A Phase 2 Study of Nivolumab + BMS-986016 (Relatlimab) in Patients with Metastatic Uveal Melanoma.

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Sponsor Investigator/Principal Investigator	Jose Lutzky, MD University of Miami Sylvester Comprehensive Cancer Center 1475 NW 12th Ave Miami, FL 33136
Co-Investigators	J. William Harbour, MD
	Lynn Feun, MD
Funding Collaborator	Bristol-Myers Squibb Research and Development Route 206 & Province Line Road Lawrenceville, NJ 08543
Study Drug(s) Name	**Nivolumab** (also referred to as BMS-936558, MDX1106, or ONO-4538) and **Relatlimab** (also referred to as BMS-986016)
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LIST OF STUDY CONTACTS

IND Sponsor Investigator/Principal Investigator	Jose Lutzky, MD Sylvester Comprehensive Cancer Center 1120 NW 14th St. Miami, FL 33136 [redacted]
Co-Investigator	J. William Harbour, MD Bascom Palmer Eye Institute 900 NW 17th Street Miami, FL 33138 [redacted]
Co-Investigator	Lynn Feun, MD Sylvester Comprehensive Cancer Center [redacted]
Biostatistician:	Deukwoo Kwon, PhD, Research Assistant Professor Division of Biostatistics, Department of Public Health Sciences Sylvester Biostatistics and Bioinformatics Shared Resource (BBSR) University of Miami Leonard M. Miller [redacted]
Protocol Writer	Norma Magallanes, MS, CCRP Sylvester Comprehensive Cancer Center University of Miami [redacted]
Funding Source:	Bristol-Myers Squibb
Regulatory Sponsor:	Sylvester Comprehensive Cancer Center (SCCC) Miami, FL 33136
Investigational Drug Sponsor	Bristol-Myers Squibb

Investigational Agent(s):	**Nivolumab** (also referred to as BMS-936558, MDX1106, or ONO-4538) and **Relatlimab** (also referred to as BMS-986016)
IND Status:	IND#: 152402

STATEMENT OF COMPLIANCE

I confirm that I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practices, and the applicable federal, state, and local laws, rules, and regulations relating to the conduct of the protocol.

I have read and understand the information in the Investigators' Brochure (and/or other such pertinent safety information) regarding the risks and potential benefits.

I agree to inform all those who assist/collaborate with me in the conduct of this study of their responsibilities and obligations.

Once the protocol has been reviewed and approved by the Institutional Review Board (IRB) I understand that any change(s) made during the course of the study must also (first) be approved by the IRB prior to implementation, except when such modification is made to remove any immediate hazard(s) to the subject(s).

I certify that I and the study staff responsible, have received the requisite training to conduct this research protocol.

I agree to maintain adequate and accurate records in accordance with the University of Miami policies, federal, state and local laws and regulations.

I agree to maintain the confidentiality of all information received and/or developed in connection with this protocol.

eProst Number: 20200847	
Protocol Version Number: Version 3.0	Protocol Version Date: 4 February, 2023

Signature of Investigator:	Date:
Name of Investigator (printed):	Institution:

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ADA	Anti-drug antibodies
AE	Adverse event
AUC	Area under the curve
BMS	Bristol-Myers Squibb
CHO	Chinese hamster ovary
CTCAE	Criteria for Adverse Events
CTLA-4	Cytotoxic T lymphocyte antigen 4
CNS	Central nervous system
CR	Complete response
CRT	Case report form
DCR	Disease control rate
DOR	Duration of response
EC	Effective concentration
ePPND	Enhanced pre- and postnatal development
FDC	Fixed dose combination
HIV	Human immunodeficiency virus
HSCT	Hematopoietic stem cell transplantation
GLP	Good laboratory practice
IB	Investigator’s brochure
IFN-γ	interferon-gamma
IGG4	Immunoglobulin G4
IgSF	Immunoglobulin superfamily
IO	Immuno-oncology
irAEs	Immune related adverse events
IRB	Institutional review board
IV	Intravenous
LAG-3	lymphocyte activation gene 3
mDOR	Median duration of response
MHC	Major histocompatibility complex
MLR	Mixed lymphocyte reaction
MTD	Maximum tolerated dose
NK	Natural killer
NOAEL	No-observed-adverse-effect-level
ORR	Overall response rate
OAS	Overall survival

OS	Overall survival
PD-1	Programmed death-1
PD-L1	Programmed death ligand-1
PD-L2	Programmed death ligand-2
PFS	Progression free survival
Q2W	Every 2 weeks
Q4W	Every 2 weeks
SAE	Serious adverse event
SCCC	Sylvester Comprehensive Cancer Center
ULN	Upper limit of normal
UM	Uveal melanoma
T-Half	Elimination half life
TIL	Tumor infiltrating lymphocytes
TME	Tumor microenvironment

PROTOCOL SUMMARY

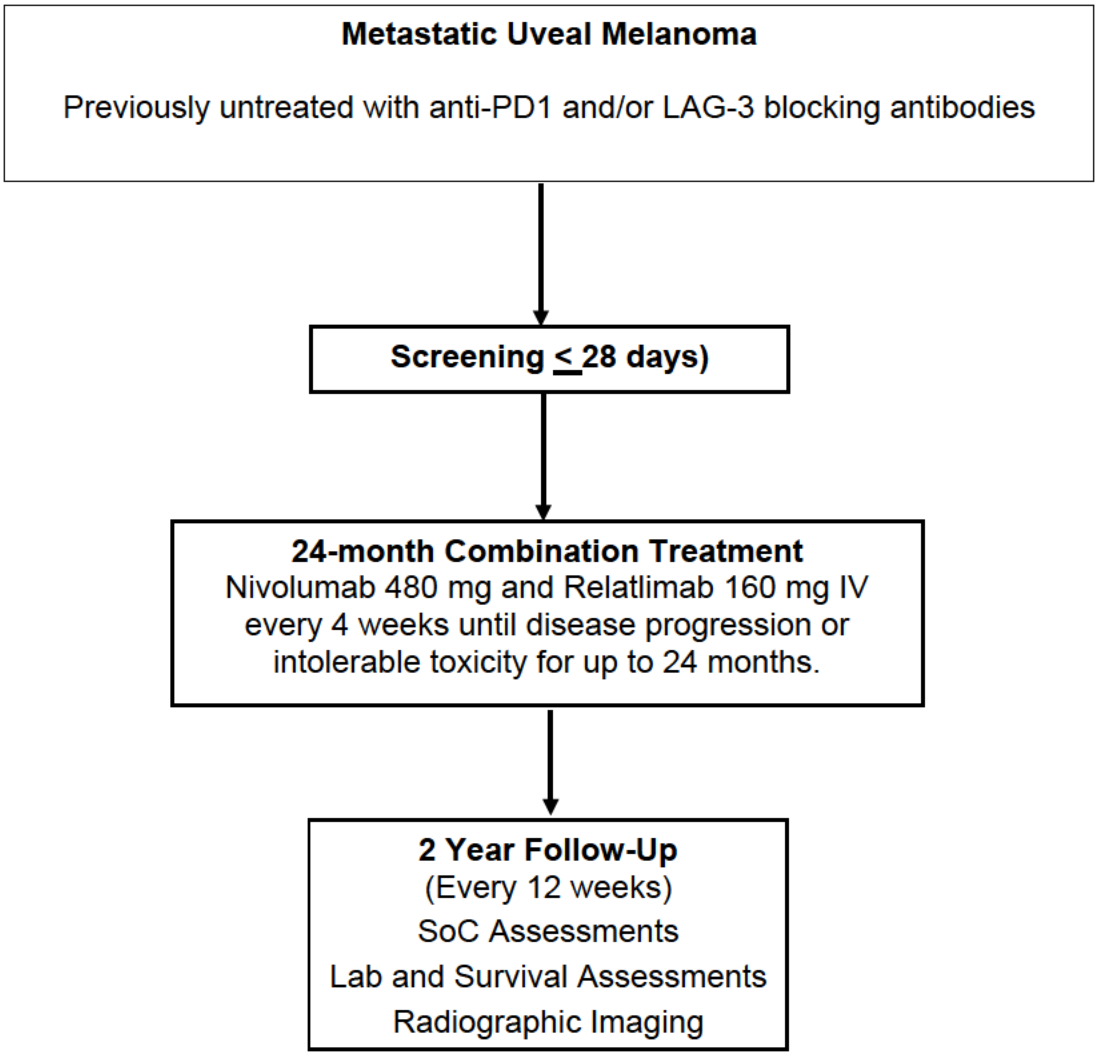
Title	A phase 2 study of nivolumab + BMS-986016 (relatlimab) in patients with metastatic uveal melanoma.
Background	The standard of care treatment for cutaneous melanoma has experienced rapid and significant changes. It has evolved from mostly ineffective chemotherapy and minimally successful immunotherapy to the current anti-CTLA4 and anti-PD1/checkpoint inhibitors that have resulted in survival prolongation. For patients whose tumors harbor a BRFA V600 mutations, combinations of BRAF plus MEK inhibitors provide another highly successful treatment option. On the other hand, progress in the treatment of metastatic uveal melanoma has remained dismal. Uveal melanoma (UM) is a rare malignancy that arises from melanocytes within the uveal tract of the eye. The overall mean age-adjusted incidence of primary uveal melanoma in the US over the 41-year period from 1973 to 2013 was 5.2 per million population (95% CI 5.0–5.4). Although UM is often diagnosed at an early stage, 50% of patients will develop metastatic disease with 6–12 months survival from metastatic diagnosis. A meta-analysis of 796 patients treated for metastatic uveal melanoma with various forms of therapy demonstrated an overall response rate of 10.3% with 0.6% complete responses (CRs). For patients treated with immunotherapy the median PFS was 2.8 months and the median OAS was 8.9 months.[1] The various treatment modalities used to treat metastatic uveal melanoma include liver-directed therapies, immunotherapy, targeted therapy and chemotherapy. Chemotherapy has been found to be largely ineffective. A number of phase II trials with the anti-CTLA-4 blocking antibodies ipilimumab and tremelimumab have reported ORR between 0-7.7% and median OS of 5.2-10.3 months. Algazi et al. summarized the clinical experience from various institutions with PD-1/PD-L1 blocking antibody treatment for metastatic uveal melanoma in 56 patients. The ORR was 3.6% with a median PFS of 2.6 months and median OS of 7.6 months. [2]

	Outcomes appear to be improved when a the combination of ipilimumab (3 mg/kg) and nivolumab (1 mg/kg)have been used in two recent reports comprising a total of 135 patients.The ORR, median PFS and OS were respectively 12%/9%, 3.3/2.7 months and 12.7/15 months (Rodriguez, 2018; Najar, 2018). Another recent abstract on 30 patients with metastatic uveal melanoma treated with ipilimumab plus nivolumab reported a 17% ORR with 3% CR.[3] Molecularly targeted therapies for the MAPK and/or the PI3K/AKT pathways have demonstrated only limited activity. Other areas of clinical research include studies of HDAC inhibitors and BET protein inhibitors.	
Phase:	Phase 2	
Objectives/Endpoints	Objectives	Endpoints
Primary	To evaluate efficacy of the combination of nivolumab and BMS-986016 in terms of objective response rate (ORR) according to RECISTv1.1	Primary endpoint for this study will be best objective response rate (ORR).
Secondary	To evaluate the disease control rate (DCR), progression-free survival (PFS), overall survival (OS), duration of response (DOR) and safety profile of the combination of nivolumab and BMS-986016	Secondary endpoints will include disease control rate (DCR), progression-free survival (PFS), overall survival (OS), median duration of response (mDOR) and safety profile (AEs, SAEs).
Exploratory	Tumor microenvironment (TME) in fresh biopsies pre- and post-treatment and at progression	Evaluate pre-treatment characteristics of the TME that may predict for response or lack of response. Learn the effects of treatment on the TME
	Blood samples at baseline and predetermined post-treatment time points and at progression	T cell receptor profiling Circulating tumor cell DNA
Study Drug(s)	**Nivolumab** (also referred to as BMS-936558, MDX1106, or ONO-4538) and **Relatlimab** (also referred to as BMS-986016)	
Indication	Metastatic uveal melanoma.	

Study Design	This is an open-label, single arm, single site investigator-initiated phase II study based Simon minimax two-stage design.
Treatment Plan	Enrolled patients will be treated in the outpatient setting. Nivolumab 480 mg will be mixed in the same bag with Relatlimab 160 mg and will be administered intravenously over 60 minutes (+ or –5 minutes) every 4 weeks. Each cycle will be approximately 4 weeks in length. Both drugs will be administered until disease progression or intolerable toxicity for up to 24 months.
Correlative Studies	Correlative studies will be conducted for research use only. For participants who consent to additional correlative studies, archival tissue, blood, and fresh/fresh-frozen tumor from pre- and post- treatment biopsy will be collected for correlative biomarker analysis including but not limited to tumor single-cell RNA-sequencing with single-cell TCR/BCR profiling, metastatic tumor mutation profiling, blood-based bulk TCR profiling, and blood-based cell-free DNA mutation profiling. **Correlative Studies, Solid Tumors:** Archival FFPE primary or previous metastatic tumor specimen, if available, may be collected from previous/current surgeries or biopsies for biomarker analysis including but not limited to mutation analysis and immunohistochemistry of LAG-3 and PD-1. A minimum of 3 10-micron sections will be required. Fresh/fresh-frozen tumor tissue from pre- and post- treatment biopsies will be collected for biomarker analysis including but not limited to tumor single-cell RNA-sequencing with single-cell TCR/BCR profiling. Mutation analysis may be conducted on fresh-frozen tumor tissue from pre- and post- treatment biopsy, if quantity permits. **Correlative Studies, Blood:** Blood will be obtained using EDTA purple top tubes and will be stored as plasma and buffy coat at -80 °C. Blood sample analysis will consist of but is not limited to bulk TCR profiling and cell-free DNA profiling.
Number of Patients	During the **first stage**, the investigational treatment will be tested on 13 patients. The trial will be terminated if there are no responses in these 13 patients. If the trial goes on to the **second stage**, an additional 14 patients will receive the investigational treatment.
Target Population	Up to 27 participants (13 in stage 1, 14 in stage 2) will be enrolled in the study.

