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VICC MEL 18114: A Phase II Two-Arm Open-Label Study of Nivolumab plus Relatlimab or Ipilimumab in Metastatic Melanoma Stratified by MHC-II Expression

Principal Investigator: Elizabeth Davis, M.D.

Co-Principal Investigator: Douglas Johnson, M.D.

Study Statistician: Fei Ye, Ph.D.

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APPENDICES

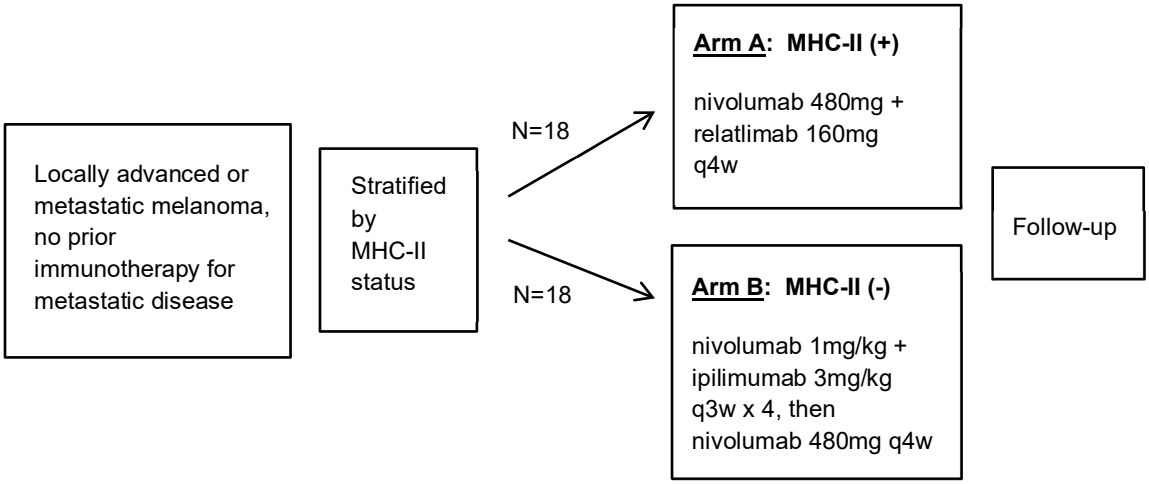
1. SYNOPSIS

Trial Title	A Phase II Two-Arm Open-Label Study of Nivolumab plus Relatlimab or Ipilimumab in Metastatic Melanoma Stratified by MHC-II Expression.
Trial Sites	Vanderbilt University Medical Center and approximately 2 additional academic medical centers in the United States.
Overall Design	This is an open-label, non-randomized two arm Phase 2 study of intravenous nivolumab plus intravenous ipilimumab or intravenous relatlimab in patients with metastatic melanoma stratified by MHC-II expression.
Hypothesis	Patients with MHC-II expressing melanomas will have high rates of change in activated GZMB+ CD8+ T-cell density intratumorally with nivolumab and relatlimab therapy; MHC-II expression is an effective stratifying marker in melanoma that can be used in future studies to select optimal treatment.
Study Design	Patients will be stratified into 2 arms: Arm A: MHC-II positive patients, and Arm B: MHC-II negative patients. Arm A: Treatment will consist of cycles lasting 28 days (4 weeks) per cycle (nivolumab + relatlimab): • On Day 1 of each 28-day cycle, all patients are scheduled to receive nivolumab and relatlimab intravenously. Arm B: Treatment will consist of four initial cycles lasting 21 days (3 weeks) per cycle (nivolumab + ipilimumab); followed by cycles lasting 28 days (4 weeks) for nivolumab monotherapy: • On Day 1 of cycles 1-4, all patients are scheduled to receive ipilimumab and nivolumab intravenously. Starting with cycle 5, patients will receive nivolumab intravenously every 4 weeks.
Duration of Treatment	It is intended that patients will be treated until RECIST 1.1 confirmed disease progression, until intolerable toxicity, or up to a maximum of 2 years after initiation of study treatment.
Objectives and Efficacy Measures	Primary Objective: • To evaluate the efficacy, measured by change in activated GZMB+ CD8+ T-cell density intratumorally, of two immunotherapy regimens in patients with advanced melanoma: — nivolumab plus relatlimab in patients with MHC-II (+) melanoma, and — nivolumab plus ipilimumab in patients with MHC-II (-) melanoma. Secondary Objectives: • To evaluate the response rate, median progression free survival, overall survival, and safety and tolerability of nivolumab plus relatlimab in patients with MHC-II (+) melanoma, and of nivolumab plus ipilimumab in patients with MHC-II (-) melanoma.

	Exploratory Objectives: • To explore potential associations of biomarkers with clinical efficacy and/or incidence of adverse events due to study drug by analyzing biomarker measures within the peripheral blood and tumor microenvironment. Primary Efficacy Measure: • Change in activated GZMB+ CD8+ T-cell density intratumorally. Secondary Efficacy Measures: • Response rate (RR) • Median progression free survival (mPFS) • Median overall survival (mOS) • Adverse events.
Inclusion and Exclusion Criteria	See Section 5.
Number of Patients and Study Duration	Approximately 36 evaluable patients accrued across 18 months (average accrual rate of 2 per month), with up to 2 years of survival follow-up. The total duration for study enrollment is estimated as 24 months.
Study Assessments	See the Schedule of Assessments in Section 7.

2. SCHEMA

The study design schematic is presented in **Figure 1**:



Approximately 18 participants will be enrolled in each arm of the study. Accrual in a given arm will stop when 18 participants in the arm have enrolled. All participants may receive study treatment: until confirmed progression of disease, unacceptable toxicity, participant withdrawal of consent, or study closure.

The study will consist of three phases: screening, treatment, and follow-up as detailed below.

2.1. Screening Phase

- Begins by signing of the informed consent form (ICF) and establishing the participant's eligibility.
- Participant is assessed for complete study eligibility as described in Section 5.
- A pregnancy test for WOCBP documented within 72 hours prior to the start of the first dose of study medication.
- Tumor tissue must be received at Vanderbilt University Medical Center (VUMC) for MHC-II testing in order for the participant to be enrolled in the correct arm of the study. MHC-II positivity is defined as ≥5% of tumor cells expressing MHC-II.

2.2. Treatment Phase

- Begins upon subject's initiation of protocol-indicated treatment.
- Arm A: Nivolumab 480 mg IV and Relatlimab 160mg IV are administered on day 1 of every 4 week cycle until disease progression, discontinuation due to unacceptable toxicity, withdrawal of consent or study closure, or 104 weeks of treatment.
- Arm B: Nivolumab 1mg/kg IV and Ipilimumab 3mg/kg IV are administered on day 1 of every 3 week cycle for 4 doses. Then, nivolumab 480mg IV is administered on day 1 of every 4 week

cycle until disease progression, discontinuation due to unacceptable toxicity, withdrawal of consent or study closure, or 104 weeks of treatment.

- Treatment beyond initial investigator-assessed RECIST 1.1-defined progression is permitted if the subject has investigator-assessed clinical benefit and is tolerating treatment.
- Study assessments are to be collected as outlined in Section 7.
- This phase ends when the participant is discontinued from study therapy or at a maximum of 2 years of treatment.

2.3. Post-treatment Follow-up Phase

- Begins after 2 years of treatment or when the decision is made to discontinue a participant from study therapy.
- Subjects who discontinue treatment for reasons other than disease progression will continue to have tumor assessments (if clinically feasible) according to the schedule in Section 7 until progression or the start of any subsequent therapy, whichever occurs first.
- Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All treatment-related serious adverse events will be documented for a minimum of 100 days after the last dose of study.
- After completion of the follow-up visit, subjects will be followed every 3 months (± 14 days) after patient's last dose of study treatment – until death, end of the study, until lost to follow-up or patient withdraws consent, or for a maximum of 2 years after a patient's final study treatment– whichever comes first. Survival contact can be made via clinic visit, chart review, obituary or similar observation (e.g. Social Security death index), or by telephone. The sponsor-investigator and/or BMS may request that survival data be collected on all treated subjects outside of the protocol defined window. At that time of this request, each subject will be contacted to determine their survival status unless the subject had withdrawn consent for all contact.
- Study assessments are to be collected as outlined in Section 7.

3. BACKGROUND AND RATIONALE

3.1. Introduction

Advanced melanoma is historically associated with a dismal prognosis and limited therapeutic options. Recently, advances in targeted and immune therapies have resulted in durable responses for nearly half of treated patients. In particular, immune checkpoint inhibitors have driven long-term responses for a substantial fraction of treated patients. Despite this, both intrinsic and acquired resistance remains a major limitation and at least half of patients still die of metastatic disease.

Immune checkpoint inhibitors are agents that remove negative regulators of T cell responses. Immune checkpoints are terms for molecules such as programmed death-1 (PD-1), programmed death-ligands 1 (PD-L1) and 2 (PD-L2) that downregulate the host anti-tumor immune response, and are expressed in many cancer types. Thus, these molecules play a key role in evading anti-tumor immunity.

Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the PD-1 cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by

activated T and B lymphocytes. Binding of PD-1 to its ligands, PD-L1 and 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 has recently shown clinical efficacy in numerous cancers, including melanoma, renal cell carcinoma, NSCLC, Hodgkin lymphoma, and others.

