compared to post-treatment markers with the signed rank test. Percent LAG3 and percent PD1 expression in TIL are recognized as primary endpoints and each will be tested at level .05. For other yet unspecified biomarkers, test p values will adjusted for false discovery.
    - Evaluate association between change in immune biomarkers and change in tumor size. Change in tumor size over the lead-in phase will be assessed by restricted cubic spline linear regression on contemporaneous change in immune biomarkers. Association with LAG3 and PD1 in TIL are recognized as priority biomarkers and each will be tested at level .05. Remaining test p values will be adjusted for false discovery.

Combination phase

- Estimate antitumor activity of the combination of nivolumab and relatlimab as measured by overall response rate (defined as complete response + partial response / total patients assessed) with 90% confidence intervals. Response assessment will be based on RECIST v1.1 criteria initially assessed at 12 weeks after initiation of combination phase compared to baseline imaging obtained immediately prior to initiating combination. Subsequent response staging will

occur as needed at 12 week intervals until progression Confirmation of objective response will be determined by subsequent target lesion imaging no fewer than 28 days of the initial response assessment.

Secondary Objectives:

- Estimate clinical benefit, defined as the combination of complete response, partial response, and stable disease as assessed by RECIST v1.1. Assessement will at 12 weeks after initiation of combination phase and will be compared to baseline imaging obtained immediately prior to initiating combination. Assessments will be repeated as needed at 12 week intervals until progression, with confirmation of progression determined by target lesion imaging no fewer than 28 days following the initial CT imaging. The clinical benefit rate will be calculated with a 90% confidence interval.
- Estimate duration of response, defined as the time measurement criteria are first met for complete response or partial response (whichever is first recorded) until the first date that progressive disease is objectively documented. Duration of response will be estimated by the Kaplan-Meier method
- Estimate progression-free survival, defined as the time between the date of randomization and the first date of documented progression or death due to any cause, whichever occurs first. Progression-free response will be estimated by the Kaplan-Meier method
- Estimate overall survival, defined as the time between the date of randomization and the date of death due to any cause. Overall survival will be estimated by the Kaplan-Meier method
- Describe safety as measured by adverse events that will be graded using the Cancer Therapy Evaluation Program (CTEP) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 Adverse events will be captured during treatment and up to 12 weeks after discontinuing treatment, with clinical follow-up mandated at 4 weeks and then again at 12 weeks. All subjects who receive at least one dose of relatlimab or nivolumab will be analyzed for safety. The proportion of individual patients experiencing grade III or IV SAEs will be estimated with a 90% confidence interval.
- Conduct correlative analysis of immune filtrate on tumor biopsy and peripheral blood performed prior to the first dose of study drug, following 1 cycle (4 weeks) of the assigned lead-in treatment, and following 3 cycles of combination treatment in all three groups (12 weeks after initiating combination phase). Analysis of the effects of treatment of anti-LAG3 alone, anti-PD1 alone, and anti-LAG3/PD1 in combination will proceed with a mixed effects linear model in which lead-in treatment is a fixed constant factor, LAG3 and PD1 in TIL are time-varying fixed effects and individual patients are random effects to be described with a random intercept. The dependent variable will be change in tumor size over the combination treatment period
- Additional biomarkers to be analyzed with mixed effect linear model at weeks 0, 4, 16 and at time of progression include:
    - Expression of exhaustion markers and metalloproteases: Immune correlates from peripheral blood and tumor infiltrating lymphocytes obtained within 2 weeks prior to the first dose of study drug (days -42 to -29), at the completion of the 4-week lead-in phase (days -7 to -1), 12 weeks after initiation of the combination phase (days 78 - 84), and at the time of progression if previously demonstrated complete response, partial response, or stable disease may include, but are not limited to

assessment of inhibitory receptors (PD1, LAG3, CTLA4, TIM3, TIGIT, 2B4 [CD244], CD160, NRP1) and the metalloproteases ADAM10 and ADAM17. P values will be adjusted for false discovery.