Expected number of centers	One Center: • Sylvester Comprehensive Cancer Center (SCCC) inclusive of the constituent satellite sites.
Participant duration	Following enrollment, participants will be treated with an investigational treatment of nivolumab 480 mg and relatlimab 160 mg every 4 weeks. Both drugs will be administered until disease progression or intolerable toxicity for a total treatment duration of up to 24 months. Patients will be followed for 2 years to obtain information on disease progression and overall survival. Total participant duration is approximately 3 years.
Study Duration	The expected study duration is 4 to 4.5 years. The expected enrollment is a total of 27 evaluable patients within a period of 2 to 2.5 years.

Schema


Metastatic Uveal Melanoma
Previously untreated with anti-PD1 and/or LAG-3 blocking antibodies
Screening ≤ 28 days)
24-month Combination Treatment
Nivolumab 480 mg and Relatlimab 160 mg IV every 4 weeks until disease progression or intolerable toxicity for up to 24 months.
2 Year Follow-Up
(Every 12 weeks)
SoC Assessments
Lab and Survival Assessments
Radiographic Imaging

1 INTRODUCTION

1.1 Clinical Background on Uveal Melanoma

The standard of care treatment for cutaneous melanoma has experienced rapid and significant changes. It has evolved from mostly ineffective chemotherapy and minimally successful immunotherapy to the current anti-CTLA4 and anti-PD1/checkpoint inhibitors that have resulted in survival prolongation. For patients whose tumors harbor a BRFA V600 mutations, combinations of BRAF plus MEK inhibitors provide another highly successful treatment option.

On the other hand, progress in the treatment of metastatic uveal melanoma has remained dismal. Uveal melanoma (UM) is a rare malignancy that arises from melanocytes within the uveal tract of the eye. The overall mean age-adjusted incidence of primary uveal melanoma in the US over the 41-year period from 1973 to 2013 was 5.2 per million population (95% CI 5.0–5.4).

Although UM is often diagnosed at an early stage, 50% of patients will develop metastatic disease with 6–12 months survival from metastatic diagnosis.
A meta-analysis of 796 patients treated for metastatic uveal melanoma with various forms of therapy demonstrated an overall response rate of 10.3% with 0.6% CRs. For patients treated with immunotherapy the median PFS was 2.8 months and the median OAS was 8.9 months.[1]

The various treatment modalities used to treat metastatic uveal melanoma include liver-directed therapies, immunotherapy, targeted therapy and chemotherapy. Chemotherapy has been found to be largely ineffective.

A number of phase II trials with the anti-CTLA-4 blocking antibodies ipilimumab and tremelimumab have reported ORR between 0-7.7% and median OS of 5.2-10.3 months.

Algazi et al. summarized the clinical experience from various institutions with PD-1/PD-L1 blocking antibody treatment for metastatic uveal melanoma in 56 patients. The ORR was 3.6% with a median PFS of 2.6 months and median OS of 7.6 months. [2]

Outcomes appear to be improved when a the combination of ipilimumab (3 mg/kg) and nivolumab (1 mg/kg)have been used in two recent reports comprising a total of 135 patients.The ORR, median PFS and OS were respectively 12%/9%, 3.3/2.7 months and 12.7/15 months (Rodriguez, 2018; Najar, 2018). Another recent abstract on 30 patients with metastatic uveal melanoma treated with ipilimumab plus nivolumab reported a 17% ORR with 3% CR.[3]

Molecularly targeted therapies for the MAPK and/or the PI3K/AKT pathways have demonstrated only limited activity. Other areas of clinical research include studies of HDAC inhibitors and BET protein inhibitors.

1.2 Lymphocyte activation gene 3 (LAG-3) and recent pre-clinical data:

LAG-3 is an immune checkpoint receptor with a biological role in T cell regulation. Analysis of immune-cell infiltrates from human tumors show that a subset of CD4+ and/or CD8+ cells co express LAG-3 and PD-1 and may be associated with decreased T-cell effector function and tumor escape.[4] Preclinical models have provided evidence that dual inhibition of LAG-3 and PD-1 blockade offers synergistic anti-tumor activity.[5]

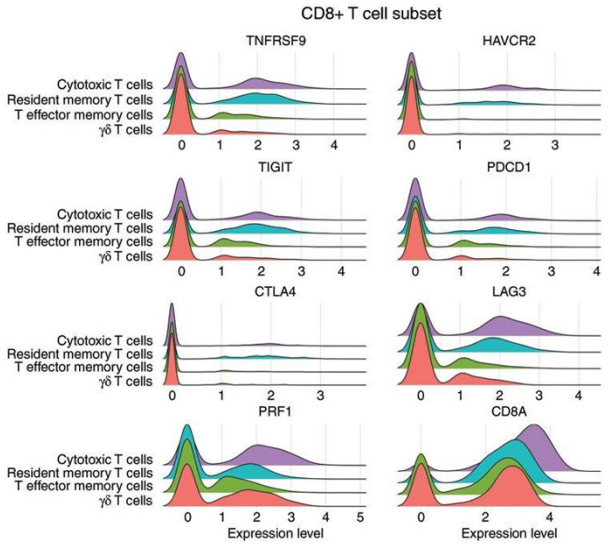
Recently published data from Dr. William Harbour's laboratory at the University of Miami/Bascom Palmer Eye Institute has shed light on relevant new data regarding uveal melanoma.[6]

The uveal melanoma tumor microenvironment (TME) was interrogated at single-cell resolution using sc-RNA-seq of 59,915 tumor and non-neoplastic cells from 8 primary and 3 metastatic samples. Analysis of tumor cells confirms the global genomic landscape established from bulk analysis and reveals newly described subclonal genomic complexity and transcriptional states consistent with phenotype plasticity. The immune compartment was shown to be comprised of a previously unrecognized diversity of cell types, including CD8+ T cells expressing the checkpoint marker LAG3, as opposed to PD1 or CTLA4.

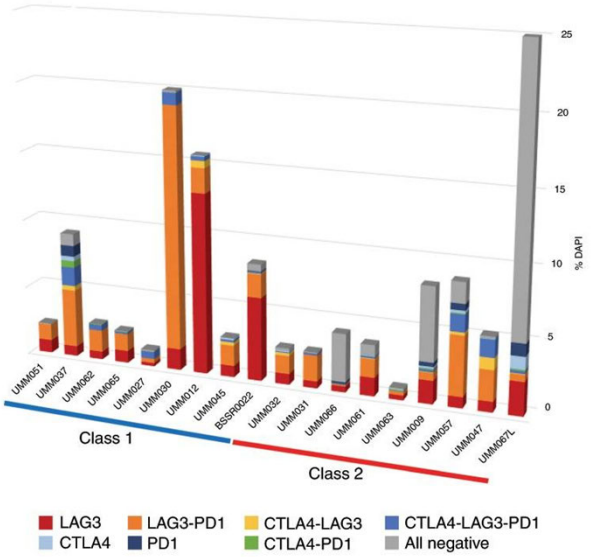
As seen in **Figure 1** below, T cells are present in all samples but are most prevalent in class 2 primary tumors and in metastatic samples. Most T cells are CD8+, with smaller populations of CD4+ cells, including follicular helper cells, FOXP3+ regulatory cells, and naïve lymphocytes. V(D)J recombination analysis of T and B cell receptors from sc-RNA-seq data reveals clonally expanded T cells in only three samples, all class 2 primary tumors. CD8+ T cell expression of exhaustion-associated immune checkpoint molecules is strongest for LAG3, variable for TIGIT, and minimal for PD1, CTLA4, TIM3, and TNFRSF9. Protein expression of LAG3, CTLA4 and PD1 were orthogonally validated using multi-color IHC in 18 samples. These findings, coupled with the absence of PD-L1 and PD-L2 expression in tumor cells may explain the ineffectiveness of CTLA and PD1 blockade in metastatic UM.[7]CD14+ monocytes/macrophages are present in all primary and metastatic samples, with CD68+ macrophages displaying a spectrum from M1- to M2-polarization, the latter being enriched in class 2/BAP1^{mut} samples, consistent with previous reports from bulk analysis. Few NK cells are present, and they are distributed equally across tumor samples without class predilection. B cells and plasma cells are rare in most samples.

The discovery of LAG3 as the dominant exhaustion marker in UM may explain the failure of previous checkpoint blockade targeting CTLA4 and PD1, and it nominates LAG3 as a potential candidate for checkpoint inhibitor immunotherapy in UM. Additionally, early data from Karlsson's group from Sweden seem to corroborate these findings in several samples of metastatic uveal melanoma.[7]

Figure 1.**Immune microenvironment of uveal melanomas with V(D)J recombination repertoire sequencing of B- and T- lymphocytes**



a.



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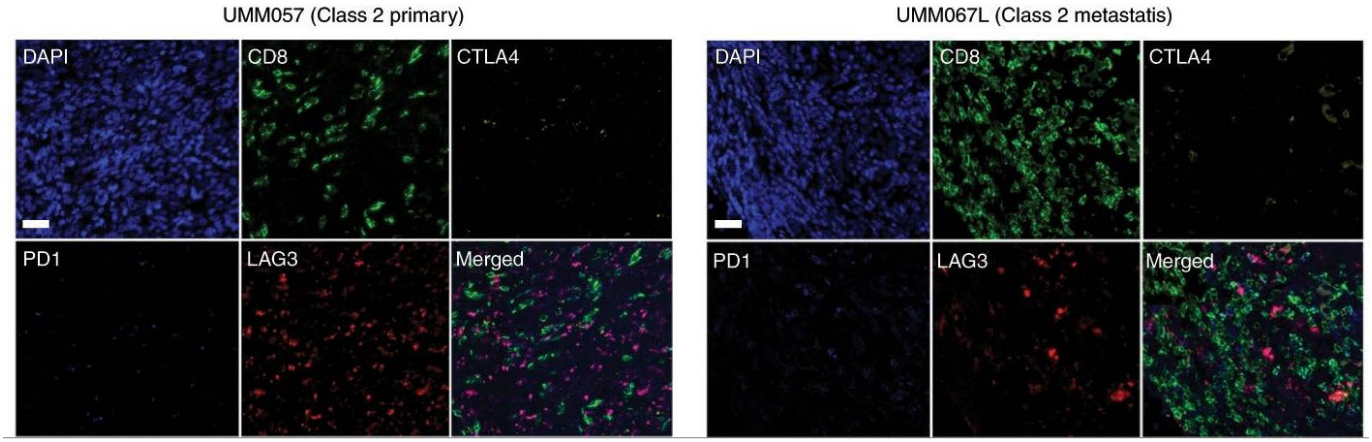

c.

a. Ridge plot of CD8⁺ T cell subset demonstrating strong expression of *LAG3*, moderate expression of *TIGIT*, and minimal expression of *PD1*, *CTLA4*, *TIM3*, and *TNFRSF9*.
b. Quantification of multi-color IHC for CD8, LAG3, PD1, CTLA4, and DAPI. 18 total samples were analyzed by IHC including 7 that were analyzed by scRNA-seq and an additional 11 samples. Metastatic samples include BSSR0022 and UMM067L. Other samples represent primary tumors. Quantitation of each sample was performed by whole-slide scanning of a single slide. Source data are provided as a Source Data file.
c. Representative multi-color IHC images of a primary and a metastatic class 2 UM stained for CD8, LAG3, PD1, CTLA4, and DAPI (scale bar, 50 μm).

From: *Durante, M.A., Rodriguez, D.A., Kurtenchbach, S., et al. Single-cell analysis reveals new evolutionary complexity in uveal melanoma. Nature communications. 2020;11(1):496*

1.3 Background on Nivolumab

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor.[8] PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

OPDIVO™ (nivolumab) is approved for the treatment of several types of cancer in multiple regions including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (JP,Jul-2014). Nivolumab is also being investigated in various other types of cancer as monotherapy or in combination with other therapies. Single-dose nivolumab monotherapy was also investigated in a Phase 1b study and a Phase 1/2 study of patients with sepsis who were also managed according to established best practice care for sepsis.

1.3.1 Nonclinical Studies

Nonclinical studies on nivolumab are discussed in detail in the Nivolumab **Investigator's Brochure (IB).** Nivolumab has been shown to bind specifically to the human PD-1 receptor and not to related members of the cluster of differentiation 28 ICD28) family.[9, 10] Nivolumab inhibits the interaction of PD-1 with its ligands, PD-L1 and PD-L2, resulting in enhanced T-cell proliferation and interferon-gamma (IFN-γ) release in vitro.[11-13] Nivolumab binds with high affinity to activated human T-cells expressing cell surface PD-1 and to cynomolgus monkey PD-1.[10] In a mixed lymphocyte reaction (MLR), nivolumab promoted a reproducible concentration-dependent enhancement of IFN- γ release.[14]

In intravenous (IV) repeat-dose toxicology studies in cynomolgus monkeys, nivolumab was well tolerated at doses up to 50 mg/kg, administered weekly for 5 weeks, and at doses up to 50 mg/kg, administered twice weekly for 27 doses. While nivolumab alone was well tolerated in cynomolgus monkeys, combination studies have highlighted the potential for enhanced toxicity when combined with other immunostimulatory agents.[15]

In addition, an enhanced pre- and postnatal development (ePPND) study in pregnant cynomolgus monkeys with nivolumab was conducted.Administration of nivolumab at up to 50 mg/kg twice weekly was well tolerated by pregnant monkeys; however, nivolumab was determined to be a selective developmental toxicant when administered from the period of organogenesis to parturition at ≥10 mg/kg (area under the concentration-time curve [AUC] from time zero to 168 hours [AUC(0-168 h)] 117,000 µg •h/mL). Specifically, increased developmental mortality (including late gestational fetal losses and extreme prematurity with associated neonatal mortality) was noted in the absence

of overt maternal toxicity. There were no nivolumab-related changes in surviving infants tested throughout the 6-month postnatal period. Although the cause of these pregnancy failures was undetermined, nivolumab-related effects on pregnancy maintenance are consistent with the established role of PD-L1 in maintaining fetomaternal tolerance in mice.[16]

1.3.2 Clinical Studies

The PK, clinical activity, and safety of nivolumab have been assessed in approximately 80 clinical studies sponsored by BMS or ONO. The description and status of studies with reference safety information included in Appendix 1 of the Investigator's Brochure are provided in Appendix 5 of the Investigator's Brochure. Across those studies, approximately 23,507 subjects have received nivolumab monotherapy in single- or multiple-dose Phase 1/2/3 studies or studies with nivolumab in combination with other therapeutics (ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies). Results from the ongoing studies are preliminary and are subject to change.