Recent studies have also conclusively demonstrated that combining ipilimumab, an inhibitor of cytotoxic T lymphocyte antigen-4, increases the response rate and progression free survival in patients with metastatic melanoma. The response rate was 58% vs. 43% vs. 19% for the combination, nivolumab, and ipilimumab respectively ($p<0.001$), while median PFS was similarly improved (median 11.5 vs. 6.9 vs. 2.9 months, $p<0.001$)[1]. Overall survival was also increased numerically (58% vs. 52% at 3 years), although this was not statistically significant[2]. Still, the same limitations of intrinsic and acquired resistance still occur, limiting the effectiveness of therapy in many patients.

Despite the activity of nivolumab and ipilimumab + nivolumab in these studies, markers to prospectively identify patients most likely to respond are needed. Early studies suggested that expression of PD-L1 was required for response to nivolumab[3], however subsequent studies have not confirmed this. Importantly, when PD-L1 was examined in patients treated with nivolumab or ipilimumab+ nivolumab, no difference in PFS was observed. This contrasted with patients with low PD-L1 expression, which correlated with improved PFS in the combination. However, overall survival was not statistically different in either group, and response rate was superior for the combination in both groups. Overall, PD-L1 positivity correlates with response to therapy, but does not allow accurate response prediction. Thus, better predictive biomarkers are needed to stratify patients to immunotherapy treatment, particularly in the first-line setting.

Nivolumab and relatlimab has also demonstrated efficacy in patients with advanced melanoma. Among heavily pre-treated patients, all of which had previously failed single-agent anti-PD-1 therapy, a response rate of 11.5% was observed (7 of 61), with a disease control rate of 49%. Biomarker analyses suggested that subjects whose TIL expressed more LAG-3 had a higher response rate, with a greater than 3-fold increase in ORR observed in subjects with evidence of LAG-3 expression in at least 1% of nucleated cells within the tumor margin, compared to less than 1% LAG-3 expression (18.2% [6/33] and 5.0% [1/20], respectively). PD-L1 expression did not appear to enrich for response.

3.2. Rationale for Ipilimumab and Nivolumab in Melanoma

Ipilimumab and nivolumab in combination have demonstrated efficacy in several trials in advanced melanoma. Checkmate-065, a randomized phase II study, showed that the combination improved outcomes compared with single agent ipilimumab in BRAF wild type, metastatic melanoma. The response rate (61% vs. 11%), and median PFS (not reached vs. 4.4 months) were substantially improved with monotherapy, leading to an initial approval for this combination in BRAF wild type melanoma[4]. The efficacy of the combination was then confirmed in Checkmate-067, a phase III study comparing nivolumab, ipilimumab, and the combination of both. This study confirmed superior response rates for the combination and anti-PD-1 compared to ipilimumab (58%, 44%, and 19%), as well as superior PFS (median 11.5 vs. 6.9 vs. 2.5 months)[1].

The safety profile of ipilimumab and nivolumab has been acceptable. Immune-related adverse events are increased compared with either monotherapy (59% grade 3-4 treatment related events compared with 21% and 28% with nivolumab and ipilimumab, respectively) (See **Table 1**). However, treatment related deaths are rare, and most toxicities resolved with steroid administration or other immunosuppressive treatments[1].

TABLE 1: Selected Adverse Drug Reactions in Patients Treated with Nivolumab in Combination with Ipilimumab in Clinical Studies (N=4,849)

Toxicity	Overall frequency: n(%)	Serious (grade 3-4)	Fatal
Myocarditis	9 (1.19)	8 (0.16)	4 (0.08)
Hypothyroidism	480 (9.9)	13 (0.27)	None
Hypophysitis	202 (4.17)	79 (1.53)	None
Diabetes	20 (0.41)	9 (0.19)	None
Diarrhea	1192 (24.58)	291 (6)	None
Colitis	337 (6.95)	250 (5.16)	1 (0.02)
Pancreatitis	55 (1.13)	32 (0.66)	None
Hepatitis	76 (1.57)	40 (0.82)	None
Myositis	13 (0.27)	5 (0.10)	1 (0.02)
Encephalitis	9 (0.19)	9 (0.19)	None
Myasthenia gravis	4 (0.08)	3 (0.06)	1 (0.02)
Pneumonitis	247 (5.09)	12 (2.56)	7 (0.14)
Pruritis	867 (17.88)	3 (0.06)	None
Rash	33 (15.12)	24 (0.49)	None

3.3. Rationale for Nivolumab and Relatlimab in Melanoma

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 IgG4 antibody. Relatlimab binds to the LAG-3 receptor with high affinity, and thus 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). Using surrogate antibodies recognizing mouse LAG-3 (C9B7W and 19C7), anti-tumor activity mediated by LAG-3 blockade has been demonstrated in 3 murine syngeneic in vivo tumor models (Sa1N fibrosarcoma, MC38 colon adenocarcinoma, and A20 B-cell lymphoma). Both tumor inhibition and the number of tumor-free mice were increased by anti-LAG-3 monotherapy, while the combination of anti-LAG-3 with a blocking anti-programmed cell death protein 1 (PD-1) antibody provided enhanced anti-tumor activity higher than the activity of either agent alone and higher than the activity of anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody in some mice. Several other studies have clearly demonstrated the role of LAG-3, and the additive effects of PD-1 and LAG-3 blockade both in pre-clinical models of cancer and chronic infection.

Single agent studies using relatlimab (CA224020 and CA224022) demonstrated partial responses in non-small cell lung cancer and marginal zone lymphoma, with numerous other patients showing stable disease. Relatlimab in combination with nivolumab has shown the capacity to induce responses in previously heavily treated advanced solid tumors, with the added ability to trigger responses in tumors that have demonstrated resistance to nivolumab therapy. As of the cutoff date of 15-Jun-2017 for Part B of Study CA224020, in subjects treated with relatlimab and nivolumab combination therapy, partial responses were seen in subjects with melanoma, cervical cancer, NSCLC, and squamous cell carcinoma of the head and neck (SCCHN). As of the cutoff date of 07-Apr-2017 for Study CA224022 in subjects treated with relatlimab and nivolumab combination therapy, partial responses have been seen in subjects with relapsed/refractory Hodgkin lymphoma, with stable disease observed in 1 subject for 6 months (and treatment was continuing). In subjects with melanoma treated with relatlimab and nivolumab combination therapy in Part C of Study CA224020, the overall objective response rate (ORR) was 11.5% (7/61, response evaluable) with a disease control rate of 49%. Biomarker analyses suggested that

subjects whose TIL expressed more LAG-3 had a higher response rate, with a greater than 3-fold increase in ORR observed in subjects with evidence of LAG-3 expression in at least 1% of nucleated cells within the tumor margin, compared to less than 1% LAG-3 expression (18.2% [6/33] and 5.0% [1/20], respectively). PD-L1 expression did not appear to enrich for response.

The safety profile of nivolumab + relatlimab has been largely similar to nivolumab monotherapy. LAG-3 knockout in mice has minimal effects, but combination PD-1 and LAG-3 knockout leads to multiorgan autoimmunity. This result has not been recapitulated in humans. Overall, among 304 patients treated with this combination, 157 (51.6%) had at least one treatment related event, most commonly fatigue (12.2%), diarrhea (6.6%; grade 3 in 1%), pruritus (6.9%), and infusion reaction (5.9%). One patient had a grade 5 event (myocarditis); 10.2% had grade 3-4 toxicities.

TABLE 2: Summary of Adverse Events Reported in At Least 5% of Subjects During Combination Therapy in Study CA224020, Parts B and C (N = 304)

Preferred Term	All AEs (Regardless of Causality)			Drug-related AEs		
	Any Grade AEs n (%)	Grade 3 - 4 AEs n (%)	Grade 5 AEs n (%)	Any Grade AEs n (%)	Grade 3 - 4 AEs n (%)	Grade 5 AEs n (%)
Total Subjects with an Event	256 (84.2)	76 (25.0)	48 (15.8)	157 (51.6)	31 (10.2)	1 (0.3)
Fatigue	69 (22.7)	4 (1.3)	0	37 (12.2)	0	0
Malignant Neoplasm Progression	47 (15.5)	3 (1.0)	42 (13.8)	0	0	0
Diarrhoea	41 (13.5)	3 (1.0)	0	20 (6.6)	3 (1.0)	0
Nausea	40 (13.2)	0	0	12 (3.9)	0	0
Asthenia	39 (12.8)	1 (0.3)	0	7 (2.3)	0	0
Pyrexia	38 (12.5)	1 (0.3)	0	13 (4.3)	1 (0.3)	0
Decreased Appetite	34 (11.2)	1 (0.3)	0	6 (2.0)	0	0
Dyspnoea	33 (10.9)	4 (1.3)	0	10 (3.3)	2 (0.7)	0
Arthralgia	32 (10.5)	0	0	17 (5.6)	0	0
Cough	31 (10.2)	0	0	4 (1.3)	0	0
Constipation	30 (9.9)	0	0	1 (0.3)	0	0
Anaemia	28 (9.2)	9 (3.0)	0	1 (0.3)	0	0
Abdominal Pain	25 (8.2)	6 (2.0)	0	5 (1.6)	0	0
Vomiting	24 (7.9)	1 (0.3)	0	2 (0.7)	0	0
Headache	23 (7.6)	0	0	5 (1.6)	0	0
Pruritus	23 (7.6)	0	0	21 (6.9)	0	0
AST Increased	21 (6.9)	5 (1.6)	0	12 (3.9)	4 (1.3)	0
Back Pain	20 (6.6)	1 (0.3)	0	4 (1.3)	0	0
ALT Increased	18 (5.9)	4 (1.3)	0	11 (3.6)	2 (0.7)	0
Infusion Related Reaction	18 (5.9)	0	0	18 (5.9)	0	0
Myalgia	16 (5.3)	0	0	6 (2.0)	0	0
Rash	16 (5.3)	0	0	11 (3.6)	0	0

Notes: MedDRA Version 20.0, CTC Version 4.0; includes events reported between the first dose and 135 days after the last dose of study treatment. All reported AEs were as of the database lock on 15-Jun-2017.