- Correlates of tumoricidal activity: Evaluation of peripheral blood and tumor infiltrating lymphocytes obtained within 2 weeks prior to the first dose of study drug (days -42 to -29), at the completion of the 4-week lead-in phase (days -7 to -1), 12 weeks after initiation of the combination phase (days 78 - 84), and at the time of progression if previously demonstrated complete response, partial response, or stable disease for known correlates of tumoricidal activity will be performed, including but not limited to measurement of percentage and number of CD8+ and CD4+ tumor infiltrating lymphocytes, along with CD8+:Treg and CD4+:Treg ratio, as well as markers of effector function (IFN-g, TNF-a-IL-2, granzyme B (CD8+ lytic capacity), CD107a (Lamp1, indicator of CTL granule exocytosis)), effector/memory status (CD44, CD62L, CD127, KLRG1), and activation and maturation of dendritic cells (MHC class II, CD80, CD86, CD40, CD83, PD-L1/CD274, PD-L2, CD273). P values will be adjusted for false discovery.
- T cell proliferation and/or survival: Evaluation of peripheral blood and tumor infiltrating lymphocytes obtained within 2 weeks prior to the first dose of study drug (days -42 to -29), at the completion of the 4-week lead-in phase (days -7 to -1), 12 weeks after initiation of the combination phase (days 78 - 84), and at the time of progression if previously demonstrated complete response, partial response, or stable disease with dye dilution-based in vitro proliferation assay and Ki67 staining (in G1-S-G2); cell death by active caspase (apoptosis marker) and Bcl-2 (survival factor). P values will be adjusted for false discovery.
- Increased soluble LAG3: Evaluation of peripheral blood obtained within 2 weeks prior to the first dose of study drug (days -42 to -29), at the completion of the 4-week lead-in phase (days -7 to -1), 12 weeks after initiation of the combination phase (days 78 - 84), and at the time of progression if previously demonstrated complete response, partial response, or stable disease to assay soluble LAG3. P values will be adjusted for false discovery.
- Treg: Tumor samples obtained within 2 weeks prior to the first dose of study drug (days -42 to -29), at the completion of the 4-week lead-in phase (days -7 to -1), 12 weeks after initiation of the combination phase (days 78 - 84), and at the time of progression if previously demonstrated complete response, partial response, or stable disease will be assessed for expression of known Treg markers and mediators (effectors of suppressive activity (TGFb, GARP, CD39, GrzB, CD107a), inhibitory receptors (CTLA4, PD1, LAG3, TIGIT, TIM3), mediators of inhibitory receptors i.e. metalloproteases ADAM 10/17, mediators of migration egress (CCR4, S1pr1), transcription factors (Foxp3, Eos), activation/maturation status (CD25, Klrg1), and IL10/IL35 expression. Proliferation will be determined by Ki67 staining. Staining for active caspase and Bcl-2 will assess survival profile. Markers previously shown to be associated with Treg stability will be assessed by flow cytometry (NRP1, Helios, ICOS, CXCR3). P values will be adjusted for false discovery.

Exploratory Objectives

- Single cell RNA sequencing: To be performed on matching peripheral blood lymphocytes and tumor biopsies from 14 subjects per treatment arm (BMS-986016 alone, nivolumab alone, and combination with BMS-986016 and nivolumab) obtained within 2 weeks prior to the first dose of study drug (days -42 to -29), at the completion of the 4-week lead-in phase (days -7 to -1), 12 weeks after initiation of the combination phase (days 78 - 84), and at the time of progression if previously demonstrated complete response, partial response, or stable disease to assess the mechanistic effects of the individual and combined therapies.

- Assessment of pathological response on biopsy at 4 weeks following 1 cycle of assigned lead-in treatment with relatlimab, nivolumab, or the combination of nivolumab+relatlimab. A semiquantitative scale of irPR will be generated based on the following features: tumor infiltrating lymphocytes, neovascularization, fibrosis, plasma cells, lymphoid aggregates. Residual viable tumor (RVT) % will be calculated. irPR score will be scaled from 0-3 based on study of Stein et al.[24], 0 no features of irPR; 1 <3 colocalized features of irPR (e.g. TIL and/or fibrosis), or if more features are present, they are not colocalized; 2 at least 3 colocalized features of irPR are present and there is >10% RVT; and 3 MPRbx; at least three features of irPR present and 10% RVT). The assessment of irPR will be reported among first 21 patients and at the time of completion of trial accrual.
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14.2 Sample Size/Accrual Rate

The expected clinical response rate with nivolumab in naïve unresectable stage IIIB, stage IIIC, or stage IV melanoma patients is assumed to equal 40% (1,2). An increase to 60% due to the addition of relatlimab would be of sufficient interest to warrant further study of this combination in the presence of an acceptable safety profile . A single arm one stage design with $\alpha = \beta = .10$ has been selected that will require 41 patients to provide 90% power for a one sample one tailed exact binomial test. In that patients are to be randomly assigned to one of three lead-in regimens, 42 patients response-evaluable patients will be accrued and complete 12 weeks of treatment. Forty-two patients will permit exactly 14 patients per lead-in group. Additional accrual may be necessary to replace patients who do not complete the 12 week response evaluation or are otherwise non-evaluable for response.

Our institution is a major referral center for patients with melanoma, and has more than 500 new patient visits annually for evaluation for melanoma of which greater than one-third are newly diagnosed metastatic melanoma. Based on our institution's clinical volume and prior experience with melanoma clinical trials, we expect accrual of 42 patients to take between 12 to 18 months.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	1	1	0	0	**2**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	2	2	0	0	**0**
White	18	18	0	0	**36**
More Than One Race	0	0	0	0	**0**
Total	**21**	**21**	**0**	**0**	**42**

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1. Two-sample t-test or Wilcoxon Rank Sum test will be used to compare LAG3 expression at baseline between responders and non-responders.

14.3 Reporting and Exclusions

14.3.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with nivolumab or relatlimab.

14.3.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (*with the exception of those who received no study medication*) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.

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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 CONTRACEPTION

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 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 2.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence

NOTES:

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

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

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

Unacceptable Methods of Contraception*

- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal Sponge with spermicide
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus).
- Spermicide only
- Lactation amenorrhea method (LAM)

*** 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.