Nivolumab has demonstrated clinical activity in NSCLC, melanoma, RCC, cHL, SCCHN, UC, CRC, HCC, SCLC, ESCC (approved indications) and other tumor types (Section 5.4 of the Investigator's Brochure) as monotherapy or in combination with ipilimumab or other therapeutics. The majority of responses were durable and exceeded 6 months. In randomized, controlled studies, nivolumab monotherapy demonstrated statistically significant improvement in OS over standard of care in subjects with advanced or metastatic melanoma, subjects with advanced or metastatic NSCLC, subjects with advanced RCC, and subjects with recurrent or metastatic SCCHN (see Appendix 2 and Appendix 3 of the Investigator's Brochure). In randomized, controlled studies, nivolumab in combination with ipilimumab demonstrated statistically significant improvement in PFS and ORR over ipilimumab monotherapy in subjects with advanced or metastatic melanoma (see Appendix 2 and Appendix 3 of the Investigator's Brochure).

All available data suggest that nivolumab monotherapy has a consistent AE profile across tumor types. The safety profile is generally consistent across completed and ongoing clinical trials, with no maximum tolerated dose (MTD) reached at any monotherapy dose tested up to 10 mg/kg. The safety profile of nivolumab in combination with ipilimumab was consistent with the mechanisms of action of nivolumab and ipilimumab. The nature of the AEs was similar to that observed with either agent used as monotherapy; however, both frequency and severity of most AEs were increased with the combination. A dose of 3 mg/kg nivolumab/3 mg/kg ipilimumab exceeded the MTD, and both 1 mg/kg nivolumab/3-mg/kg ipilimumab and 3 mg/kg nivolumab/1 mg/kg ipilimumab were identified as the MTD.[17] Across all studies conducted to date, drug-related AEs have included pulmonary toxicity, renal toxicity (including acute renal failure), endocrine abnormalities, GI toxicity, dermatologic toxicity (including rash, Stevens-Johnson syndrome [SJS], toxic epidermal necrolysis [TEN]), hepatotoxicity, and myotoxicity. For nivolumab monotherapy and combination therapy, the majority of these AEs have been managed successfully with supportive care and, in

more severe cases, a combination of dose delay, permanent discontinuation, and/or use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in the management guidelines provided in Appendix 3.

1.4 Background on Relatlimab (BMS-986016)

Relatlimab (also referred to as BMS-986016, BMS-986016-01, and anti-lymphocyte activation gene 3 [LAG-3]) is a fully human LAG-3-specific antibody that was isolated following immunization of transgenic mice expressing human immunoglobulin (Ig) genes. It is expressed as an immunoglobulin G4 (IgG4) isotype antibody and includes a stabilizing hinge mutation (S228P). Relatlimab binds to the LAG-3 receptor with high affinity and blocks LAG-3 interactions with its known ligand, major histocompatibility complex (MHC) Class II, which is the peptide antigen presentation molecule recognized by CD4+ T cells. Relatlimab binding inhibits the negative regulatory function of LAG-3 in vitro. By blocking the downregulatory pathway, relatlimab enhances the anti-tumor immune response and, thus, has the potential to inhibit the growth of multiple malignancies when administered as a single agent or in combination with other therapeutic immuno-oncology (IO) monoclonal antibodies (mAbs). BMS-986213 is a fixed dose combination (FDC) of relatlimab plus nivolumab at a 1:3 ratio and is reported in a separate IB.

1.4.1 Non-Clinical Studies

The nonclinical pharmacology of relatlimab and surrogate LAG-3 antibodies has been studied in vitro using binding and functional assays as well as in vivo in mouse syngeneic tumor models. Briefly, relatlimab binds with high affinity to both human and cynomolgus monkey LAG-3 receptor expressed on activated primary T cells (half maximal effective concentration [EC50] = 0.11 nM and 29.11 nM, respectively) and prevents binding of LAG-3 to cells bearing its ligand, MHC Class II, the peptide antigen presentation molecule recognized by CD4+ T cells. Relatlimab binding inhibits the negative regulatory function of LAG-3 in vitro, leading to enhancement of effector T cell function. Relatlimab does not bind to mouse LAG-3; therefore, surrogate antibodies recognizing mouse LAG-3 (clones C9B7W and 19C7), which block the negative regulation following interaction between LAG-3 and MHC Class II, were used to assess anti-tumor activity mediated by LAG-3 blockade, both alone and in combination with programmed cell death protein 1 (PD-1) or cytotoxic T lymphocyte antigen 4 (CTLA-4) blockade, in Sa1N fibrosarcoma and MC38 colon adenocarcinoma or CT26 colon adenocarcinoma murine syngeneic in vivo tumor models, respectively. While LAG-3 monotherapy displays relatively marginal single-agent activity, both in terms of tumor growth inhibition and the number of tumor—free mice[18], the combination of anti-LAG-3 with a blocking anti-PD-1 antibody provided enhanced anti- tumor activity compared to either agent alone. Therefore, blockade of the LAG-3 negative regulatory pathway has the potential to inhibit the growth of multiple malignancies, especially when administered in combination with other therapeutic IO mAbs.

In a repeat-dose study in monkeys, following weekly intravenous (IV) doses of relatlimab monotherapy (30 and 100 mg/kg) or doses of relatlimab in combination with the anti-PD-1 antibody nivolumab (100 mg/kg of relatlimab and 50 mg/kg of nivolumab)

for 4 weeks, the total serum clearance (CLT) of relatlimab was 0.12 mL/h/kg, and the elimination half-life (T-HALF) was 414 hours (estimated by population pharmacokinetic [PK] analysis of pooled data from all 3 groups). There was no apparent PK drug-drug interaction between relatlimab and nivolumab.

The cynomolgus monkey was selected as the toxicology species because relatlimab binds to macaque LAG-3, albeit less strongly than to human LAG-3, and is pharmacologically active in monkeys (i.e. increases T cell subsets and responses to immunogenic challenge).[19-21] In Good Laboratory Practice (GLP)-compliant studies up to 3 months in duration, relatlimab was generally well tolerated by cynomolgus monkeys when administered IV QW up to 100 mg/kg. In the 3- month study, 1 male monkey at 30 mg/kg exhibited clinical observations (including tremors, decreased activity, hunched posture, retching, and/or emesis) and complement activation that were considered to be secondary to relatlimab-related treatment-emergent anti-drug antibodies (ADAs) and, therefore, were not factored in determining the no-observed-adverse-effect-level (NOAEL). The NOAEL was considered to be 100 mg/kg/week (mean sex-combined AUC(0-168h)] = 1,180,000 μg•h/mL). In the 1-month study, relatlimab was also administered at 100 mg/kg in combination with 50 mg/kg of nivolumab (mean relatlimab AUC[0-168h] = 514,000 μg•h/mL) and was generally well tolerated in 8 of 9 monkeys with no clinical signs, with the exception of moribundity in 1 male monkey attributed to central nervous system vasculitis. Histopathological findings in this monkey included the following: slight lymphoplasmacytic inflammation of the choroid plexus; minimal to moderate lymphohistiocytic inflammation of the vasculature of the brain parenchyma, meninges, and spinal cord; and minimal to moderate mixed-cell inflammation of the epididymis, seminal vesicles, and testes. Additional findings in the combination therapy group were limited to minimal to slight irreversible lymphoplasmacytic inflammation of the choroid plexus in the brain in both sexes and minimal lymphohistiocytic inflammation of the vasculature of the brain parenchyma in 1 male monkey.

In an exploratory 4-week toxicity study, LAG3.1-G4P, a predecessor nonclinical molecule differing from relatlimab by 2 amino acids, was clinically well tolerated by cynomolgus monkeys, with no adverse findings when administered IV QW as a monotherapy at 50 mg/kg or when administered at 10 or 50 mg/kg in combination with 50 mg/kg of nivolumab. Therefore, the NOAEL was considered to be 50 mg/kg/week for LAG3.1-G4P monotherapy (combined sex mean AUC[0-168h] = 231,000 μg•h/mL) and 50/50 mg/kg/week for LAG3.1-G4P/nivolumab combination therapy (combined sex mean LAG3.1-G4P AUC[0-168h] = 210,000 μg•h/mL; combined sex mean nivolumab AUC[0-168h] = 159,500 μg•h/mL).

In exploratory in vitro assays, neither relatlimab alone nor relatlimab in combination with nivolumab induced cytokine release or resulted in T, B, or natural killer (NK) cellular activation in human peripheral blood mononuclear cells (PBMCs).

Developmental and reproductive toxicology studies were conducted in mice using both syngeneic and allogeneic breedings, the latter of which is designed to elicit feto-

maternal tolerance through mating of genetically distinct mouse strains in which paternally contributed alloantigens induce an immune response in the pregnant dam. Due to the lack of cross-reactivity of relatlimab in rodent species, surrogate anti-mouse LAG-3 antibodies (clone MLAG3.4 MG1-D265A [19C7] or C9B7W) were used. Both antibodies were well tolerated by dams at the highest dose tested, and there were no maternal or developmental toxicities detected in either syngeneic or allogeneic breedings, with resulting maternal and developmental NOAELs of 50 mg/kg (MLAG3.4 MG1-D265A [19C7]) and 51.5 mg/kg (C9B7W). Despite these results, the risk for adverse human pregnancy outcomes associated with relatlimab administration is considered to be of concern for 2 reasons: 1) checkpoint targets, including LAG-3, are likely to have a role in maintaining maternal tolerance to the developing fetus and 2) the present indication requires that relatlimab be administered in combination with nivolumab, which has been shown to increase third trimester pregnancy loss in cynomolgus monkeys.

Overall, the nonclinical toxicology assessment of relatlimab has demonstrated an acceptable profile, supporting its continued clinical use in humans.

1.4.2 Clinical Studies

Safety information presented in this Investigator Brochure (IB) focuses primarily on information obtained from Phase 1/2a studies (Studies: CA224020 [advanced solid tumors], CA224022 [advanced hematologic malignancies], CA224034 [advanced solid tumors] a Phase 1 study conducted in Japan and CA224048 [advanced malignant tumors]). Dose levels studied include 4 ascending flat doses of relatlimab monotherapy (20, 80, 240, and 800 mg) given every 2 weeks (Q2W) and ascending flat doses of relatlimab and nivolumab combination therapy given Q2W or every 4 weeks (Q4W). The combination doses include 20 mg relatlimab/80 mg nivolumab Q2W, 20 mg relatlimab/240 mg nivolumab Q2W, 80 mg relatlimab/240 mg nivolumab Q2W, 160 mg relatlimab/240 mg nivolumab Q2W, 240 mg relatlimab/240 mg nivolumab Q2W, as well as 160 mg relatlimab/480 mg nivolumab Q4W, 240 mg relatlimab/480 mg nivolumab Q4W, 320 mg relatlimab/480 mg nivolumab Q4W and 480 mg relatlimab/480 mg nivolumab Q4W. Study CA224048 is a triple combination of relatlimab, nivolumab and BMS-986205 (IDO-1 inhibitor) or ipilimumab. The combination doses include relatlimab 80/160 mg Q4W + nivolumab 480 mg Q4W + BMS-986205 (IDO-1 inhibitor) (25/50/100 mg QD) or ipilimumab 1mg/kg Q8W.

As of the clinical data cutoff dates of 15-May-2019 for CA224034 and CA224048 and 03-Jun-2019 and 26-Jun-2019 for CA224020 and CA224022 respectively, 1348 subjects have been treated with relatlimab or relatlimab in combination with nivolumab in 4 ongoing studies (Studies CA224020, CA224022, CA224034 and CA224048) assessing PK, clinical efficacy, and safety (Table 1.3-1 of the Investigator's Brochure). The current clinical program is evaluating advanced solid tumors (special focus in advanced melanoma that has previously progressed on prior anti-PD1 therapy) in Study CA224020, relapsed-refractory hematological malignancies (Hodgkin lymphoma) in CA224022, advanced solid tumors (special focus in a Japanese population) in Study CA224034 and in study CA224048, the focus is on advanced solid tumors including

melanoma, non-small cell lung cancer (NSCLC), squamous cell cancer of head and neck (SCCHN), renal cell cancer (RCC), and gastric cancer (GC/GEJ).

Exposure to relatlimab as of the database cutoff dates cited above, is summarized in Table 1.3-1 of the Investigator's Brochure.

1.5 Combination Treatment Phase 1 Trials

Lipson et al. (*J Immunother Cancer*. 2016;4[s1]:173 [P232]) reported first-in-human phase I/IIa activity data for BMS-986016, a fully human IgG4 monoclonal antibody that targets LAG-3, alone and in combination with nivolumab (anti-PD-1) in 89 patients with advanced B cell malignancies or solid tumors. The maximum tolerated dose (MTD) was not reached with BMS-986016 monotherapy and when used in combination with nivolumab treatment emergent AE's were infrequent and consisted of manageable toxicities typically associated with immune checkpoint blocking agents with no treatment-related deaths. Objective tumor regression was observed with LAG-3 monotherapy, with combination therapy in PD-1-naive patients and in patients with disease progression on nivolumab monotherapy.

Additional clinical data from 55 patients with metastatic melanoma who had progressed on immunotherapy with checkpoint inhibitors and treated with the combination of BMS-986016 and nivolumab was presented at the ASCO 2017 annual meeting by Ascierto et al. Of the 55 patients, 58%% had prior anti–CTLA-4 and 95% had prior anti-PD1/PD-L1 treatment. In the 48 efficacy-evaluable patients, the ORR was 13% and DCR was 54%. LAG-3 expression was > 1% in 25/48 and < 1% in14/48 whereas PD-1 expression was 13% and 21% respectively. ORR in the > 1% LAG-3 expressors was 20% compared to 7.1% in the <1% LAG-3 expressors. The safety profile was similar to that of nivolumab monotherapy.[22]

Hong et al. presented data on a phase I/II study of LAG525 ± spartalizumab (PDR001) in patients with advanced.[23] LAG525 + spartalizumab led to durable RECIST responses (11 PR, 1 CR) in 121 patients with a variety of solid tumors, including mesothelioma (2/8 patients) and triple-negative breast cancer (TNBC; 2/5 patients). In TNBC tumor biopsies, a trend in conversion of immune-cold to immune-activated biomarker profiles was seen.