CTC = Common Toxicity Criteria; MedDRA = Medical Dictionary for Regulatory Activities.

Source: Study CA224020, BMS_GBS\CA224\BYA62589\Biostatistics\Production\Tables\rt-ae-all.sas Run Date: 07JUL2017:12:08, BMS_GBS\CA224\BYA62589\Biostatistics\Production\Tables\rt-ae-allrel.sas Run Date: 07JUL2017:12:09

3.4. Rationale for Flat Dosing of Nivolumab Monotherapy

Nivolumab monotherapy has been extensively studied in a number of tumor types including NSCLC, melanoma, RCC, and CRC with body weight normalized dosing (mg/kg). Nivolumab pharmacokinetics (PK) and exposures of subjects in these studies have been characterized by population pharmacokinetic (PPK) analysis of data collected these studies, together with PK data from several phase 1, 2, and 3 clinical studies of nivolumab monotherapy in solid tumors. Population PK (PPK) analyses have shown that the PK of nivolumab are linear, with dose proportional exposures over a dose range of 0.1 mg/kg to 10 mg/kg, and are similar across tumor types. Nivolumab clearance and volume of distribution were found to increase with increasing body weight, but the increase was less than proportional, indicating that a mg/kg dose represents an over-adjustment for the effect of body weight on nivolumab PK. Given the relationship between nivolumab PK and body weight, a flat dose is expected to lead to lower exposures in heavier patients, relative to the exposures in lighter patients.

Using the PPK model, nivolumab steady-state trough, peak and time-averaged concentration (C_{minss}, C_{maxss}, and C_{avgss}, respectively) were predicted for a flat nivolumab dose of 240 mg Q2W and compared to those following administration of 3 mg/kg Q2W in NSCLC subjects. A dose of 240 mg nivolumab is identical to a dose of 3 mg/kg for subjects weighing 80 kg, which is the approximate median body weight of NSCLC subjects in the 3 Phase 2 and 3 BMS clinical studies of nivolumab monotherapy. The geometric mean values of C_{minss}, C_{maxss}, and C_{avgss} with flat dosing are slightly (< 15%) higher than that produced by a 3 mg/kg dose, and the coefficient of variation (cv%) in these measures of exposure are only slightly (< 10%) greater than that of 3 mg/kg dosing.

Across the various tumor types in the BMS clinical program, nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy has been found to be relatively flat. Taken together, the PK, safety, and efficacy data indicate that the safety and efficacy profile of 240 mg nivolumab will be similar to that of 3 mg/kg nivolumab.

3.5. Rationale for Using Major Histocompatability Class II (MHC-II) for Treatment Stratification

MHC-II expression is typically restricted to professional antigen presenting cells such as dendritic cells. In this context, these molecules present antigens to CD4+ Helper T cells to promote immune responses. By contrast, MHC class I molecules are ubiquitous across all nucleated cell types, present antigens to cytotoxic, CD8+ T cells. Given the known critical role of tumor cell killing by cytotoxic T cells, most studies historically have examined the role of MHC-I in tumors as opposed to MHC-II.

It has been well known, however, that a subset of tumors across the cancer spectrum expresses MHC-II, although the mechanism of this finding has not been well-understood. We observed that MHC-II expression in breast cancer correlated with T cell infiltration and improved clinical outcomes compared to MHC-II negative tumors.[5] More importantly, we published a strong correlation between MHC-II expression and response to anti-PD-1 monotherapy (**Figure 1**).[6] In discovery and validation cohorts, response rates were improved in the MHC-II populations (79% and 75% vs. 38% and 27%; p=0.01 and 0.03, respectively). PFS and OS were also superior in the MHC-II expressors (median PFS not reached vs. 3.2 months, p=0.02); median OS not reached vs. 27.5 months, p = 0.003). In addition, expression of MHC-II strongly correlated with improved outcomes in Hodgkin lymphoma patients treated with nivolumab.[7] An additional independent cohort using multiparameter immunofluorescence assessment also demonstrated improved clinical outcomes in patients with high expression of MHC-II.[8] Thus, multiple independent cohorts have confirmed the benefits of anti-PD-1 therapy in tumors with high expression of MHC-II.

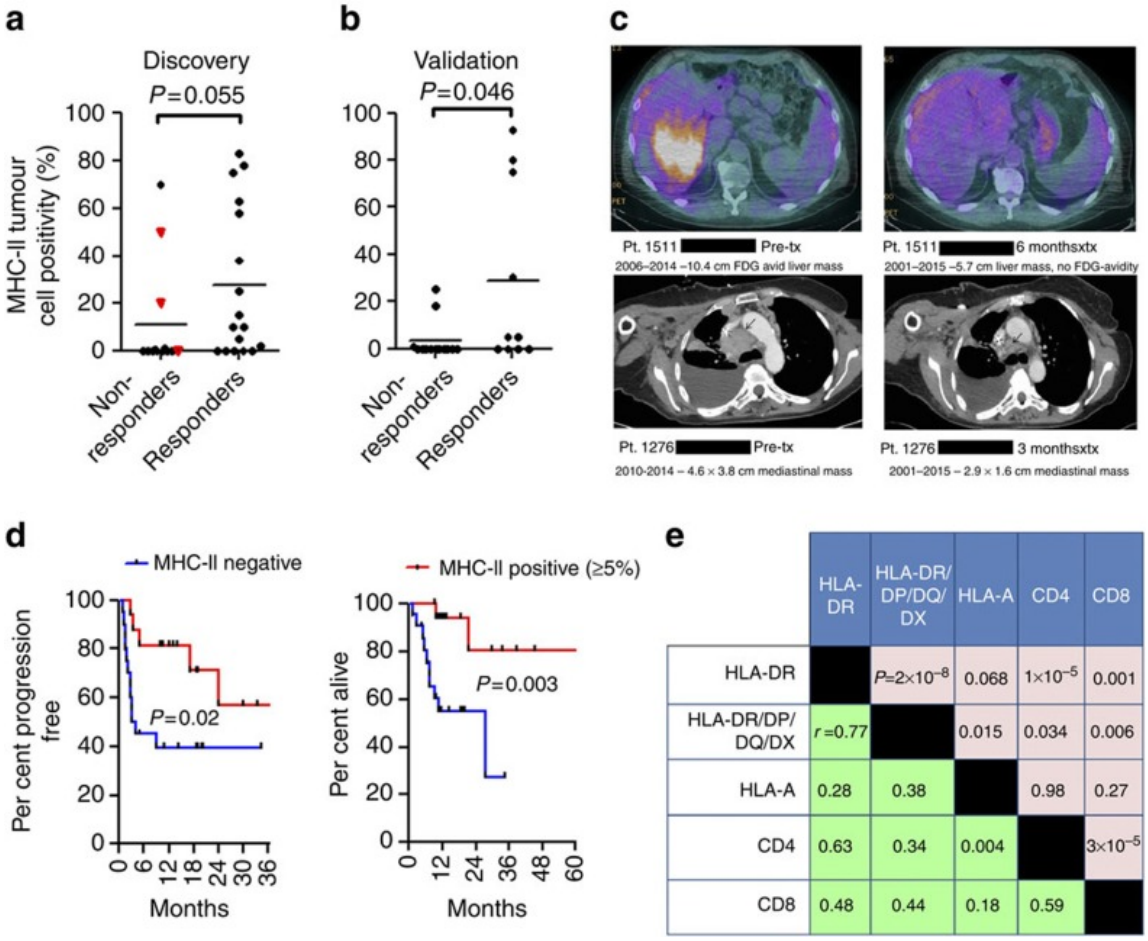


Figure 1: MHC-II positivity and response in (A) discovery and (B) validation cohort. Example of response in MHC-II+ patient (C). (D) Progression free and overall survival in combined cohort by MHC-II expression. (E) Correlation matrix of IHC markers. P values for the Pearson's correlation appear above the diagonal and correlation coefficients (r) appear below the diagonal.

We performed several studies to explain this finding mechanistically. MHC-II positive cell lines were enriched for gene signatures including the previously defined “PD-1 signaling,” “allograft rejection,” and “T cell receptor signaling.” Importantly, MHC-II positive tumors were also highly infiltrated with CD4+ and CD8+ T cells.[6] Gene expression signatures for MHC-II positive tumors were also enriched with interferon-γ gene signatures and immune checkpoint molecules. To understand the functional role of MHC-II, we enforced the master regulator of MHC-II expression, CIITA in a murine cancer model. Notably, enforced CIITA tumors were rejected by the mice at a higher rate than control tumors (**Figure 2A**). Those that did establish had higher immune cell infiltrate with both CD4+ and CD8+ T cells. Importantly, LAG3, a cognate antigen and antagonist of MHC-II, was also highly expressed in the MHC-II expressing mouse tumors as well (**Figure 2B**). Increased expression of LAG-3 was also observed in human melanomas that developed acquired resistance to anti-PD-1 (**Figure 2C**). Combination blockade of LAG-3 and PD-1 was particularly active in this subpopulation, suggesting that LAG-3 may counteract the pro-immune effects of MHC-II (**Figure 2D**). This suggests that 1) MHC-II plays a functional role in anti-PD-1 mediated T cell rejection of tumors; 2) LAG-3 mediates resistance to anti-PD-1, at least in part; and 3) Co-targeting MHC-II positive tumors by LAG-3 and PD-1 blockade may be synergistic.

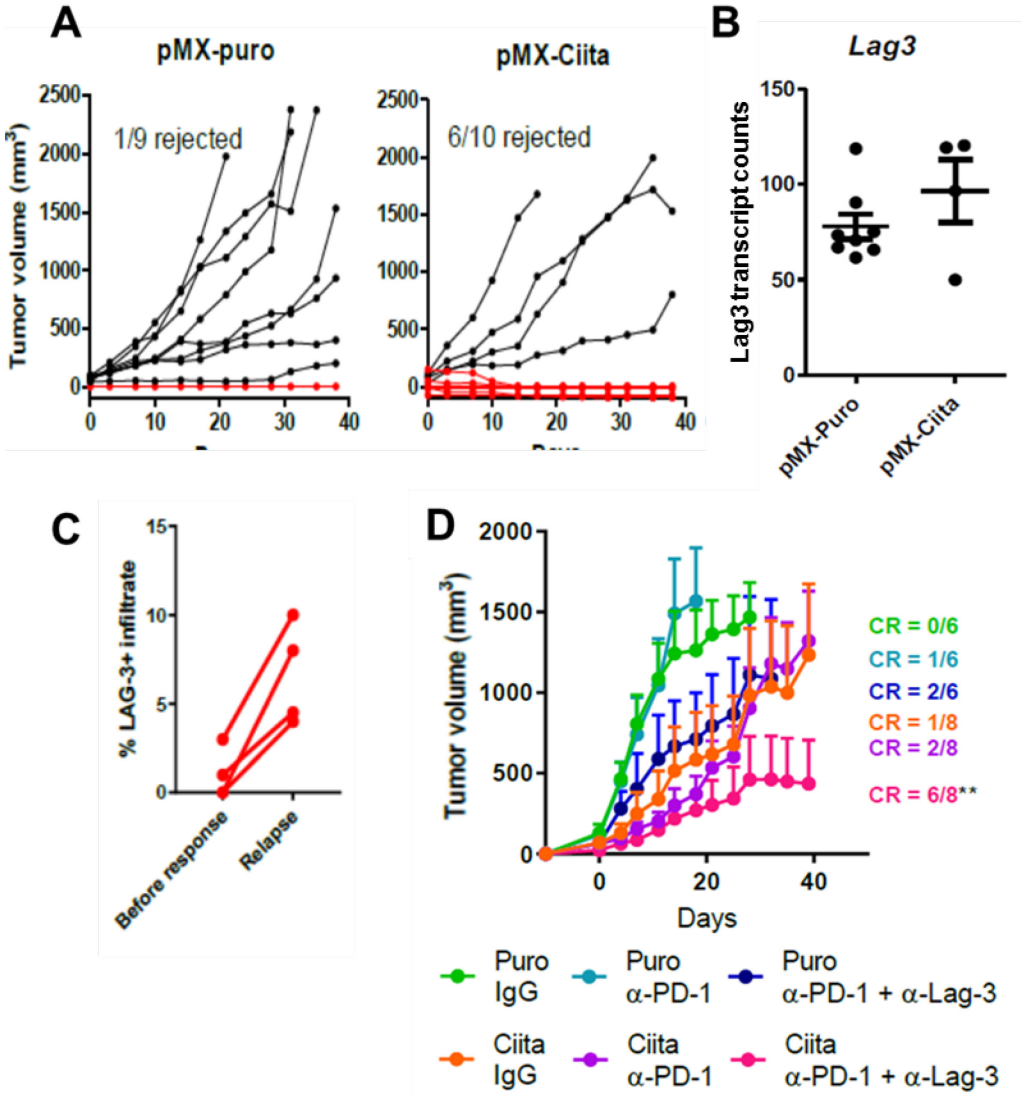


Figure 2: (A) Tumor growth of MHC-II negative (pMx-puro) or MHC-II positive (pMX-CIITA) MMTV-neu tumors in mouse models, showing increased rejection for MHC-II positive. (B) LAG-3 expression in MHC-II positive vs. negative tumors. (C) LAG-3+ tumor infiltrating lymphocytes at baseline, and after acquired resistance to anti-PD-1 therapy, demonstrating that LAG-3 expression is increased at resistance. Treatment with IgG (placebo), anti-PD-1, and anti-LAG-3 in MHC-II positive (Ciita) and MHC-II negative (Puro), demonstrating high response rates for combination treatment in MHC-II positive mouse tumors (pink line).

By contrast, MHC-II non-expressing tumors have less evidence of adaptive immunity and T cell infiltration, particularly CD4+ T cells. Thus, we hypothesize that the combination of ipilimumab and nivolumab will augment CD4+ T cell help and overcome the limitations of PD-1 targeting alone.

3.6. Rationale for Permitting Continued Treatment in Select Cases of Progressive Disease

Accumulating clinical evidence indicates some subjects treated with immune system stimulating agents may develop progression of disease (by conventional response criteria) before demonstrating clinical objective responses and/or stable disease. This phenomenon was observed in up to 10% of patients treated with nivolumab or pembrolizumab, and also with ipilimumab monotherapy.[9,10] Two hypotheses have been put forth to explain this phenomenon. First, enhanced inflammation within tumors could lead to an increase in tumor size which would appear as enlarged index lesions and as newly visible small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease leading to overt signs of clinical improvement. Alternatively, in some individuals, the kinetics of tumor growth may initially outpace anti-tumor immune activity. With sufficient time, the anti-tumor activity will dominate and become clinically apparent. Therefore, subjects will be allowed to continue study therapy after initial investigator-assessed RECIST 1.1 defined progression if they are assessed to be deriving clinical benefit and tolerating study drug (Section 9.8). Such subjects must discontinue study therapy upon evidence of further progression.

3.7. Rationale for Primary Endpoint

The primary endpoint for this study is change in CD8+ T cell infiltration. Several studies have demonstrated influx of CD8+ T cells as demonstrating immunologic recognition and targeting, and as an early surrogate for treatment response.[11,12] For example, one study demonstrated that expression of CD8 in early on-treatment biopsies was completely non-overlapping in responders compared with non-responders.[11] Thus, this metric can serve as an accurate surrogate of immunologic recognition and tumor responses, and is likely more reliable than a metric such as complete pathologic response, particularly in the setting of bulky tumors that may require additional time for complete regression. In addition, in this signal finding phase II study, we are evaluating two arms with likely active treatments in parallel, rather than comparing these interventions. Sample size is further based on doubling of CD8+ T cell infiltration from analysis of responding patients in two studies, with a standard deviation of 1000.[11,12]

3.8. Research Hypotheses

Patients with MHC-II expressing melanomas will have high rates of change in activated GZMB+ CD8+ T-cell density intratumorally with nivolumab and relatlimab therapy; MHC-II expression is an effective stratifying marker in melanoma that can be used in future studies to select optimal treatment.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary • To evaluate the efficacy, measured by change is activated GZMB+ CD8+ T-cell density intratumorally, of two immunotherapy regimens in patients with advanced melanoma: nivolumab plus relatlimab in patients with MHC-II (+) melanoma; and nivolumab plus ipilimumab in patients with MHC-II (-) melanoma.	• Change in activated GZMB+ CD8+ T-cell density intratumorally.
Secondary • To evaluate the response rate, median progression free survival, overall survival, and safety and tolerability of nivolumab and relatlimab in patients with MHC-II (+) melanoma; and of nivolumab plus ipilimumab in patients with MHC-II (-) melanoma.	• Response rate (RR) • Median progression free survival (mPFS) • Median overall survival (mOS) • Adverse events, clinical laboratory values, vital signs, ECGs, and other safety biomarkers.
Exploratory • To explore potential associations of biomarkers with clinical efficacy and/or incidence of adverse events due to study drug by analyzing biomarker measures within the peripheral blood and tumor microenvironment.	• Automatic quantitative analysis (AWUA), single cell RNA sequencing, mass cytometry, T-cell receptor sequencing, germline DNA/HLA haplotyping.

5. PATIENT SELECTION

Questions regarding patient eligibility must be addressed and resolved by the investigator in consultation with the sponsor-investigator or designee prior to enrollment.