1.6 Hypothesis

The null hypothesis is that the true response rate is 5%, it will be tested against a one-sided alternative response rate of 20%. In the first stage, 13 patients will be accrued. If there are no responses in these 13 patients, the study will be stopped. Otherwise, 14 additional patients will be accrued for a total of 27. The null hypothesis will be rejected if 4 or more responses are observed in 27 patients. This design yields a type I error rate of 0.0416 and power of 0.8011 when the true response rate is 20%

1.7 Rationale

1.7.1 Rationale for Current Study

Our hypothesis is that in light of the preclinical data published by Durante et al. (section 1.2) documenting the high prevalence of LAG-3 expression in metastatic uveal melanoma cells, the combination of nivolumab and BMS-986016 will result in superior response rates when compared with historical PD-1/PD-L1 blocking antibody response data in patients with metastatic uveal melanoma. The addition of relatlimab might engender enhancement of the therapeutic activity of nivolumab in patients whose tumor infiltrating lymphocytes (TIL) express LAG-3 constitutively and may abrogate the upregulation of LAG-3 expression in TIL that do not.

1.7.2 Rationale for Study Design

This is an exploratory trial based on new preclinical data and a two-stage design was felt to be most appropriate to detect a signal in this limited population of patients with a rare disease. Additional patient cohorts may be added in the future depending on the initial outcomes of this trial.

1.7.3 Rationale for Patient Population

Uveal melanoma is a rare but often lethal disease with about 50% of patients eventually developing metastatic disease, primarily to the liver. Metastatic melanoma has been uniformly fatal with very limited options and no curative approaches so far. The new insight into the biology of the tumor microenvironment and the discovery of high levels of expression of LAG-3 in the T-cells infiltrating these tumors is a promising new avenue of research. The selection of patients with no previous exposure to PD-1 and/or LAG-3 exposure is meant to enrich the patient population with the individuals most likely to respond to this intervention.

1.7.4 Rationale for Dose Selection:

The dose and schedule for this trial has been based on the most recent phase I data on the combination of nivolumab in combination with relatlimab. An alternative dosing schedule is the sequential administration of both drugs. The current schedule was selected because of the patient convenience afforded by a single infusion of both drugs.

1.8 Risk/Benefit Assessment

1.8.1 Nivolumab Known Potential Risks

The potential risks from treatment with nivolumab are described in detail in section 7.1 of the investigator’s brochure. These include the following adverse events: pulmonary, gastrointestinal, hepatic, endocrinopathies, dermatologic, renal, neurologic, infusion reactions, lipase/amylase elevations, uveitis and visual complaints, and other immune-mediated adverse events such as myotoxicity (myositis, myocarditis, and rhabdomyolysis), solid organ and tissue transplant rejection, rapid-onset and severe graft-versus-host-disease GVHD, and complications of allogenic hematopoietic stem cell transplantation (HSCT).

1.8.2 Known Potential Benefits

As noted in the protocol background section treatment with single agent nivolumab results in response rated in the single digits. Patients who respond, however, do seem to derive clinical benefit. Toxicity of single agent immunotherapy is quite modest and tolerable in patients of all age groups. The response rate in the phase I data of the combination of nivolumab and relatlimab in patients with cutaneous melanoma refractory to PD-1 blocking antibodies was as high as 20% in patients with LAG-3 expression > 1%. Preclinical data previously mentioned documented the high level of LAG-3 expression in samples of both primary and metastatic melanoma suggesting potentially increased activity for this combination in the clinical setting.

1.8.3 Relatlimab Known Potential Risks

The potential risks from treatment with relatlimab are described in detail in **Section 7.1 of the investigator's brochure**. These include the following immune-mediated adverse events: pneumonitis, colitis, hepatitis, nephritis, endocrinopathy, and neurologic and dermatologic AEs.

Across 4 studies with clinical data cutoff dates, (**Studies;** CA224020, 03-June-2019, CA224022, 26-June-2019, CA224034 and CA224048, 15-May-2019), relatlimab monotherapy has been administered to 66 subjects across multiple doses: 20 mg (8 subjects), 80 mg (13 subjects), 240 mg (27 subjects) and 800 mg (18 subjects) relatlimab, flat dose, Q2W. The safety profile of relatlimab monotherapy appears manageable with no maximum tolerated dose (MTD) reached. The MAD was 800 mg Q2W. There were 4 drug-related SAEs in monotherapy: Grade 3 pneumonitis, Grade 2 pneumonitis, and Grade 3 allergic reaction in monotherapy in Study CA224020 at a dose of 800 mg relatlimab Q2W; and a Grade 3 aseptic meningitis in monotherapy in Study CA224022 at a dose of 800 mg relatlimab Q2W. There was no apparent relationship in the incidence, severity, or causality of AEs to relatlimab at these dose levels. (Section 5.5 of the Investigator's Brochure). All AEs were reversible or manageable (in the setting of immune-mediated endocrine events) by withholding drug administration and following treatment algorithms specified in the protocols where applicable. There were 5 Grade 1 to Grade 2 infusion-related reactions with relatlimab monotherapy (1 in Study CA224020 and 4 in Study CA224022), which were manageable and reversible with recommended treatment guidelines in the protocol. A total of 27 subjects died due to malignant neoplasm progression following relatlimab monotherapy (19 in Study CA224020, 7 in Study CA224022, and 1 in Study CA224034).

1.8.4 Nivolumab and Relatlimab Combination Therapy Potential Risks

The potential risks from treatment with relatlimab in combination are described in detail in **Section 7.1 the investigator's brochure**. These include the following immune-mediated adverse events: neurotoxicity, infusion related reaction and cytokine release, immunosuppression, cardiovascular events such as myocarditis.

As of the clinical data cutoff dates, cited in **section 1.8.3** of this protocol, the treatment with relatlimab in combination with nivolumab or ipilimumab or BMS 986205 has been

administered to 1282 subjects, in Studies CA224020 (1166 subjects), CA224022 (66 subjects), CA224034 (26 subjects) and CA224048 (24 subjects). The safety profile of relatlimab combined with nivolumab is manageable with currently no MTD reached, as combination dose evaluation remains ongoing.

Across Studies CA224020, CA224022, CA224034 and CA224048, overall drug-related AEs were reported in 847 subjects. The most frequent drug-related AEs included fatigue, decreased appetite, pruritus, diarrhea, rash, rash maculo-papular, anemia, asthenia, hypothyroidism, and hyperthyroidism. The types of drug-related AEs, as well as the rates of these drug-related AEs, appeared comparable to historical nivolumab monotherapy rates. The majority of all drug-related AEs, except for 1 Grade 4 myocarditis (240 mg relatlimab/240 mg nivolumab Q2W), as well as 1 Grade 4 potential drug-induced liver injury, 1 Grade 5 dyspnea, and 1 Grade 3 pneumonitis (all at a dose level of 80 mg relatlimab/240 mg nivolumab Q2W), were reversible or manageable by withholding study drug administration, providing standard medical care, and/or following immune-related AE algorithms. Safety results to date indicate that sequential, coadministration and the FDC of relatlimab + nivolumab have similar safety profiles

1.8.5 Assessment of Potential Risks and Benefits

The safety profile of nivolumab in combination with relatlimab has been assessed in the dose finding studies mentioned above. The important identified risks are irAEs. Based on the currently available safety information the adequate risk identification and minimization described in the investigator’s brochure, the emerging preliminary activity of this combination in patients with PDL-1 antibody refractory cutaneous melanoma and the preclinical data suggesting significant potential for clinical activity in uveal melanoma, the benefit-risk is considered favorable for continued clinical studies in these and other indications.

2 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To evaluate efficacy of the combination of nivolumab and BMS-986016 in terms of objective response rate (ORR) according to RECIST v1.1.	Primary endpoint for this study will be best objective response rate (ORR).
Secondary	
To evaluate the disease control rate (DCR), progression-free survival (PFS), overall survival (OS), duration of response (DOR) and safety profile of the combination of nivolumab and BMS-986016	Secondary endpoints will include disease control rate (DCR), progression-free survival (PFS), overall survival (OS), median duration of response (mDOR) and safety profile (AEs, SAEs).
Exploratory	
Tumor microenvironment (TME) in fresh biopsies pre- and post-treatment and at progression	Evaluate pre-treatment characteristics of the TME that may predict for response or lack of response. Learn the effects of treatment on the TME.
Blood samples at baseline and predetermined post-treatment time points and at progression	T cell receptor profiling Circulating tumor cell DNA.

3 STUDY DESIGN

3.1 Overall Design

This is an open-label, single arm, single site investigator-initiated phase II study. Approximately 27 patients will be enrolled based on Simon minimax two-stage design. The primary objective is to evaluate efficacy of the combination of nivolumab and BMS-986016 in terms of objective response rate (ORR) in patients with biopsy-proven metastatic uveal melanoma either untreated or previously treated with up to 5 lines of therapy.

1. **Study Design:** This is an open-label, single arm, single site investigator-initiated phase II study based Simon minimax two-stage design.
2. **Study Population and Setting:** During the **first stage**, the investigational treatment will be tested on 13 patients. The trial will be terminated if there are no responses in these 13 patients. If the trial goes on to the **second stage**, an additional 14 patients will receive the investigational treatment.
3. **Intervention:** Participants will be treated with a combination treatment of Nivolumab 480 mg and Relatlimab 160 mg which will be administered intravenously over 60 minutes (+ or –5 minutes) every 4 weeks. Each treatment cycle is four weeks in length and the nivolumab and relatlimab combination treatment will be administered until disease progression or intolerable toxicity for up to 24 months.
4. **Description of facilities enrolling patients:** This study will identify, recruit, enroll, and treat patients at the University of Miami Sylvester Comprehensive Cancer Center inclusive of the constituent satellite sites.
5. **Participant Duration:** Following enrollment, participants will be treated with an investigational treatment of nivolumab in combination with relatlimab until disease progression or intolerable toxicity for up to 24 months. Patients will be followed for 2 years to obtain information on disease progression and overall survival. Total participant duration is approximately 3 years.
6. **Study Duration:** The expected study duration is 4-5 years. The expected enrollment is 27 evaluable patients within a period of 2 to 2.5 years.

4 STUDY POPULATION

4.0 Inclusion Criteria

Patients participating in this study must:

1. Have a biopsy-proven diagnosis of metastatic uveal melanoma, previously untreated with anti-PD-1,CTLA-4 and/or LAG-3 blocking antibodies.
2. Agree to undergo a pre-treatment and a post-treatment fresh biopsy of the tumor, if needed, safe and feasible as determined by the investigator.
3. Have completed all previous therapy for a minimum of 3 weeks before the first dose of experimental treatment. All adverse events of previous therapy must have resolved. Palliative radiation therapy to a limited field is allowed within this 3 week period.
4. Be willing and able to provide written informed consent/assent for the trial.
5. Be ≥ 18 years of age on day of signing informed consent.
6. Have measurable disease based on RECIST 1.1.
7. Have a performance status of 0-2 on the ECOG Performance Scale.
8. LVEF assessment with documented LVEF ≥50% by either TTE or MUGA (TTE preferred test) within 6 months from first study drug administration
9. Demonstrate adequate organ function as defined in **Error! Reference source not found.**. All screening labs should be performed within 10 days of treatment initiation.

Table 1. Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥30 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** **≤** 5 X ULN for subjects with liver metastases
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy

	as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

10. If a female of childbearing potential, have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
11. If a female of childbearing potential, be willing to use an adequate method of contraception as outlined in Section 5.8 Contraception, for the course of the study through 24 weeks after the last dose of study medication. Must abstain from ova donation for a minimum of 5 months after the end of treatment.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

12. If a male of childbearing potential, agree to use an adequate method of contraception as outlined in Section 5.8- Contraception, starting with the first dose of study therapy through 7 months after the last dose of study therapy. Must abstain from sperm donation for a minimum of 24 weeks after the end of treatment.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject

4.1 Exclusion Criteria

Patients will be excluded from participation in this trial if they:

1. Are currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 3 weeks of the first dose of treatment.
2. Have a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. Patients on replacement doses of corticosteroids and patients who received steroids as pre-medication to prevent an imaging contrast allergy are allowed.
3. Have a known history of active tuberculosis (Bacillus Tuberculosis)
4. Have had prior treatment with a PD-1 and/or LAG-3 targeted agent
5. Have hypersensitivity to nivolumab, relatlimab or any of their excipients.
6. Have had a prior anti-cancer monoclonal antibody (mAb) within 3 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from clinically significant adverse events due to agents administered more than 3 weeks earlier.
7. Have had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 3 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from clinically significant adverse events due to a previously administered agent.

- Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.
- Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
- Note: Patients will be allowed necessary and palliative radiation therapy to limited fields during the trial, as long as it does not encompass a target lesion.

8. Have a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma or squamous cell carcinoma of the skin that has undergone potentially curative therapy, in situ cervical cancer, ductal carcinoma in situ (DCIS), incidentally discovered asymptomatic thyroid cancer, PSA recurrence of prostate cancer stable on hormonal therapy with no otherwise detectable disease, and a previous diagnosis of malignancy that has shown no evidence of disease progression for 5 years or longer.
9. Have known active central nervous system (CNS) metastases and/or carcinomatous meningitis as well as a history of previous or current significant brain hemorrhage. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids to treat edema for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis, which will be excluded regardless of clinical stability.
10. Have active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
11. Have known history of, or any evidence of active, non-infectious pneumonitis.
12. Have an active infection requiring systemic therapy.
13. Have a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
14. Have known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
15. Are pregnant or breast feeding or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.

16. Have a diagnosis or known history of Human Immunodeficiency Virus (HIV), unless controlled on antiretroviral drugs and have undetectable levels of HIV antibodies.
17. Have known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C.
18. Have received a live vaccine within 30 days of planned start of study therapy.
19. Have a history of myocarditis, regardless of etiology
20. Have a troponin T (TnT) or I (TnI)
    - i) > 2x institutional upper limit of normal (ULN) : patient is excluded.
    - ii) between > 1 to 2 x ULN enrollment will be permitted if a repeat assessment remains $\leq$ 2 x ULN and participant undergoes a cardiac evaluation and is cleared by a cardiologist or cardio-oncologist
21. Are patients with impaired decision-making capacity
22. Are prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included as a participant. Strict conditions apply and Bristol-Myers Squibb approval is required).
23. Are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness
24. Have psychological, familial, sociological, or geographical conditions that potentially hamper compliance with the study protocol and follow-up schedule; those conditions should be discussed with the participant before registration in the trial.

4.2 Strategies for Recruitment and Retention

Both men and women of all races and ethnic groups are eligible for this trial. Subjects will be recruited at Sylvester Comprehensive Cancer Center (SCCC) via clinical practice offices.

5 TREATMENT PLAN

5.1 Method of Treatment Assignment

All patients will be treated on this single arm, open label, investigator-initiated Phase 2 study with an investigational treatment of nivolumab in combination with relatlimab until disease progression or intolerable toxicity for up to 24 months.

5.2 Dosing and Administration

Enrolled patients will be treated in the outpatient setting. Nivolumab 480 mg will be mixed in the same bag with Relatlimab 160 mg and will be administered intravenously over 60 minutes (+ or –5 minutes) every 4 weeks. Each cycle will be approximately 4 weeks in length. Both drugs will be administered until disease progression or intolerable toxicity for up to 24 months.

Table 2**.Dosing and Administration Schedule Nivolumab + Relatlimab Combination Treatment (All cycles)**

Drug	Dose	Day 1 (+/– 3 days)	Day 28 (+/– 3 days)
Nivolumab	480 mg	X	X
Relatlimab	160 mg	X	X

5.3 Missed doses

Patients who miss a nivolumab plus relatlimab dose at the usual required time should skip additional therapy until the next cycle.

5.4 Concomitant Therapy

Nivolumab and relatlimab will be administered concomitantly every 4 weeks (qw4) until disease progression or intolerable toxicity for up to 24 months. For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements.

5.5 Premedication

No premedication is recommended or required.

5.6 Prohibited Therapies

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol

- Chemotherapy
- Investigational agents other than nivolumab and relatlimab
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Radiation therapy
    - Note: Palliative radiation therapy or treatment to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion as previously described
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic/replacement doses of corticosteroids is allowed.
- Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

5.7 Study Intervention Compliance

All doses of study treatments (nivolumab and relatlimab) will be administered at the investigational site by designated medical staff.

The information related to each trial drug administration, including the date, time, and dose of study drug, will be recorded on Velos. The Investigator will make sure that the information entered into the CRF regarding drug administration is accurate for each patient. Any reason for noncompliance should be documented.

Noncompliance is defined as a patient missing 2 doses of nivolumab plus relatlimab for non-medical reasons. If $\geq$ 2 doses of the study drug treatment are missed and the interval between the subsequent dose and the last administered treatment is longer than 6 weeks for nonmedical reasons, the criteria of insufficient compliance will have been met as well.

Non-compliant patient slots can be replaced by a new eligible patient.

5.8 Contraception

Contraception Requirements for Women:
The study drug may be absorbed into bodily secretions such as vaginal fluids and then passed on to the female participant's partner during sex. Male sexual partners must wear a condom to avoid being exposed to the study drug.

The study drug may harm a fetus or a breastfeeding baby.

If a woman is pregnant or breastfeeding, she cannot take part in this study.

If woman thinks she may be pregnant, she should not volunteer for this study.

Women of childbearing potential must have a pregnancy test before beginning the study and while in the study.

Women of childbearing potential must not get pregnant or breastfeed while in this study and for at least 24 weeks after the last dose of the study drug. Women must not donate an egg for at least 5 months after the last dose of study medication.

Women of childbearing potential must take measures to avoid becoming pregnant while in this study.

The following are acceptable measures of contraception:

- Abstinence (not having sexual relations with a person of the opposite sex)
- Implantable hormone (e.g. Norplant)
- Intrauterine Device (IUD)
- Male partner has had a vasectomy
- Female sterilization
- Hormonal injection
- Oral contraceptives

Participants must use contraception, at least starting at screening before starting study treatment unless they abstain from sexual intercourse. Participants must use contraception during study treatment and for at least 24 weeks after stopping study treatment.

Contraception Requirements for Men
Study drug may be absorbed into bodily secretions such as semen and then passed on to partners during sex. Participants must wear a condom to avoid being exposed to the study drug.

There may be risks to the embryo/fetus if female sexual partner is pregnant or becomes pregnant while the participant in this study. If the participant's partner is a woman of child bearing potential, the participant and their partner must either practice total abstinence or use effective contraception while participating in this study. One of the following forms of contraception should be used by the participant and their partner:

- Abstinence (not having sexual relations with a person of the opposite sex)
- Implantable hormone (e.g. Norplant)
- Intrauterine Device (IUD)
- Vasectomy
- Female sterilization
- Hormonal injection
- Oral contraceptives

Participants must use contraception during study treatment and for at least 7 months after stopping study treatment. Participants should also refrain from donating semen during therapy and for 24 weeks after stopping the therapy.

There is theoretical concern that study treatment can result in sperm abnormalities and/or can transmit harmful substances in their semen during sex. Therefore, males must remain abstinent or use a condom, even if they have undergone a vasectomy.

If a participant's female partner becomes pregnant or suspects becoming pregnant during study treatment or within 24 weeks after completing study treatment, the participant must inform the Study Doctor immediately. The Study Doctor may want to follow the pregnancy and may ask the female partner to sign a consent form so they can collect information about the outcome of the pregnancy.

5.9 Breast Feeding

Participants must not breast-feed while receiving study treatment and for 24 weeks following the last dose of study treatment.

5.10 Blood Donation

Participants must not donate blood during the study or for 12 weeks after the last dose of protocol therapy.

5.11 Duration of Follow Up

All study subjects will be followed as per standard of care for tumor recurrence. Following the completion of the combination nivolumab and relatlimab therapy, patients will be followed for 2 years to obtain information on disease progression and overall survival.

5.12 End of Study Definition

A study participant is considered to have completed the study once he or she completes all phases of the study treatment and study related laboratory tests. The primary and secondary clinical aims endpoints will be available for analysis once all patients have been followed for 2 years after completing the nivolumab and relatlimab combination therapy. Therefore, the clinical trial will be considered completed when the last participant has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), and the clinical endpoints are available for analysis.

6 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

6.1 Discontinuation of Study Intervention

Discontinuation from nivolumab plus relatlimab does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the protocol. Patients who received at least 2 doses of the combination treatment will be considered evaluable and the remaining study procedures should be completed as indicated by the protocol in Section 6.2.

If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the Investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Progression Free Survival
- Overall Survival
- Adverse events

6.2 Participants Taken Off Study

Patients who are enrolled but do not receive at least one dose of nivolumab or relatlimab because of noncompliance or clinical reasons will be taken off study and will receive standard treatment. These patients will not be included in the efficacy analysis and will replaced.

6.3 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request. An Investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- Lost-to-follow up; unable to contact subject
- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study
- Disease progression which requires discontinuation of the study intervention
- Participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive nivolumab and relatlimab combination treatment for 2 cycles over a period of 12 weeks.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF).

6.3.1 Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials

An investigator may ask a subject who is withdrawing whether the subject wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the subject would distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review, and address the maintenance of privacy and confidentiality of the subject's information.

If a subject withdraws from the interventional portion of the study, but agrees to continued follow-up of associated clinical outcome information as described in the previous bullet, the investigator must obtain the subject's informed consent for this limited participation in the study (assuming such a situation was not described in the original informed consent form). In accordance with FDA regulations, IRB approval of informed consent documents would be required (21 CFR 50.25, 56.109(b), 312.60, 312.66, 812.100).

6.4 Participant Replacement Criteria

Subjects who sign the informed consent form and do not receive the study intervention may be replaced. Subjects who sign the informed consent, receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study due to non-compliance will be replaced by a new eligible patient.

6.5 Lost to follow up

A participant will be considered lost to follow-up if he or she fails to return for two scheduled treatment cycles over a period of 12 weeks and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit 3 times and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7 TREATMENT DISCONTINUATION AND ADVERSE EVENT MANAGEMENT

Dose reductions or dose escalations are not permitted in this study. Dose delay criteria as noted below apply for all drug-related adverse events regardless of whether or not the event is attributed to nivolumab, relatlimab, or both. All study drugs must be delayed until treatment can resume. Reasons for permanent treatment discontinuation include the following:

• Any drug-related/immune-related Grade 4 toxicity, except for endocrinopathy and asymptomatic elevations of amylase and lipase.
• Any Grade 3 elevation of liver function tests or colitis not responding to steroids, infliximab and/or mycophenolate mofetil.
• Any other drug-related/immune-related Grade 3 toxicity, **EXCLUDING**:
  − *Grade 3 nausea/vomiting controlled by medical intervention within 72 hours*
  − *Grade 3 immune-related AEs (other than ocular events, colitis, myocarditis and pneumonitis) that improve to Grade ≤ 1 or baseline within 14 days after the initiation of supportive care or corticosteroid therapy*
  − *Grade 3 endocrinopathy that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject is asymptomatic or minimally or transiently symptomatic based on Investigator assessment*
  − *Grade 3 fatigue lasting ≤ 7 days from onset*
  − *Grade 3 rash in the absence of desquamation, with no mucosal involvement, that does not require systemic steroids, that does not interfere with activities of daily living and resolves to Grade 1 by the next dose of scheduled treatment or 14 days, whichever is longer*
  − *Any grade vitiligo or alopecia*
• Grade 2 or higher episcleritis, uveitis, or iritis
• Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 3 days of initiation of maximal supportive treatment.

If treatment is withheld > 6 weeks from the last dose, the participant must be permanently discontinued from study therapy.

Table 3. **Adverse Event Management Rules**

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose
	3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold therapy for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume therapy when patients are clinically and metabolically stable
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 6 weeks
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 6 weeks
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy can be continued while thyroid replacement therapy is instituted	Therapy with can be continued while thyroid replacement therapy is instituted
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 6 weeks
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 6 weeks
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[c]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 6 weeks
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

[a] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

[b] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose.

[c] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 6 weeks of the last dose.

8 NIVOLUMAB

8.1 Description of Investigational Product

Nivolumab is a soluble protein consisting of 4 polypeptide chains, which include 2 identical heavy chains and 2 identical light chains. Nivolumab is produced from cell culture using a Chinese Hamster Ovary (CHO) cell line. The physical and chemical properties of nivolumab drug substance are provided in Table 3.1-1 of the Investigator's Brochure.

8.2 Mechanism of Action

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T- cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition results in enhanced T-cell function that is greater than the effects of either antibody alone, and results in improved anti-tumor responses in metastatic melanoma and advanced RCC. In murine syngeneic tumor models, dual blockade of PD-1 and CTLA-4 resulted in increased anti-tumor activity.

8.3 Dosage Form, Agent Preparation, Handling & Storage Guidelines

8.3.1 Dosage Form

The nivolumab (Opdivo™) dosage forms are provided in Table 3.2.1-1 of the Investigator's Brochure. The drug products are sterile, non-pyrogenic, single-use, isotonic aqueous solutions for intravenous (IV) infusion. Nivolumab Injection, 40 mg/Vial (10 mg/mL), 100 mg/Vial (10 mg/mL), and 240 mg/Vial (10 mg/mL) are also referred to as nivolumab injection.

8.3.2 Acquisition and Accountability

The Investigator or designee is responsible for maintaining accurate dispensing records of the study treatment throughout the clinical study. The study treatment accountability log includes information including a patient identifier, amount and date dispensed, and amount and date returned to the pharmacy, if applicable. Product returned to the research pharmacy will be stored under the same conditions as products not yet dispensed but will be marked as 'returned' and kept separate from the products not yet dispensed. All dispensing and accountability records should be stored as per IND regulations. The pharmacist will dispense study treatment for each participant according to the pharmacy reference manual.

8.3.3 Preparation and Administration

Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding (polyethersulfone membrane) in-line filter at the protocol-specified doses and infusion times. It is not to be administered as an IV push or bolus injection. When the dose is based on patient weight (ie, mg/kg), nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% sodium chloride injection or 5% dextrose injection to protein concentrations as low as 0.35 mg/mL. When the dose is fixed (eg, 240 mg, 360 mg, or 480 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 160 mL. For patients weighing less than 40 kilograms (kg), the total volume of infusion must not exceed 4 mL per kg of patient weight.

During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Instructions for dilution and infusion of nivolumab injection will be provided to the clinical site. Care must be taken to ensure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

8.3.4 Packaging, Labeling, and Storage

Upon supply to site, study drugs will be labeled “for investigational use only” as per FDA regulations.

Nivolumab Injection
Vials of nivolumab injection must be stored at 2°C to 8°C (36°F to 46°F) and protected from light and freezing. The unopened vials can be stored at room temperature (up to 25°C, 77°F) and room light for up to 48 hours.

Undiluted Nivolumab Injection and Diluted Nivolumab Injection in the IV Container
The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°C to 8°C, 36°F to 46°F) for up to 24 hours, and a maximum of 8 hours of the total 24 hours can be at room temperature (up to 25°C, 77°F) and room light. The maximum of 8 hours under room
temperature and room light conditions includes the product administration period.

8.4 Disposal and Destruction

All unused and/or partially used Investigational Medicinal Product will be destroyed on site as per Institutional SOP and the destruction documented. Copy of the drug destruction document will be provided to BMS. IMP handling document will be provided at the time of Study activation.

9 RELATLIMAB

9.0 Description of Investigational Product

Relatlimab, also referred to as BMS-986016-01, BMS-986016, or anti-LAG-3, was selected for dosage form development. Relatlimab is a soluble protein consisting of 4 polypeptide chains that include 2 identical heavy chains and 2 identical light chains and is a human IgG4 monoclonal antibody directed against human LAG-3. Relatlimab is produced from cell culture using a Chinese hamster ovary (CHO) cell line. The physical and chemical properties of relatlimab drug substance are summarized in Table 3.1-1 of the Investigator's Brochure.

9.1 Mechanism of Action

Upon administration, relatlimab binds to LAG-3 on tumor infiltrating lymphocytes (TILs). This may activate antigen-specific T lymphocytes and enhance cytotoxic T cell-mediated tumor cell lysis, which leads to a reduction in tumor growth. LAG-3 is a member of the immunoglobulin superfamily (IgSF) and binds to major histocompatibility complex (MHC) class II. LAG-3 expression on TILs is associated with tumor-mediated immune suppression.[24]

9.2 Dosage Form, Agent Preparation, Handling & Storage Guidelines

9.2.1 Dosage Form

Relatlimab will be given as an intravenous (IV) infusion. There are three drug products available for intravenous (IV) administration; information relating to the drug products are provided in Table 3.2.1-1 of the Investigator's Brochure. The drug products are sterile, non-pyrogenic, single-use, isotonic aqueous solutions.