5.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Signed and dated written informed consent.
2. ≥ 18 years of age at the time of informed consent.
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
4. Histologically confirmed locally advanced/unresectable or metastatic melanoma.
5. Patients who have received prior anti-CTLA-4 or anti-PD-1/PD-L1 for adjuvant treatment of melanoma are eligible if > 6 months have elapsed between the last dose of adjuvant treatment and starting this study – provided there is no history of life-threatening toxicity related to such prior treatment, or such toxicity is unlikely to re-occur with standard countermeasures (e.g. hormone replacement after endocrinopathy).
6. Patients who have received adjuvant therapy with interferon and/or a BRAF inhibitor and/or MEK inhibitor for adjuvant therapy are permitted to enroll.
7. At least one measurable target lesion as defined by RECIST 1.1 which can be followed by CT or MRI.
    - If located in a previously irradiated area, a tumor lesion is considered a measurable/target lesion only if subsequent disease progression in the lesion has been documented at least 90 days following completion of radiotherapy.
8. Adequate organ and bone marrow function ≤ 14 days prior to first dose of protocol-indicated treatment:
    - White blood cell count (WBC) ≥ 2,000/mm^3.
    - Absolute neutrophil count (ANC) ≥ 1,500/mm^3.
    - Platelets ≥ 75,000/mm^3.
    - Hemoglobin ≥ 8.0 g/dL.
    - Serum creatinine ≤ 2.0x upper limit of normal (ULN), or calculated creatinine clearance (CrCl) > 40 mL/min per the Cockcroft-Gault formula (Appendix 1).
    - Total bilirubin ≤ 1.5x ULN (except patients with Gilbert Syndrome, who must have total bilirubin < 3.0 mg/dL).
    - AST (aspartate aminotransferase) and ALT (alanine aminotransferase) ≤ 3.0x ULN (≤ 5.0x ULN in those with hepatic metastases).

9. Acceptable troponin level ≤ 14 days prior to first dose of protocol-indicated treatment:
    - Troponin T (TnT) or I (TnI) ≤ 2× institutional ULN.
    - Subjects with TnT or TnI levels between >1 to 2× ULN will be permitted if repeat levels within 24 hours are ≤ 1x ULN.
    - If TnT or TnI levels are >1 to 2× ULN within 24 hours, the subject may undergo a cardiac evaluation and be considered for treatment based on the discretion of the PI.
    - When repeat levels within 24 hours are not available, a repeat test should be conducted as soon as possible.
    - If TnT or TnI repeat levels beyond 24 hours are < 2x ULN, the subject may undergo a cardiac evaluation and be considered for treatment, based on the discretion of the PI.
10. Arm A: Corrected QT interval (QTc) by Fridericia's method (QTcF) assessed by electrocardiogram (ECG) completed ≤ 28 days before initiation of protocol treatment (Section 8.9), and resulted as:
    - QTcF ≤ 480 msec
11. Tumor tissue from a biopsy or resection obtained since completion of the last systemic therapy must be available for analysis of MHC-II status and for biomarker analysis. If a sample is not available or if the quantity or quality of tissue is insufficient to provide adequate results, an additional biopsy may be performed for MHC-II analysis. Patients cannot be enrolled on the study unless MHC-II is known.
12. Women must not be breastfeeding.
13. A woman of childbearing potential (WOCBP) – see Appendix 4 for definition of WOCBP – must have a negative serum pregnancy test within 14 days prior to receiving first dose of protocol-indicated treatment, and must agree to follow instructions for using acceptable contraception (Appendix 4) from the time of signing consent, and for 165 days (24 weeks) after her last dose of protocol-indicated treatment.
14. A man able to father children (see Appendix 4 for definition) who is sexually active with a WOCBP must agree to follow instructions for using acceptable contraception (Appendix 4), from the time of signing consent, and for 225 days (33 weeks) after his last dose of protocol-indicated treatment.

5.2. Exclusion Criteria

Patients meeting any of the following criteria will not be permitted to enter the trial:

1. Patients with uveal melanoma.
2. Prior systemic anticancer therapy for unresectable or metastatic melanoma.
3. Prior treatment with LAG-3 targeted agents.
4. Subjects with active, known, or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

5. Uncontrolled or significant cardiovascular disease including, but not limited to, any of the following:
    - Myocardial infarction (MI) or stroke/transient ischemic attack (TIA) within the 6 months prior to consent.
    - Uncontrolled angina within the 3 months prior to consent.
    - Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, torsades de pointes, or poorly controlled atrial fibrillation).
    - QTc prolongation > 480 msec.
    - History of other clinically significant cardiovascular disease (i.e., cardiomyopathy, congestive heart failure with New York Heart Association [NYHA] functional classification III-IV, pericarditis, significant pericardial effusion, significant coronary stent occlusion, poorly controlled deep venous thrombosis, etc).
    - Cardiovascular disease-related requirement for daily supplemental oxygen.
    - History of two or more myocardial infarctions or two or more coronary revascularization procedures within the past 3 years.
    - Subjects with history of myocarditis, regardless of etiology.
6. A confirmed history of encephalitis, meningitis, or uncontrolled seizures in the year prior to informed consent.
7. Participants with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days of enrollment. Inhaled or topical steroids, and adrenal replacement steroid doses >10 mg daily prednisone or equivalent, are permitted in the absence of active autoimmune disease.
8. Subjects with active central nervous system (CNS) metastases, active brain metastases or leptomeningeal metastatic foci. For the subjects with brain metastases, if they are asymptomatic, they are eligible to participate in this study. If participants have received treatment for brain metastases and have no clinical evidence of progressive disease at least 1 week after completion of treatment for brain metastases and within 28 days prior to the first dose of protocol-indicated treatment on this study, they are eligible to participate in this study.
9. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).
10. Known history of hepatitis B or hepatitis C.
11. Any significant medical condition, laboratory abnormality, or psychiatric illness, that would prevent the subject from participating in the study or place the subject at unacceptable risk if he/she were to participate in the study, or any condition that confounds the ability to interpret data from the study.
12. Subjects with life expectancy < 6 months.
13. Subjects receiving any other investigational or standard antineoplastic agents.

14. Prior malignancy active within the previous 3 years currently requiring treatment except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.

15. Prisoners or participants who are involuntarily incarcerated.

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

17. 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.

5.3. Inclusion of Underrepresented Populations

Women and men of all races and ethnic groups are eligible for this trial. There is no bias towards gender, age, or race in the clinical trial outlined.

5.4. Number of Patients and Replacement of Patients Who Discontinue Early

Approximately 36 evaluable patients with advanced melanoma are anticipated to enroll in this study at Vanderbilt University Medical Center and approximately two additional academic medical centers in the U.S.

In general, it intended that patients will be treated until confirmed disease progression or intolerable toxicity. The criteria for patient discontinuation are listed in Section 9.9.

If a patient discontinues protocol treatment in the first cycle for reasons clearly not related to protocol treatment after completing fewer than 1 planned cycle of study therapy, then that patient will be considered not evaluable for toxicity and will be replaced with a new patient.

6. ENROLLMENT PROCEDURES

The Vanderbilt-Ingram Cancer Center (VICC) Coordinating Center will coordinate enrollment in the study.

Prior to registration, a copy of the IRB approval at the site will be kept on file at the Vanderbilt-Ingram Cancer Center (VICC) Coordinating Center. Eligible participants will be entered on study centrally at the VICC Coordinating Center. All sites should email the Coordinating Center at Coordinating.Center@vumc.org to verify slot availability prior to enrollment.

All patients MUST be registered with the VICC Coordinating Center prior to the start of protocol treatment. Registration can only be conducted during the business hours of 8AM – 5PM Central Time, Monday through Friday.

1) All sites must email the VICC CTSR Coordinating Center at Coordinating.Center@vumc.org to notify of upcoming registration and ensure slot availability. The following information should be included in this email:
    - Study number.
    - Patient initials.
    - Disease type.
    - Anticipated consent date.
    - Anticipated start date.

2) If a subject ID number is required prior to patient enrollment (i.e. at screening due to sample collection requirement), the site must submit the following documents with their email notification to the Coordinating Center:
    - Copy of the patient's signed and dated Informed Consent including documentation of the consent process.
    - HIPAA authorization form (if separate from the main consent form).
    - VICC Patient Enrollment Form.

    The Coordinating Center will then provide a subject ID number via email.

3) Email the following documents to the Coordinating Center for eligibility review and patient enrollment (Coordinating.Center@vumc.org):
    - Copy of the patient's signed and dated Informed Consent, including documentation of the consent process.
    - HIPAA authorization form (if separate from the main consent form).
    - VICC Patient Enrollment Form.
    - Eligibility supporting documents such as pathology reports, laboratory tests, etc. *or* EMR access. Note: all source documents should be de-identified and screening/subject ID number added prior to sending.
    - Tissue Block Registration Form (see the **Lab Manual**).

- Signed and completed Eligibility Checklist. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criterion listed in the eligibility checklist.**

Note: All study documents should be received 24-48 hours prior to the patient's anticipated start date. Same day treatment registrations will only be accepted with prior notice and discussion with the Coordinating Center. Please email the Coordinating Center if enrollment is needed sooner.

Upon satisfactory review of eligibility documents submitted, the Coordinating Center will approve enrollment and issue a subject ID number if one was not issued at screening. Once registration/enrollment confirmation from Coordinating Center is received, proceed with protocol procedures.

Please contact the assigned Study Contact with any questions regarding this process. You can also reach out to your assigned CRA once the study is activated.

The VICC Coordinating Center will assign Subject ID numbers to all patients whose eligibility has been confirmed. Only patients deemed eligible will be registered to investigational treatment. Sequence/study ID numbers will not be re-used if a patient screen fails. Following registration, eligible participants should begin study treatment consistent with the protocol no later than 7 days after registration/enrollment by the VICC Coordinating Center. If a participant does not receive protocol therapy following registration within the allowed time period, the participant's registration on the study will be canceled. The Study Contact should be notified of cancellations as soon as possible. Patients being re-screened will need to consent to repeated procedures. As such, the Coordinating Center will require a new, signed Informed Consent document.