9.2.2 Acquisition and Accountability

The Investigator or designee is responsible for maintaining accurate dispensing records of the study treatment throughout the clinical study. The study treatment accountability log includes information including a patient identifier, amount and date dispensed, and amount and date returned to the pharmacy, if applicable. Product returned to the research pharmacy will be stored under the same conditions as products not yet dispensed but will be marked as 'returned' and kept separate from the products not yet dispensed. All dispensing and accountability records should be stored as per IND regulations. The pharmacist will dispense study treatment for each participant according to the pharmacy reference manual.

9.2.3 Preparation and Administration

9.2.3.1 *For Intravenous Administration*

Relatlimab Injections
Relatlimab injections (10 mg/mL) are to be administered as an IV infusion through a compatible low-protein binding in-line filter at the protocol-specified doses. They are not

to be administered as an IV push or bolus injection. Relatlimab injection can be diluted with 0.9% (w/v) sodium chloride injection (normal saline, NS) or 5% (w/v) dextrose injection (D5W) to protein concentrations no lower than 0.2 mg/mL.
Care must be taken to assure sterility of the prepared solution, as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities have been observed between relatlimab injection and ethylvinyl acetate (EVA), polyolefin (PO) or polyvinyl chloride (PVC) IV containers, di(2-ethylhexyl)phthalate (DEHP)-plasticized PVC IV sets, DEHP-free IV sets, or in-line filters with 0.2 µm or 1.2 µm polyethersulfone (PES), 0.2 µm nylon, or 0.2 µm polyvinylidene fluoride (PVDF) membranes.

Detailed instructions for drug product dilution and administration are provided in the pharmacy manual for the clinical study.

Co-administration of Relatlimab Injection and Nivolumab Injection
Relatlimab injections (10 mg/mL) can be co-administered with nivolumab injection (also referred to as BMS-936558 injection) as an IV infusion through a compatible low-protein-binding in-line filter at the protocol-specified doses. Relatlimab injection combined with nivolumab injection can be diluted with NS or D5W to a total protein concentration no lower than 0.8 mg/mL (0.2 mg/mL of relatlimab and 0.6 mg/mL of nivolumab).

Care must be taken to assure sterility of the prepared solution, as the products do not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between the combined drug products and EVA, PO, or PVC IV containers, DEHP-plasticized PVC IV sets, DEHP-free IV sets and in-line filters with 0.2 µm or 1.2 µm PES, 0.2 µm nylon, or 0.2 µm PVDF membranes.

Detailed instructions for drug product dilution and administration are provided in the pharmacy manual for the clinical study.

9.2.4 Packaging, Labeling, and Storage

Upon supply to site, study drugs will be labeled “for investigational use only” as per FDA regulations.

9.2.4.1 *For Intravenous Administration*

Relatlimab Injection, 10 mg/mL
The drug products should be stored at 2°C to 8°C (36ºF to 46ºF) with protection from light. Do not freeze the drug products.

Relatlimab Injection Infusions and Combinations of Relatlimab Injection and Nivolumab Injection Infusions
The IV administration of relatlimab infusions or combined relatlimab and nivolumab infusions must be completed within 24 hours of preparation. If not used immediately, the infusion solutions may be stored in a refrigerator at 2ºC to 8ºC (36ºF to 46ºF) for up to 24 hours and a maximum of 4 hours of the total 24 hours can be at room temperature

(15ºC to 25ºC; 59ºF to 77ºF) and exposed to room light. The maximum 4-hour period under room temperature and room light conditions includes the product administration period.

9.3 Disposal and Destruction

All unused and/or partially used Investigational Medicinal Product will be destroyed on site as per Institutional SOP and the destruction documented. Copy of the drug destruction document will be provided to BMS. IMP handling document will be provided at the time of Study activation.

10 SCHEDULE OF ASSESSMENTS

10.1 Screening

Screening assessments are to be conducted within 28 days prior to initiating study unless otherwise specified. At screening, the following procedures/tests will be performed:

- Informed Consent
- Eligibility (Inclusion/Exclusion criteria)
- Demographic and medical history
- Prior and concomitant medication review
- Physical Exam
- Vital Signs: systolic and diastolic blood pressures, and temperature
- ECOG Performance Status
- 12-Lead ECG
- Echocardiogram
- Laboratory Evaluations
  - Pregnancy Test (Urine or Serum β-HCG[2])
  - CBC with differential
  - Comprehensive metabolic panel
  - LDH
  - T3, free T4, TSH
  - ACTH and serum cortisol
  - Amylase
  - Lipase
  - Urinalysis
  - HBsAg, HBsAb, Hep C Ab, HB core antibody
  - Troponin T
  - PT/INR
  - PTT
- CT chest plain
- MRI brain with and without contrast
- MRI abdomen and pelvis with and without contrast (EOVIST® preferred)
- Correlative studies
  - Blood
  - Archival tissue
  - Fresh tumor biopsy if needed, safe and feasible as determined by investigator

10.2 Cycle 1, 3, 5, 7, Day 1 + or – 3 days

The following assessments will be performed

- Review adverse events
- Review concomitant medication

- Physical Exam
- Vital Signs: systolic and diastolic blood pressures, and temperature
- ECOG Performance Status
- Administration of nivolumab plus relatlimab
- Laboratory Evaluations
    - Pregnancy Test (Urine or Serum β-HCG[2])
    - CBC with differential
    - Comprehensive metabolic panel
    - LDH
    - Amylase
    - Lipase
    - Urinalysis
    - Troponin T (Only cycle 1)
- CT chest plain (Only for cycles 3,5,7, Day 1 (+ or – 3 days))
- MRI abdomen and pelvis with and without contrast (EOVIST® preferred) (Only for cycles 3,5,7, Day 1 (+ or – 3 days))
- Correlative studies
    - Blood for correlative studies to be obtained on
        - Cycle 1, Day 1 (+ or – 3 days)
        - Cycle 3, Day 1 (+ or – 3 days)
        - upon progression or response
    - Fresh tumor biopsy if needed, safe and feasible as determined by investigator.

10.3 Cycles 2, 4, 6, 8, Day 1 + or – 3 days

The following assessments will be performed at each cycle unless otherwise specified:

- Review adverse events
- Review concomitant medication
- Physical Exam
- Vital Signs: systolic and diastolic blood pressures, and temperature
- ECOG Performance Status
- Administration of nivolumab plus relatlimab
- Laboratory Evaluations
    - Pregnancy Test (Urine or Serum β-HCG[2])
    - CBC with differential
    - Comprehensive metabolic panel
    - LDH
    - T3, free T4, TSH
    - ACTH and serum cortisol
    - Amylase
    - Lipase
    - Urinalysis

- Troponin T (Only cycle 2)
- Correlative Studies
  - Blood for correlative studies to be obtained on Cycle 2, Day 1 (+ or – 3 days)) upon progression or response
  - Fresh tumor biopsy if needed, safe and feasible as determined by investigator..

10.4 Subsequent Treatment Cycles

Subsequent treatment cycles are to be repeated every 4 weeks until progression or toxicity up to 24 months. Cycles will follow the schedule of assessments outlined in section 10.2 (odd cycles) and section 10.3 (even cycles)

10.5 End of Treatment Visit, 28 days after the last dose of Nivolumab and Relatlimab combination treatment (+ or – 14 days)

The following assessments will be performed during the end of treatment visit:

- Review adverse events
- Review concomitant medication
- Physical Exam
- Vital Signs: systolic and diastolic blood pressures, and temperature
- ECOG Performance Status
- Laboratory Evaluations
  - Pregnancy Test (Urine or Serum β-HCG[2])
  - CBC with differential
  - Comprehensive metabolic panel
  - LDH
  - T3, free T4, TSH
  - ACTH and serum cortisol
  - Amylase
  - Lipase
  - Urinalysis

10.6 Safety Follow-Up, 30 days (+ or – 7 days) post discontinuation

The following assessments will be performed during the end of treatment visit:

- Post-study anticancer therapy status
- Review adverse events
- Review concomitant medication
- Physical Exam
- Vital Signs: systolic and diastolic blood pressures, and temperature
- ECOG Performance Status
- Laboratory Evaluations
  - Pregnancy Test (Urine or Serum β-HCG[2])

- CBC with differential
- Comprehensive metabolic panel
- LDH
- T3, free T4, TSH
- ACTH and serum cortisol
- Amylase
- Lipase
- Urinalysis

10.7 Survival Follow-Up, Every 12 weeks (+ or – 7 days) for 2 years

The following assessments will be performed during the survival follow-up visit:

- Post-study anticancer therapy status
- Survival status

10.8 STUDY CALENDAR

Trial Period:	Screening Phase	Treatment Cycles								End of Treatment	Post-Treatment	
Treatment Cycle/Title:	Screening	1	2	3	4	To be repeated every 4 weeks until progression or toxicity up to 24 months: 5	6	7	8	EOT (at time of discontinuation)	Safety Follow-up	Survival Follow-Up[1]
Scheduling Window (Days):	(-28 to -1 days)		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	30 days (+ or – 7 days) post discontinuation	Every 12 weeks (+ or – 7 days)
Administrative Procedures												
Informed Consent	X											
Inclusion/Exclusion Criteria	X											
Demographics and Medical History	X											
Prior and Concomitant Medication Review	X											
Post-study anticancer therapy status											X	X
Survival Status												X
Clinical Procedures/Assessments												
Review Adverse Events		X	X	X	X	X	X	X	X	X	X	
Review Concomitant Medication		X	X	X	X	X	X	X	X	X	X	
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs (temperature/pulse/respiratory rate/blood pressure and weight)	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG	X											
Echocardiogram	X											
Administration of nivolumab plus relatlimab over 60 minutes IV		X	X	X	X	X	X	X	X			
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory												
Pregnancy Test – Urine or Serum β-HCG[2]	X	X	X	X	X	X	X	X	X	X	X	
CBC with Differential	X	X	X	X	X	X	X	X	X	X	X	

Trial Period:	Screening Phase	Treatment Cycles								End of Treatment	Post-Treatment	
Treatment Cycle/Title:	Screening	1	2	3	4	To be repeated every 4 weeks until progression or toxicity up to 24 months: 5	6	7	8	EOT (at time of discontinuation)	Safety Follow-up	Survival Follow-Up[1]
Scheduling Window (Days):	(-28 to -1 days)		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	30 days (+ or – 7 days) post discontinuation	Every 12 weeks (+ or – 7 days)
Comprehensive Serum Chemistry Panel	X	X	X	X	X	X	X	X	X	X	X	
LDH	X	X	X	X	X	X	X	X	X	X	X	
T3, freeT4 and TSH[3]	X		X		X		X		X	X	X	
ACTH and serum cortisol[3]	X		X		X		X		X	X	X	
Amylase[3]	X	X	X	X	X	X	X	X	X	X	X	
Lipase[3]	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	
HBsAg, HBsAb, Hep C Ab, HB core antibody[4]	X											
Troponin T[3,5]	X	X	X									
PT/INR and PTT	X											
Efficacy Measurements												
CT chest plain	X			X		X		X				
MRI Brain with and without contrast[6]	X											
MRI abdomen/ pelvis with EOVIST™ with and without contrast[7]	X			X		X		X				
Archival Tissue Collection/Correlative Studies Blood												
Correlative Studies Blood Collection[8]	X	X	X	X	X[8]							
One additional blood sample for correlative studies		X[9]										
Archival Tumor Tissue Collection[10]	X											
Fresh Tumor Biopsies [11]	X	X[11]										

1. For two years.
2. For women who are able to become pregnant only.
3. Also as needed according to clinical signs and symptoms
4. For patients with treated hepatitis C, undetectable viral load is required with positive antibodies
5. For the first two months then as dictated by clinical signs and symptoms thereafter
6. At baseline, every 6 months and as needed as dictated by clinical signs and symptoms.
7. EOVIST contrast preferred but not mandatory
8. Blood for correlative studies to be obtained on day 1 of cycles 1-3 prior to treatment and upon progression/response
9. One additional blood sample for correlative studies will also be collected at any point after treatment started and before progression of disease or end of treatment
10. If fresh biopsy determined to be not safe and archival tissue available, then fresh biopsy waived.
11. Fresh tumor biopsies will be obtained at screening and upon progression or response if needed, safe and feasible as determined by the investigator.

11 CORRELATIVE STUDIES

Research Sampling	Time point	Contents
Archival Tissue	Screening	FFPE Tumor Tissue
FFPE Biopsy Tissue	Pre-treatment Biopsy	FFPE Biopsy Tissue
	Treatment Response or Progression	
Fresh Tissue, Fresh-Frozen Tissue	Pre-treatment Biopsy	Fresh Tumor Tissue, Fresh-Frozen Tumor Biopsy Tissue
	Treatment Response or Progression	
Blood	Pre-treatment C1	4- 10mL EDTA purple top tube
	Pre-Treatment C2	
	Pre-Treatment C3	
	One additional blood sample for correlative studies will also be collected at any point after treatment started and before progression of disease or end of treatment	
	At time of Response or Progression	

Correlative studies will be conducted for research use only.

For participants who consent to additional correlative studies, archival tissue, blood, and fresh/fresh-frozen tumor from pre- and post- treatment biopsy will be collected for correlative biomarker analysis including but not limited to tumor single-cell RNA-sequencing with single-cell TCR/BCR profiling, metastatic tumor mutation profiling, blood-based bulk TCR profiling, and blood-based cell-free DNA mutation profiling.

Correlative Studies, Solid Tumors:
Archival FFPE primary or previous metastatic tumor specimen, if available, may be collected from previous/current surgeries or biopsies for biomarker analysis including but not limited to mutation analysis and immunohistochemistry of LAG-3 and PD-1. A minimum of 3 10-micron sections will be required. Fresh/fresh-frozen tumor tissue from pre- and post- treatment biopsies will be collected for biomarker analysis including but not limited to tumor single-cell RNA-sequencing with single-cell TCR/BCR profiling. Mutation analysis may be conducted on fresh-frozen tumor tissue from pre- and post- treatment biopsy, if quantity permits.

Correlative Studies, Blood:
Blood will be obtained using EDTA purple top tubes and will be stored as plasma and buffy coat at -80 °C. Blood sample analysis will consist of but is not limited to bulk TCR profiling and cell-free DNA profiling.

Sample Storage and Analysis
Storage and analysis for tumor and blood will be conducted at:
The laboratory of J. William Harbour
Department of Ophthalmology
1501 NW 10th Ave
Biomedical Research Building
Room 832, Suite H-I

12 EVALUATION CRITERIA

12.1 Parameters of Outcome –RECIST 1.1 Criteria

12.2 Definition of Measurable Lesions

Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest dimension to be recorded). Each lesion must be ≥ 20 mm when measured by conventional techniques, including palpation, plain x-ray, CT, and MRI, or ≥ 10 mm when measured by spiral CT.

12.3 Treatment Beyond Progression

If disease progression is noted on imaging, patients may stay on drug and be re-evaluated for disease progression with restaging scans within 4 weeks, but no later than 6 weeks, after initial determination of progression. Patients who remain on therapy after initial disease progression must have stable ECOG status and no clinical symptoms and signs of disease progression to qualify for continuing treatment until the next imaging assessment.

12.4 Baseline documentation of “Target” and “Non-Target” lesions

All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest dimension) and their suitability for accurate repetitive measurements by one consistent method of assessment (either by imaging techniques or clinically). A sum of the longest dimension (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the progression of the measurable dimension of the disease. Tumor within a previously irradiated field will be designated as “non-target” lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and each of these lesions should be followed as stable (the persistence of a non-target lesion), complete response (the disappearance of a non-target lesion) or progressive disease (the unequivocal progression of a non-target lesion).

All baseline evaluations of disease status should be performed as close as possible to the start of treatment and never more than 4 weeks before the beginning of treatment.

Measurement of the longest dimension of each target lesion size is required for follow-up. Change in the sum of these dimensions affords some estimate of change

in tumor size and hence therapeutic efficacy. All disease must be assessed using the same technique as baseline.

12.5 Definition of disease progression

Progression for patients with measurable disease at baseline is defined as ANY of the following:

- At least a 20% increase in the sum of LD target lesions taking as reference the smallest sum LD recorded since study entry
- In the case where the ONLY target lesion is a solitary pelvic mass measured by physical exam which is not radiographically measurable, a 50% increase in the LD is required taking as reference the smallest LD recorded since study entry
- The appearance of one or more new lesions
- Death due to disease without prior objective documentation of progression
- Global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of progression
- Unequivocal progression of existing non-target lesions, other than pleural effusions without cytological proof of neoplastic origin, in the opinion of the treating physician (in this circumstance an explanation must be provided)

12.6 Progression for Patients with Non-Measurable Disease at Baseline

Defined as increasing clinical, radiological, or histological evidence of disease since study entry. Survival is the observed length of life from the date of study entry to death or the date of last contact.

12.7 Progression-Free Survival

Defined as the period from the date of study entry until disease progression or death (whichever occurs first). Cases who have not had an event will be censored at the date of last disease assessment documenting the patient was free of progression. Progression will be evaluated by RECIST v1.1.

12.8 Subjective Parameters

The performance status, specific symptoms, and side effects are graded according to the CTCAE 5.0.

13 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting.

13.1 Definition of Adverse Events

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

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

13.2 Definition of Serious Adverse Events

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

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

Although pregnancy and potential drug-induced liver injury (DILI), are not always serious by regulatory definition, however, these events must be reported within the SAEs timeline.

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

NOTE: (PI determines if this information regarding hospitalizations are considered SAEs and should be included in the protocol. This is supplemental information that is included in BMS-sponsored trials)

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

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

13.3 Non-Serious Adverse Event

- Non-serious Adverse Events (AE) are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [e.g., IND US trial] as part of an annual reporting requirement.
- Non-serious AE information should also be collected from following the subject's written consent to participate in the study.

Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE information should begin following the subject's written consent to participate in the study. 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) 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.

Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported to BMS as such.

The following laboratory abnormalities should be documented and reported appropriately:

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

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

13.4 Classification of an Adverse Event

13.4.1 Severity of Event

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

13.4.2 Relationship to Study Intervention

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. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

13.4.3 Expectedness

The Sponsor-Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the

nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

13.4.4 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs will be captured on the appropriate case report form (CRF) as well as in the Adverse Event reporting section in Velos, a HIPAA AND 21 CFR part 11 compliant database and will be reported to the University of Miami's IRB per institutional requirements.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Study personnel will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

13.5 Adverse Event Reporting

Adverse Events may be spontaneously identified by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

The Sponsor-Investigator, is responsible for reporting adverse events (AEs) to any regulatory agency, to the Sponsor-Investigator's IRB and to the Investigational Drug Sponsor (See Section 13.3 Non-Serious Adverse Event).

13.6 Serious Adverse Event Reporting

Generally, any AE considered serious by the PI or Sub-investigator or which meets the definition of an SAE included in **Section 13.2, Definition of Serious Adverse Events.**

SAEs will be captured on the appropriate case report form (CRF) as well as in the Serious Adverse Event reporting section in Velos, a HIPAA AND 21 CFR part 11 compliant database and will be reported to the University of Miami's IRB per institutional requirements.

All SAEs that occur following the subject's written consent through 100 days of discontinuation of dosing must be reported to BMS Worldwide Safety, whether related or not related to study drug. SAEs will be reported to BMS Worldwide safety using the Medwatch 3500A Reporting form. The Sponsor-Investigator or designee will report the SAE to BMS Worldwide **within 24 hours of his/her becoming aware of these events regardless of relationship of the SAE to the use of study drug**.

According to 21 CFR 312.32(c)(1), "the sponsor must notify FDA 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… 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. 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) 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);
> (B) 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);
> (C) 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."

Furthermore, according to 21 CFR 312.32(c)(2), "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."

13.7 Adverse Event Collection and Reporting Information:

- 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 (e.g., 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.

An appropriate SAE form (e.g. ex-US = CIOMS form or USA = Medwatch form) should be used to report SAEs to BMS. If the sponsor-investigator prefers to use their own Institutional form, it must be reviewed by the BMS Protocol Manager prior to study initiation to ensure that at a minimum all of the data elements on the CIOMS form are present. Note: Please include the BMS Protocol number on the SAE form or on the cover sheet with the SAE form transmission.

- ✓ The CIOMS form is available at: http://www.cioms.ch/index.php/cioms-form-i
- ✓ The MedWatch form is available at: MedWatch 3500 Form

- For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection.
- The Sponsor will reconcile the clinical database AE cases (**case level only**) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com).
  - The Investigator will request from BMS GPV&E, **aepbusinessprocess@bms.com** the SAE reconciliation report and include the BMS protocol number every 3 months and prior to data base lock or final data summary
  - GPV&E will send the investigator the report to verify and confirm all SAEs have been transmitted to BMS GPV&E.
  - The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS (Worldwide.Safety@bms.com).
- In addition to the Sponsor Investigator's responsibility to report events to their local HA, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).
- In accordance with local regulations, BMS will notify sponsor investigators of all reported SAEs that are suspected (related to the investigational product) and

unexpected (ie, not previously described in the IB). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Sponsor investigator notification of these events will be in the form of either a SUSAR Report or a Semi-Annual SUSAR Report.

- ✓ Other important findings which may be reported by BMS as an Expedited Safety Report (ESR) include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor or BMS decision to end or temporarily halt a clinical study for safety reasons.
- ✓ Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours \ 1 Business Day of becoming aware of the event. SAEs must be recorded on either CIOMS, MedWatch, or approved site SAE form.

Pregnancies must be reported and submitted to BMS. BMS will perform due diligence follow-up using the BMS Pregnancy Form which the investigator must complete.

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: +1 609-818-3804

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

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours \ 1 Business Day to BMS using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

13.8 Reporting Events to Participants

Not Applicable

13.9 Events of Special Interest

Select Adverse Events

Category of Select AE	Order in the output
ENDOCRINE ADVERSE EVENT	1 (if applicable)
GASTROINTESTINAL ADVERSE EVENTS	2
HEPATIC ADVERSE EVENTS	3
PLUMONARY ADVERSE EVENTS	4
RENAL ADVERSE EVENTS	5
SKIN	6
HYPERSENSITIVITY/INFUSION REACTION	7

Immune-Mediated Adverse Events (IMAE)

Class Name of IMAE	Order in the output
PNEUMONITIS	1
DIARRHEA/COLITIS	2
HEPATITIS	3
ADRENAL INSUFFICIENCY	4
HYPOTHYROIDISM/THYROIDITIS	5
HYPOTHYROIDISM	6
THYROIDITIS	7
DIABETES MELLITUS	8

Other Events of Special Interest

Category/class of OEOSI	**Order in the output**
MYASTHENIC SYNDROME	1
DEMYELINATION EVENT	2
GUILLAIN-BARRE SYNDROME	3
PANCREATITIS EVENT	4
UVEITIS EVENT	5
ENCEPHALITIS EVENT	6
MYOCARDITIS EVENT	7
MYOSITIS EVENT	8
RHABDOMYOLYSIS EVENT	9
GRAFT VERSUS HOST DISEASE	10
CA224 OTHER MENINGITIS	11
CA224 TROPONIN	12

13.9.1 Pregnancy

Every effort should be made to prevent pregnancy throughout the entire duration of participation in this study. All patients of reproductive potential involved in the study

are required to use effective methods of contraception during the study and for 24 weeks after the last combination treatment of nivolumab and relatlimab. Female patients will be instructed to notify the Investigator as soon as possible if they discover they are pregnant; male patients will be instructed to notify the Investigator immediately if they discover that their sexual partner is pregnant.

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 (e.g., dose tapering if necessary for participant).

The investigator must immediately notify Worldwide.Safety@bms.com of this event and complete one of the following forms within 24 hours of awareness of the 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 CIOMS, MedWatch, BMS Pregnancy Surveillance Form, **or** approved site 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 to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order for Sponsor 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.

13.9.2 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, X-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

14 UNANTICIPATED PROBLEMS

14.1 Definition of Unanticipated Problems

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

14.2 Unanticipated Problem Reporting

The Sponsor-Investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB).

14.3 Reporting Unanticipated Problems to Participants

Not Applicable

15 DATA REPORTING

15.1 Data submission

Electronic case report forms for study data entry will be developed by staff at the University of Miami using Velos, a HIPAA AND 21 CFR part 11 compliant database. Only investigators and assigned research staff will have access to study data. The electronic case report forms will be available to sponsor, IRB or regulatory authorities in event of an audit

15.2 Data and Safety Monitoring

The research team will continuously monitor study accruals, toxicities, and response to treatment. The Sylvester Comprehensive Cancer Center's (SCCC) Data and Safety Monitoring Committee (DSMC) will monitor this clinical trial according to the Cancer Center's data and safety monitoring (DSM) plan to assure the well-being of patients enrolled on Investigator-Initiated Trials that do not have an outside monitoring review. In its oversight capacity, the DSMC bears responsibility for suspending or terminating this study. The activities of this committee includes ongoing review of accrual, periodic review of response adverse events including SAEs, important medical events, significant revisions or amendments to the protocol, and approval of cohort/dose escalations. The DSMC also reviews reports from internal audits of protocol compliance and data integrity conducted by the University of Miami, Office of Research Compliance Assessment. If the DSMC and/or the PI have concerns about unexpected safety issues, the study will be stopped and will not resume until the issues are resolved. The DSMC will review reports from all audits, site visits, or study reviews pertaining to this clinical trial and take appropriate action. The guidelines appearing in this section are offered for DSMC consideration in assessing adverse events and response to study treatment. The SCCC DSM Plan to which this study is subject can also be found at www.sylvester.org.

15.3 Early Stopping Guidelines

We propose the following guidelines for the Sylvester Data and Safety monitoring Committee (DSMC) in its review of accumulating data on toxicity and feasibility of study treatment. The proposed guidelines were developed using Bayesian methods, which can be applied at any stage of enrollment without advance specification of the number of interim analyses to be performed, or the number of patients evaluable for toxicity, or response, at the time such assessments are made.

Under the Bayesian method, we assign a prior probability (level of belief at the start of the trial) to a range of possible values for the true toxicity rate, and likewise for the true feasibility rate. As data on treated patients become available, each of these probability distributions is revised and the resulting posterior probability becomes the basis for recommending either early termination or continuation of the study. In the sections that follow, we provide specific stopping guidelines based on posterior

probabilities for monitoring toxicity and efficacy over the course of this trial. Underlying assumptions for the prior distributions are also presented.

15.4 Early Stopping Due to Safety

The following early stopping guidelines, which are based on a Bayesian method, will be applied to ensure safety of this trial. Safety monitoring will be based on the occurrence of treatment related (possible, probable, or definite) grade 3 or higher toxicity occurring during study treatment. We suggest a stopping rule guideline for safety as a posterior probability of a rate of grade 3 or higher toxicity exceeding 20% as 90% or higher. Table 4 shows specific instances where this guideline is met. Posterior probabilities used to derive the preceding table are calculated under a prior beta distribution with parameters $\beta 1 = 0.2$ and $\beta 2 = 1.8$, which corresponds to an expected rate of 10% based on prior information roughly equivalent to having studied 2 patients. Furthermore, this prior distribution assigns a small a priori chance (17.5%) to the possibility that the true rate of unacceptable toxicity is 20% or greater.

Table 4. **Stopping Rules for Safety**

Number of Patients with Treatment Related Grade 3+ toxicity	**Total patients Evaluated**	**Observed rate**
3	3 to 5	>60%
4	6 to 9	>44.4%
5	10 to 12	>41.7%
6	13 to 16	>37.5%
7	17 to 20	>35%
8	21 to 24	>33.3%
9	24 to 27	>33.3%

15.5 Early Stopping Due to a Lack of Efficacy

Early stopping due to a lack of efficacy is built in study design since we use Simon two-stage design.

16 STATISTICAL METHODS

16.1 Statistical Hypothesis

The primary hypothesis is that the ORR in patients treated with the combination of nivolumab and BMS-986016 is significantly higher than 20%. With the null hypothesis that the ORR of 5% or lower is considered not clinically significant.

16.2 Sample Size Determination

Based on Simon two-stage minimax design, 13 patients will be enrolled in Stage 1 and evaluated for response. If none of the 13 patients respond (CR or PR), the study will be stopped for futility. Otherwise, the study will proceed to Stage 2 and enroll additional 14 patients for a total of 27 patients. The null hypothesis will be rejected if 4 or more responses are observed among 27 patients. This design achieves 5% type I error and 80% power when the true ORR is 20%

16.3 Statistical Analyses

Demographic and disease characteristics will be summarized using descriptive statistics. Counts and percentages will be used to summarize the distribution of categorical variables. Median, range, mean, and standard deviation will be used for continuous variables. Continuous variables will be tested using Student's t-test and/or Mann-Whitney U test. All statistical tests will be two-sided and $p<0.05$ will be considered as statistical significance.