Issues that would cause treatment delays should be discussed with the sponsor-investigator. Any requests for eligibility exceptions and/or deviations must be approved in writing by the sponsor-investigator and the Vanderbilt-Ingram Cancer Center Data and Safety Monitoring Committee (VICC DSMC).

As is generally accepted, standard of care procedures performed prior to consent, but within the protocol defined screening window for each assessment, can be used for study purposes. All research-only procedures must be performed after patient consent.

7. SCHEDULE OF ASSESSMENTS

7.1. Study Calendar: Screening

Tests and Procedures	Protocol Section	SCREENING: ARM A and ARM B	Comments
		≤ 14 days	
MHC-II tumor status	8.13	X	Stratification into study arms, based on assay by Vanderbilt central lab (≤28d prior to c1d1). Arm A: MHC-II (+); Arm B: MHC-II(-).
Informed consent[1]	8.1	X	
Review eligibility	5	X	
Demography and medical history	8.1	X	
Vital Signs[2]	8.3	X	Heart rate, blood pressure and temperature (oral or tympanic).
Physical exam, weight[3]	8.4	X	
ECOG perform. status	A2	X	
Review AEs[4]	8.5 & 11	X	AE reporting: Section 13.
Review con meds[4]	8.5 & 10.2	X	Prohibited medications: Section 10.2.
Hematology[5]	8.6	X	CBC w/ Diff.
Serum chemistries[6]	8.7	X	CMP; Mg, Phos.
Additional Labs	8.8	X	LDH, TSH, free T3, free T4, cortisol, ACTH, amylase, lipase, troponin-I, CK, CK-MB.
Pregnancy test[7]	8.10	X	Serum pregnancy test at screening (in WOCBP). Contraception per Appendix 4.
12-lead ECG[8]	8.9	Arm A	Single tracing on local machine (≤28d prior to c1d1). Calculate QTcF for eligibility: Section 8.9.
CT or MRI[9]	8.11	X	Required: chest, abdomen and pelvis (all 3 regions) + brain scan.
Archival or fresh tumor tissue[10]	8.12	X	Mandatory tissue at baseline required for analysis of tumor for MHC-II status (≤28d prior to c1d1).

7.2. Study Calendar: Treatment Arm A

Tests and Procedures	Protocol Section	TREATMENT: ARM A: MHC-II (+)		Comments: Arm A *All Cycles = 28 days (4 weeks) per cycle*
		4 week cycles		
		CYCLES 1+	CYCLES 1 & 2	
		Day 1 (+1-3d)[16]	Day 15	
Physical exam, weight[3,11]	8.4	X		
Vital Signs[2]	8.3	X		Heart rate, blood pressure and temperature (oral or tympanic).
ECOG perform. status[11]	A2	X		
Review AEs[4]	8.5 & 11	X		Dose Holds: Section 11. AE reporting: Section 13.
Review con meds[4]	8.5 & 10.2	X		Prohibited medications: Section 10.2.
Hematology[5,11,17]	8.6	X		CBC w/ Diff.
Serum chemistries[6,11,17]	8.7	X		CMP; Mg, Phos.
Additional Labs[11,17]	8.8	X		LDH, TSH + reflexive (free T3 & free T4), cortisol, CK, and CK-MB.
		X		If clinically indicated: ACTH, amylase and lipase.
		c1d1 & c2d1	c1d15 & c2d15	Troponin-I
Pregnancy test[7,11]	8.10	c1d1		Serum or urine (in WOCBP) ≤72hr prior to start of c1d1 tx. Contraception per Appendix 4.
12-lead ECG[8]	8.9	c1d1 & c2d1	c1d15 & c2d15	Single tracing on local machine.
CT or MRI[9]	8.11	q12 weeks (-1 to -7d) s/p c1d1		Re-scanning every 12 weeks (-1 to -7 days) after initiation of treatment on Cycle 1, Day 1.
Fresh Tumor Biopsy	8.13		c2d15 (±7d)	(i.e. 6wk s/p c1d1)
Peripheral blood sample[12]	8.14	c1d1, c4d1, & c14d1	c1d15 & c2d15	For correlative research. Kits required for collection. (Note: c4d1 & c14d1 are s/p 13 & 53 weeks after c1d1 Arm A tx.)
TREATMENT: ARM A				
Nivolumab[13]	9.3	X		30min i.v. infusion: 480mg q4wk (on d1 of Cycles 1+).
Relatlimab[14]	9.4	X		60min i.v. infusion: 160mg q4wk (on d1 of Cycles 1+). Relatlimab infusion started AFTER completion of nivolumab infusion.

7.3. Study Calendar: Treatment Arm B

Tests and Procedures	Protocol Section	TREATMENT: ARM B: MHC-II (-)					Comments: Arm B *Cycles 1-4 = 21 days (3 weeks) per cycle* *Cycles 5+ = 28 days (4 weeks) per cycle*
		3 week cycles				*4 week cycles*	
		CYCLE 1			CYCLES 2, 3 & 4	CYCLES 5+	
		Day 1	Day 8	Day 15	Day 1 (+1-3d)[16]	Day 1 (+1-3d)[16]	
Physical exam, Weight[3,11]	8.4	X	X	X	X	X	
Vital Signs[2]	8.3	X	X	X	X	X	Heart rate, blood pressure and temperature (oral or tympanic).
ECOG perform. status[11]	A2	X	X	X	X	X	
Review AEs[4]	8.5 & 11	X	X	X	X	X	Dose Holds: Section 11. AE reporting: Section 13.
Review con meds[4]	8.5 & 10.2	X	X	X	X	X	Prohibited medications: Section 10.2.
Hematology[5,11,17]	8.6	X	X	X	X	X	CBC w/ Diff.
Serum chemistries[6,11,17]	8.7	X	X	X	X	X	CMP; Mg, Phos.
Additional Labs[11,17]	8.8	X	X	X	X	X	LDH, TSH + reflexive (free T3 & free T4). If clinically indicated: ACTH, amylase and lipase.
		X	X	X	c2d1		Cortisol, troponin-I, CK, CK-MB.
Pregnancy test[7,11]	8.10	X					Serum or urine (in WOCBP) ≤72hr prior to start of c1d1 tx. Contraception per Appendix 4.
CT or MRI[9]	8.11				q12 weeks (-1 to -7d) s/p c1d1		Re-scanning every 12 weeks (-1 to -7 days) after initiation of treatment on Cycle 1, Day 1.
Fresh Tumor Biopsy	8.13				c3d1 ±7 days		(i.e. 6wk s/p c1d1)
Peripheral blood sample[12]	8.14	X		X	c3d1	c5d1 & c15d1	For correlative research. Kits required for collection. (Note: c5d1 & c15d1 are s/p 13 and 53 Weeks of Arm B tx.)
TREATMENT: ARM B							
Nivolumab[13]	9.3	X			X	X	30min i.v. infusion: 1mg/kg q3wk (on d1 of Cycles 1-4), then 480mg q4wk (on d1 of Cycles 5+).
Ipilimumab[15]	9.5	X			X		90min i.v. infusion: 3mg/kg q3wk (on d1 of Cycles 1-4). Ipilimumab infusion started AFTER completion of nivolumab infusion.

7.4. Study Calendar: Follow-Up

Tests and Procedures	Protocol Section	FOLLOW-UP: ARM A and ARM B				Comments
		EOT (≤14d)[18]	**30d F/U** (30-37d)[20]	**100d F/U** (100-114d)[20]	**Survival F/U** q12wk (±14d)[21]	
Physical exam, weight	8.4	X	X	X		
Vital Signs[2]	8.3	X	X	X		Heart rate, blood pressure and temperature (oral or tympanic).
ECOG perform. status	A2	X	X	X		
Review AEs[4]	8.5 & 11	X	X	X		AE reporting: Section 13.
Review con meds[4]	8.5	X	X			
CT or MRI[19]	8.11	X*	X**			* If not already done within previous 28 days. ** Only for patients who discontinue nivo/rela/ipi for reason other than PD confirmed by imaging.
Hematology[5]	8.6	X	X			CBC w/ Diff.
Serum chemistries[6]	8.7	X	X			CMP; Mg, Phos.
Additional Labs	8.8	X	X			LDH; TSH + reflexive (free T3 & free T4).
Pregnancy test[7]	8.10	X	X			Serum or urine (in WOCBP). Contraception per Appendix 4.
Peripheral blood sample[12]	8.14	X	X			Kits required for collection.
Survival follow-up[21]	7.17				X	Long-term survival contact every 12 weeks (3 months) ±14d after patient's final nivo/rela/ipi dose for maximum of 2 years.

Study Calendar Notes:

1. Informed Consent: Informed consent must be obtained before any study-specific screening assessments are performed. Screening assessments are to be performed within 14 days prior to Day 1 of Cycle 1 unless otherwise noted (e.g. baseline CT or MRI scan acceptable ≤ 28 days prior to initiating protocol-indicated treatment). Assessments performed as standard of care within the screening window may be used for screening. Baseline characteristics include but are not limited to: demographics, medical and surgical history, extent of disease, prior anti-cancer treatment, and tumor histology.