The full analysis set will consist of all patients enrolled. The modified full analysis set will consist of all enrolled patients, except patients withdrawn prior to the first efficacy measurement (at Cycle 2). The per-protocol analysis set will consist of all patients from the FU analysis set without any major protocol violations. The safety analysis set will consist of all patients who get treatment regardless of completion of treatment. The safety analysis set will serve as the main analysis set for safety assessments. The modified full analysis set will serve as the main analysis set for efficacy assessments. The efficacy assessment will also be performed on the per-protocol and full analysis sets.

Response rate will be estimated along with corresponding 95% confidence interval using Fisher's exact method. Tumor response (CR, PR, SD, or PD) will be defined according to RECIST v1.1 guideline. Objective response rate (ORR) will be the proportion of patients with a confirmed CR or PR and disease control rate (DCR) is calculated by the proportion of patients with confirmed CR, PR, or SD.
Progression-free survival (PFS) is defined as the time from the date of enrollment to the date that objective progression disease is documented or death due to any cause, whichever occurs first. Overall survival (OS) is defined as the time from the date of enrollment to the date of death. Duration of response is defined as the time from the date of first documented response (CR or PR) until date of documented progression or death in the absence of disease progression.
For PFS and OS, Kaplan-Meier method will be used to estimate survival rates for pre-specified time points along with 95% confidence intervals.

Safety analysis will be include detailed tabulations of adverse events by type, grade and treatment attribution.

16.3.1 Exploratory Analyses

The exploratory endpoint is tumor-infiltrating immune cells to identify LAG3 checkpoint marker. V(D)J analysis will be conducted. Based on biopsy samples from pre-and post-treatment and blood samples at multiple time points, scRNA-seq and single-cell V(D)J profiling will be conducted

17 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

17.1 Informed Consent Process

17.1.1 Consent/Assent and other Informational Documents Provided to Participants

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

17.1.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. We anticipate to enroll non-English speaking participants, specifically Spanish-speaking participants. Consent forms will be translated to Spanish. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. The consent process will take place in a private clinic room. Participants will be given as much time as needed for them to be comfortable with participating in this study. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign and date the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

For subjects not qualified or able to give legal consent, consent must be obtained from their legally authorized representative (LAR).

The rights and welfare of the participants will be protected by emphasizing to them that they will not be penalized or lose any benefits and the quality of their medical care will not be adversely affected if they decline to participate in this study or leave the study early.

17.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigators, funding agency, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Sponsor-Investigator will promptly inform study participants, the Institutional Review Board (IRB), and the Investigational Drug Sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Investigational Drug Sponsor, IRB and/or Food and Drug Administration (FDA).

17.3 Confidentiality and Privacy

Information collected as part of this study will be destroyed or de-identified at the earliest opportunity. Information collected will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study or for other research for which the use or disclosure of PHI is permissible. Specimens obtained for this research will be de-identified and coded with the link between code and the subject's identity maintained separately from the data. Research data may be sent to the investigational drug sponsor, Bristol Myers Squibb**.** Data sent will be coded/de-identified. Information may be sent via email, fax, Fedex, UPS, USPS, courier, or via a study-specific electronic data capture system. Procedures to protect confidentiality of information being sent are the following: de-identifying/coding reports, utilizing cover sheets for faxes, sending emails via secure transmittal, password-protected files, and utilizing delivery confirmation/tracking for items shipped via courier. Specimens will not be sent to external entities. This study will access electronic medical record or other protected health information without obtaining a signed HIPAA authorization from the subject to identify potential subjects for recruitment and to obtain study data.

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the Sponsor-Investigator and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in

addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor-Investigator.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the Sponsor-Investigator, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The Sponsor-Investigator will permit access to such records.

The study participant's contact information will be securely stored in the University of Miami's password-protected electronic devices and University of Miami approved cloud-based storage systems for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or Investigational Drug Sponsor requirements.

Electronic case report forms for study data entry will be developed by staff at the University of Miami using Velos, a HIPAA AND 21 CFR part 11 compliant database. Only Investigators and assigned research staff will have access to study data.

17.4 Future Use of Stored Specimens and Data

Data collected for this study will be analyzed and stored at the University of Miami on Velos.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), biological samples will be stored at the University of Miami per institutional regulations. These samples could be used to research the causes of the condition being studied as part of this protocol or may be stored indefinitely to for research as new knowledge or technology becomes available. The laboratory storing the biological specimens will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant. The principal investigator and other designated study staff will have access to the code sheet including sub-investigators, clinical coordinators, data coordinators, clinical manager, and regulatory staff.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However,

withdrawal of consent with regard to biospecimen storage may not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through Velos and the laboratory storing the biological specimens.

17.5 Study Auditing and Monitoring

This study will be monitored (as applicable) and may be audited according to the University of Miami requirements. See also http://research.med.miami.edu/clinical-research/crors/monitoring

Following the monitoring plan, the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements.

17.5.1 Trial Monitoring, Auditing, and Inspecting

The investigator will permit trial-related monitoring, quality audits, and inspections by, government regulatory authorities, of all trial-related documents (e.g., source documents, regulatory documents, data collection instruments, case report forms). The investigator will ensure the capability for inspections of applicable trial-related facilities. The investigator will ensure that the trial monitor or any other compliance or QA reviewer is given access to all trial-related documents and trial-related facilities.

Participation as an investigator in this trial implies the acceptance of potential inspection by government regulatory authorities.

17.6 Quality Assurance and Quality Control

In addition to the Clinical Monitoring component of this protocol, Quality Assurance (QA) will be implemented to assess compliance with GCP and applicable regulatory requirements. Data or documentation audited shall be assessed for compliance to the protocol, accuracy in relation to source documents and compliance to applicable regulations.

17.7 Data Handling and Record Keeping

17.7.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the Sponsor-Investigator. The Sponsor-Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Data for electronic CRFs will be entered into Velos. A CRF is required for every patient who received any amount of study treatment. The investigator will ensure that the CRF's are accurate, complete, legible and timely. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Velos, a HIPAA AND 21 CFR Part 11-compliant data capture system provided by the University of Miami. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

17.7.2 Study Records Retention

All records and documents relating to research studies and participants must be kept confidential to the extent permitted by law; however, records and documents shall be available in a timely manner to the University authorized employees or other agents authorized by the University including IRB members and HSRO staff and appropriate governmental agencies including but not limited to DHHS, OHRP and the FDA.

Although principal investigators are responsible for the creation and maintenance of research records and documents, such records and documents (including data collected pursuant to research) are the property of the University. Until the temporal requirements for record/document retention are met, investigators or others may not remove or destroy research records or documents (or copies of such records or documents) without written permission from the Vice Provost of Research. This permission requirement extends to investigators leaving the University even if they plan to continue the research at another institution.

With certain exceptions, investigators must retain complete records and documents (including the consent documents) from their study for the duration of that study and for a minimum period of three (3) years following closure of a study. Exceptions to this 3-year minimum retention period are:

a. HIPAA REQUIREMENTS: if a study involves the collection of identifiable health information, records must be retained for a minimum of six (6) years following study closure. This retention period is consistent with the HIPAA Privacy Rule under which subjects may ask investigators for an accounting of all uses and disclosures of their study information for a period of 6 years after their participation is completed (c.f. 45 CFR 164.528)
b. FDA REQUIREMENTS FOR A STUDY INVOLVING AN INVESTIGATIONAL DRUG UNDER AN IND (c.f. 21 CFR 312.62): if a study involves the use of an

investigational drug under an IND, principal investigators must retain study records and documents until at least the later of the following dates:

a. 2-years following the date of a marketing application is approved for the drug for the indication for which it was being investigated; or
b. 2-years after the investigation is discontinued and the FDA is notified if no marketing application is to be filed or, if the application is not approved for such indication; or
c. 3-years after IRB approval of the closure of the study

c. FDA REQUIREMENTS FOR A STUDY INVOLVING AN INVESTIGATIONAL DEVICE UNDER AN IDE (c.f. 21 CFR 812.140): if a study involves an investigational device under an IDE, principal investigators must retain study records and documents until at least the later of the following dates:
    a. 2-years following the date on which the investigation is terminated or completed; or
    b. 2-years following the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol; or
    c. 3-years after IRB approval of the closure of the study.

NOTE-The FDA two-year requirements may occur during the applicable retention period or it may occur afterward and be additional to that period.

d. VA REQUIREMENTS: if a study engages the VA, investigators must retina research records and documents for a minimum of five (5) years after IRB approval of study closure. This retention period is consistent with the VA's Records Control Schedule (RCS 10-1).
e. ICH-GCP REQUIREMENTS: trial documents must be retained as specified in Essential Documents for the Conduct of a Clinical Trial and as required by the applicable regulatory requirement(s). Measures must be taken to prevent accidental or premature destruction of these documents.

Records must be retained longer than the times specified above as other requirements may apply such as may be forthcoming from sponsors in executed contracts, institutional entities or extramural funding agencies.

If your Human Research is funded by an investigational drug sponsor, contact the investigational drug sponsor before disposing of Human Research records. The protocol and clinical trial agreement/contract will also contain terms for records retention.

17.8 Compliance with Protocol

The investigator/institution should conduct the trial in compliance with the protocol agreed to by the investigational drug sponsor and, if required, by the regulatory authorities and which was given approval opinion by the IRB.

The investigator should not implement any deviation from, or changes of the protocol without agreement by the investigational drug sponsor and prior review and documented approval opinion from the IRB of an amendment, except where

necessary to eliminate an immediate hazard to trial subjects, or when the changes involves only logistical or administrative aspects of the trial (e.g. change in monitors, change of telephone numbers).

The investigator, or designee, should document and explain any deviation from the approved protocol.

The investigator may implement a deviation from, or change of, the protocol to eliminate an immediate hazard to trial subjects without prior IRB approval opinion. As soon as possible, the implemented deviation or change, the reasons for it, and if appropriate, the proposed protocol amendments should be submitted:

a. To the IRB for review and approval opinion;
b. To the investigational drug sponsor for agreement, if required,
c. To the regulatory authorities

17.9 Publication and Data Sharing

All information provided regarding the trial, as well as all information collected/documented during the course of the trial, will be regarded as confidential. The financial disclosure information will be completed prior to trial participation from all PIs and Sub-Investigators who are involved in the trial and named on the FDA 1572 form.

BMS will review of all publications 30-45 days prior to submission to any congresses and/or journals as per contract agreement.

The Sponsor-Investigator will register the trial on www.clinicaltrials.gov. In addition, Sponsor-Investigator will publish the results of the trial

17.10 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the University of Miami has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

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APPENDIX A: EXPEDITED ADVERSE EVENT (AE) REPORTING REQUIREMENTS

For all AEs that meet criteria for expedited reporting, the Sponsor-Investigator (SI) is obligated to pursue and provide follow-up reporting information until the event has resolved or until an acceptable medical endpoint has been reached (i.e. for the duration specified in the protocol), or the patient is lost to follow-up.

The SI and all applicable research study team members should become familiar with the safety profile of the investigational agent(s) and/or intervention at the start of the study and for the duration of the research, e.g. by reviewing the Investigator's Brochure (IB) and any Safety Reports released, by the Sponsor as applicable.

A. FDA Expedited Reporting
   a. Sponsor-Investigators i.e. IND Holders, have additional reporting requirements to the FDA and other committees, and should consult the applicable regulations and agency guidelines for these requirements.
   b. Since this protocol involves the use of FDA IND agent(s), completion of the FDA MedWatch 3500A Reporting Form is required for Sponsor-Investigators. The Form can be obtained electronically at: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf
      i. All serious, unexpected (unanticipated) and suspected adverse events must be directly reported to the FDA within 15 calendar days of being made known to the Principal Investigator (PI).
      ii. All fatal or life-threatening AEs must be directly reported to the FDA within 7 calendar days of being made known to the SI.
   c. For more information regarding reporting to the FDA, please refer to the FDA website for REPORTING GUIDELINES: http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm

B. IRB Expedited Reporting
   a. All Investigators should also be aware of local Institutional requirements for AE reporting. For more information regarding the IRB policy, please refer to the UM HSRO's Investigator Manual: http://hsro.med.miami.edu/documents/HRP-103_-_INVESTIGATOR_MANUAL_4.11.2014.docx and the UM HSRO SOP on New Information (HRP-024) https://eprost.med.miami.edu/eProst/Doc/0/HLJ5OTJVQEH419E0I6QPT3B199/HRP-024%20-%20SOP%20-%20New%20Information.docx
   b. All AEs that are serious, unanticipated and possibly related will be reported to the IRB within ten (10) working days of being made known to the SI.
   c. Events that are more frequent than anticipated or more severe than expected must be reported to the IRB within ten (10) working days of being made known to the SI.

d. All unanticipated deaths must be reported to the IRB within 24 hours of being made known to the SI.

C. Bristol Myers Squibb Expedited Reporting, as applicable

a. In addition to the mandatory MedWatch 3500A Form, the Sponsor-Investigator is also required to comply with all reporting requirements as supplied by Bristol Myers Squibb. Refer to Section 13.3 Non-Serious Adverse Event, 13.6 Serious Adverse Event Reporting 13.7 Adverse Event Collection and Reporting Information.

APPENDIX B: PERFORMANCE STATUS SCALES

PERFORMANCE STATUS CRITERIA					
ECOG (Zubrod)		**Karnofsky**		**Lansky**	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	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.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of, and less time spent in, play activity.
2	Ambulatory and capable of all selfcare 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.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed, participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed, needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to a bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping, play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play, does not get out of bed.
5	Dead	0	Dead	0	Dead

As published in Am J Clin Oncol: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655. The Eastern Cooperative Oncology Group, Robert Comis, MD, Group Chair.

APPENDIX C: BIOMARKER, CORRELATIVE AND SPECIAL STUDIES

Samples will be processed and stored at <insert lab>

1. Email notification
   Jose Lutzky (PI) should be contacted via email to notify him of all specimen submissions for storage.
   PI (Dr.Lutzky): jxl810@med.miami.edu to
   Laboratory Collaborator: harbour@med.miami.edu

2. Specimen Collection
   Refer to Section 11.0 Correlative Studies

3. Future Use of Specimens and Data
   Refer to Section **17.4 Future Use of Stored Specimens and Data**

4. **Storage and analysis for tumor and blood will be conducted at:**
   The laboratory of J. William Harbour
   Department of Ophthalmology
   1501 NW 10th Ave
   Biomedical Research Building
   Room 832, Suite H-I