2. Vital Signs: Vital signs to include: Heart rate (HR), blood pressure (BP), and temperature (oral or tympanic). On each day of treatment, Pre-Dose and Post-Dose vitals must be respectively recorded ≤ 30 minutes prior to the start of treatment, and ≤ 30 min after the end of each separate treatment. (Thus, on Day 1 of each cycle in *Arm A*, a minimum of 3 sets of vital signs are scheduled to be recorded: Pre-nivolumab, Post-nivolumab and Post-relatlimab. In *Arm B*, on Day 1 of each of the first four cycles, a minimum of 3 sets of vital signs are scheduled to be recorded: Pre-nivolumab, Post-nivolumab, and Post-ipilimumab. For Arm B cycles 5 onward, a minimum of 2 sets of vital signs are scheduled to be recorded: Pre-nivolumab and Post-nivolumab.)

3. Weight: Weight at Screening; prior to every dose of nivolumab/relatlimab or nivolumab/ipilimumab (at least on same day as treatment); and at the EOT, 30-day, and 100-day Follow-up visits. In Arm B: Each of the first 4 doses of nivolumab and ipilimumab (scheduled for administration on Day 1 of Cycles 1-4) must be adjusted if patient's body weight changes > ±10% from the weight used to calculate the dose (Section 8.4).

4. Concomitant Medications (CMs) and Adverse Events (AEs): Review and capture of all concomitant medications will be performed as indicated. Concomitant medications include prescription medications and over-the-counter preparations used by a patient within at least 14 days prior to first dose of protocol-defined treatment and continuing at least through the 30-day Follow-up visit (or until initiation of subsequent anticancer therapy). Adverse events will be collected as detailed in protocol Section 13.

5. Hematology: Hematology includes white blood cell count with differential, hemoglobin, hematocrit, and platelet count.

6. Serum Chemistries: Blood Chemistry to include sodium, potassium, chloride, bicarbonate or carbon dioxide, blood urea nitrogen (BUN), creatinine, glucose, total bilirubin, AST, ALT, alkaline phosphatase (ALP), calcium, albumin, total protein; and magnesium and phosphorus.

7. Pregnancy Test: For women of childbearing potential (see Appendix 4 for definition of WOCBP): Serum pregnancy test required during Screening; and either serum or urine pregnancy test required ≤ 72 hours prior to first dose of protocol-indicated treatment (unless serum pregnancy test during screening was already done ≤ 72 hours prior to initiating c1d1 treatment) and at the EOT and 30-day Follow-up visits.

8. Electrocardiogram (ECG): For patients stratified to Arm A: One standard 12-lead electrocardiogram (ECG) using local site equipment completed ≤ 28 days before initiation of protocol treatment. Per Section 8.9, the corrected QT interval (QTc) will be calculated using the method of Fridericia (QTcF). Additional ECGs to be performed every 2 weeks for the first 2 months – i.e. on Days 1 and 15, of Cycles 1 and 2. (On Cycle 1, Day 1, ECG required for Arm A need not be repeated if already done ≤ 14 days prior to c1d1.)

9. Computed Tomography (CT) / Magnetic Resonance Imaging (MRI): Baseline evaluation of disease status by CT or MRI ≤ 28 days prior to initiating protocol treatment on Cycle 1, Day 1. Baseline and subsequent scans to include imaging coverage of anatomical regions as outlined in Section 8.11. *Re-scanning to occur every 12 weeks* (minus 1-7 days) after initiating protocol treatment on Cycle 1, Day 1. [The minus 1-7 day scan window is intended for flexibility in scheduling re-scans *between Days 22-28 of Cycles 3, 6, 9, etc of every third cycle in Arm A; between Days 15-21 of Cycle 4 in Arm B; and then between Days 22-28 of Cycles 7, 10, 13, etc of every third cycle in Arm B*].

   Scanning on the same day as Day 1 of a new cycle is discouraged but allowed, provided scan results receive appropriate RECIST review prior to initiating the new cycle of study treatment. Additional disease evaluations or increased scan frequency may be performed according to the medical judgment of the patient's study physician, in accordance with the following: In the event of suspected Progressive Disease (PD), a CT/MRI is to be performed as soon as possible. In the event of a Complete or Partial Response

(CR/PR), a confirmatory CT/MRI is to be performed no earlier than 28 days after the first assessment of CR/PR.

10. Required Baseline Tumor Tissue: Archival tissue [paraffin block(s) or unstained slides from paraffin block(s)] from the primary tumor and/or a metastatic site must be available prior to initiating treatment, or patient must be willing to undergo a fresh pre-treatment standard of care tumor biopsy. Physical possession of requested tissue is required prior to initiating study treatment because all patients in this study are being stratified by MHC-II status, based on centralized testing performed at Vanderbilt.

11. Acceptability of Select Screening Items for Cycle 1, Day 1 (c1d1): On c1d1, Physical Exam, ECOG Performance Status; and laboratories designated as Hematology, Serum Chemistries or as "Additional Labs" in Section 7.2 (Arm A) and Section 7.3 (Arm B) need not be repeated if already resulted ≤ 7 days prior to first dose of protocol-indicated treatment. In women of childbearing potential (WOCBP), serum or urine Pregnancy Test required ≤ 72 hours prior to first dose of protocol-indicated treatment (unless serum pregnancy test during screening already completed ≤ 72 hours prior to first dose of protocol-indicated treatment).

12. Biomarker and Pharmacodynamic (PD) Blood: Exploratory blood samples for biomarker and possible PD research to be obtained on days as indicated (collected Pre-Dose at a single time point, prior to initiating any pre-treatment or protocol-indicated study treatment); and at the EOT and 30-day Follow-up visits. On days when these samples are scheduled to occur on same day as on-study biopsy (i.e. c2d15 in Arm A, and c3d1 in Arm B), every reasonable effort should be made to collect this blood PRIOR to biopsy procedure.

13. Nivolumab Infusion (Arm A and Arm B): The study will supply Nivolumab to the site. All patients are scheduled to receive nivolumab as a 30 minute (±10 minute) intravenous infusion.

    In Arm A: On Day 1 of each 28-day cycle, nivolumab will be completed BEFORE initiation of relatlimab.
    In Arm B: On Day 1 of each 21-day cycle (i.e. Cycles 1-4), nivolumab will be completed BEFORE initiation of ipilimumab. Starting with Cycle 5, nivolumab will be administered on Day 1 of each cycle as monotherapy.

14. Relatlimab Infusion (Arm A): The study will supply relatlimab to the site. On Day1 each 28-day cycle, all patients in Arm A are scheduled to receive relatlimab as a 60 minute (±10 minutes) intravenous infusion.

15. Ipilimumab Infusion (Arm B): The study will supply Ipilimumab to the site. On Day 1 of each 21-day cycle (i.e. Cycles 1-4), all patients in Arm B are scheduled to receive ipilimumab as a 90 minute (±10 minutes) intravenous infusion, for a maximum of four total doses of ipilimumab.

16. Administrative Scheduling Window: Beginning with Cycle 2, Day 1: Up to 3 days *delay* (i.e. *plus* 1 to 3 days; but not *minus* 1 to 3 days) in the initiation of Day 1 of a new cycle, will be permitted in order to facilitate holidays, weekends, bad weather, scheduling, or other unforeseen circumstances not including adverse events. Such administrative delay – not to be used for adverse event management – will not be considered a protocol deviation.

17. Scheduling Flexibility for On-Study Laboratory Items: For all cycles, beginning with Cycle 2, Day 1: Laboratories designated as Hematology, Serum Chemistries or as "Additional Labs" in Section 7.2 (Arm A) and Section 7.3 (Arm B) need not be repeated on days of treatment, if already resulted ≤ 3 days prior to treatment.

18. End-of-Treatment (EOT) Visit: Reasonable effort should be made to complete End-of-Treatment (EOT) procedures on the day it is decided a patient will no longer receive protocol-indicated treatment. These procedures must be completed subsequent to and not later than 14 days after investigator decision to permanently discontinue protocol-indicated treatment with nivolumab, relatlimab or ipilimumab (whichever treatment occurs last) and prior to any subsequent anti-cancer therapy.

19. Concluding Disease Assessments: At End-of-Treatment (EOT), CT/MRI required only if the previous CT/MRI was done >28 days before. At the 30-day Follow-Up visit, CT/MRI required only if disease progression was not already documented by CT/MRI done before, during or after the prior EOT visit. If a patient discontinues the study for reason other than progressive disease confirmed by CT or MRI (e.g. adverse event), then CT or MRI scans involving sites of known or suspected disease must be continued (if clinically feasible) every 12 weeks (± 7 days) for 12 months and then approximately every 24 weeks (± 4 weeks) thereafter, relative to date(s) of prior scanning, until disease progression is confirmed by imaging.

(Note: If the patient initiates treatment in another clinical trial, then any continuing scans done for this trial may terminate.)

20. 30-day and 100-day Follow-up Visits: Follow-up clinic visits are to be completed 30-37 days and 100-114 days after patient's final protocol-indicated treatment with nivolumab, relatlimab or ipilimumab (whichever occurs last). Documented attempt(s) should be made for patient return to the study clinic. It will not be considered a protocol deviation if the patient is physically unable to return for the follow-up visit; such circumstance should be recorded in the study documents, and as much of the follow-up information as possible should be obtained via feasible patient contact and from local and outside facilities.

21. Survival and Long-Term Follow-up: Each patient will be followed for survival and information about subsequent anticancer therapy every 12 weeks (3 months) ±14 days after patient's final protocol treatment with nivolumab, relatlimab or ipilimumab (whichever occurs last) until death, termination of the study, patient withdraws consent, or for a maximum of 2 years after the patient's final protocol-indicated treatment – whichever comes first. Contact can be made via clinic visit, chart review, obituary or similar observation (e.g. Social Security death index), or by telephone.

7.5. Screening Visit Assessments

Prior to performing any study-based procedures, patient informed consent must be obtained.

The following procedures must be completed ≤ 28 days prior to a patient's first dose of protocol-indicated treatment:

- Baseline evaluation of disease status by CT and/or MRI; to include imaging of the brain, chest, abdomen, and pelvis; as well as imaging of additional sites of known or suspected disease as clinically indicated per patient's study physician.
- 12-lead ECG (single recording on local equipment), with additional ECGs as clinically indicated, per patient's study physician. The corrected QT interval (QTc) will be calculated using the method of Fridericia (QTcF) – see Section 8.9.
- Archival or fresh tumor tissue [paraffin block(s) or unstained slides from paraffin block(s)] from the primary tumor and/or a metastatic site must be available for MHC-II testing. MHC-II testing will be performed centrally at Vanderbilt by a trained and board-certified pathologist.

The following procedures must be completed ≤ 14 days prior to a patient's first dose of protocol-indicated treatment:

- Medical history and Demographics.
- Physical exam.
- Vital Signs: Heart rate (HR), blood pressure (BP), and temperature.
- ECOG performance status.
- Weight.
- Concomitant medication (prescription and over-the-counter drugs taken at least 14 days prior to intended Cycle 1, Day 1 dosing) and Adverse Event review.
- Complete Blood Count (CBC) with differential (including white blood cell count with differential, hemoglobin, hematocrit, and platelet count).
- Blood Chemistry [including sodium, potassium, chloride, bicarbonate or carbon dioxide, blood urea nitrogen (BUN), creatinine, glucose, total bilirubin, AST, ALT, alkaline phosphatase (ALP), calcium, albumin, total protein; magnesium and phosphorus].
- Additional labs: LDH, TSH, free T3, free T4, cortisol, and troponin-I. &ACTH, amylase, lipase, CK, and CK-MB.
- Serum Pregnancy Test in women of childbearing potential (as defined in Appendix 4), with additional potential for serum follicle-stimulating hormone (FSH) level if the patient's postmenopausal status is considered for childbearing potential and study-required contraception – see Appendix 4).

7.6. Assessments, Arm A: Cycle 1, Day 1

On Cycle 1, Day 1, the following procedures must be completed, unless previously completed ≤ 14 days prior to a patient's first dose of protocol-indicated treatment:

- 12-lead ECG (single recording on local equipment), with additional ECGs as clinically indicated, per patient's study physician.

On Cycle 1, Day 1, the following procedures must be completed, unless previously completed ≤ 7 days prior to a patient's first dose of protocol-indicated treatment:

- Physical Exam.
- ECOG performance status.
- Complete Blood Count (CBC) with differential (including white blood cell count with differential, hemoglobin, hematocrit, and platelet count).
- Blood Chemistry [including sodium, potassium, chloride, bicarbonate or carbon dioxide, blood urea nitrogen (BUN), creatinine, glucose, total bilirubin, AST, ALT, alkaline phosphatase (ALP), calcium, albumin, total protein; magnesium and phosphorus].
- Additional labs: LDH, TSH (and if TSH is abnormal, then free T3 and free T4), cortisol, CK, CK-MB, and troponin-I. If clinically indicated: ACTH, amylase and lipase.

On Cycle 1, Day 1, the following procedures will be completed prior to first dose of protocol-indicated treatment:

- Vital Signs: Heart rate (HR), blood pressure (BP), and temperature.
- Weight.
- Concomitant medication and Adverse Event review.
- Serum or urine Pregnancy Test in women of childbearing potential (as defined in Appendix 4) – unless serum pregnancy test during screening was previously completed ≤ 72 hours prior to a patient's first dose of protocol-indicated treatment.
- Peripheral blood sample for correlative research.

On Cycle 1, Day 1, the following procedures will be completed in association with Arm A dosing:

- Pre-Dose Vital Signs (≤30 minutes prior to START of nivolumab infusion):
  - Heart rate (HR), blood pressure (BP), and temperature.
- Nivolumab infusion:
  - On Cycle 1, Day 1, all patients in Arm A are scheduled to receive nivolumab as a 30 minute (±10 minutes) intravenous infusion.
- Post-Dose Vital Signs (≤30 minutes after the END of the nivolumab infusion):
  - Heart rate (HR), blood pressure (BP), and temperature.
- Relatlimab infusion:
  - On Cycles 1, Day 1, all patients in Arm A are scheduled to receive relatlimab as

a 60 minute (±10 minutes) intravenous infusion.
  - Note: Nivolumab and relatlimab are to be administered as SEPARATE intravenous treatments. On days when both drugs are administered (i.e. scheduled for Day 1 of each cycle), the nivolumab infusion must be completed BEFORE initiation of intravenous relatlimab – see Section 9.6.

- Post-Dose Vital Signs (≤30 minutes after the END of relatlimab):
  - Heart rate (HR), blood pressure (BP), and temperature.

7.7. Additional Assessments, Arm A: Cycle 1, Day 15

On Day 15 of Cycle 1, the following additional items will be completed for patients in Arm A:

- Troponin-I.
- 12-lead ECG (single recording on local equipment), with additional ECGs as clinically indicated, per patient's study physician.
- Peripheral blood sample for correlative research.

7.8. Assessments, Arm A: Cycles 2+, Day 1

Beginning with Cycle 2, Day 1: Up to 3 days delay (i.e. plus 1 to 3 days; but not minus 1 to 3 days) in the initiation of Day 1 of a new cycle, will be permitted in order to facilitate holidays, weekends, bad weather, scheduling, or other unforeseen circumstances not including adverse events. Such administrative delay – not to be used for adverse event management – will not be considered a protocol deviation.

Also, in order to facilitate scheduling flexibility for on-study laboratory items: For all cycles, beginning with Cycle 2, Day 1: Laboratories designated as Hematology, Serum Chemistries or as "Additional Labs" in Section 7.2 (Arm A) need not be repeated on days of treatment, if already resulted ≤ 3 days prior to treatment.

On Cycles 2+, Day 1, the following procedures will be completed prior to protocol-indicated treatment:

- Physical Exam.
- Weight
- Vital Signs: Heart rate (HR), blood pressure (BP), and temperature.
- ECOG performance status.
- Concomitant medication and Adverse Event review.
- Complete Blood Count (CBC) with differential (including white blood cell count with differential, hemoglobin, hematocrit, and platelet count).
- Blood Chemistry [including sodium, potassium, chloride, bicarbonate or carbon dioxide, blood urea nitrogen (BUN), creatinine, glucose, total bilirubin, AST, ALT, alkaline phosphatase (ALP), calcium, albumin, total protein; magnesium and phosphorus].
- Additional labs: LDH, TSH (and if TSH is abnormal, then free T3 and free T4), cortisol, CK, and CK-MB. If clinically indicated: ACTH, amylase and lipase.

On the days indicated below, the following additional items will be also be completed (prior to any protocol-indicated treatment):

- Cycle 2, Day 1:
  - Troponin-I.
  - 12-lead ECG (single recording on local equipment), with additional ECGs as clinically indicated, per patient's study physician.
- Cycle 4, Day 1:
  - Peripheral blood sample for correlative research.
- Cycle 14, Day 1:
  - Peripheral blood sample for correlative research.

On Cycles 2+, Day 1, the following procedures will be completed in association with Arm A dosing:

- Pre-Dose Vital Signs (≤30 minutes prior to START of nivolumab infusion):
  - Heart rate (HR), blood pressure (BP), and temperature.
- Nivolumab infusion:
  - On Cycles 2+, Day 1, all patients in Arm A are scheduled to receive nivolumab as a 30 minute (±10 minutes) intravenous infusion.
- Post-Dose Vital Signs (≤30 minutes after the END of the nivolumab infusion):
  - Heart rate (HR), blood pressure (BP), and temperature.
- Relatlimab infusion:
  - On Cycles 2+, Day 1, all patients in Arm A are scheduled to receive relatlimab as a 60 minute (±10 minutes) intravenous infusion.
  - Note: Nivolumab and relatlimab are to be administered as SEPARATE intravenous treatments. On days when both drugs are administered (i.e. scheduled for Day 1 of each cycle), the nivolumab infusion must be completed BEFORE initiation of intravenous relatlimab – see Section 9.6.
- Post-Dose Vital Signs (≤30 minutes after the END of relatlimab):
  - Heart rate (HR), blood pressure (BP), and temperature.

7.9. Additional Assessments, Arm A: Cycle 2, Day 15

On Day 15 of Cycle 2, the following additional items will be completed for patients in Arm A:

- Troponin-I.
- 12-lead ECG (single recording on local equipment), with additional ECGs as clinically indicated, per patient's study physician.
- Peripheral blood sample for correlative research.
- Fresh tumor biopsy (±7 days).

7.10. Assessments, Arm B: Cycle 1, Day 1

On Cycle 1, Day 1, the following procedures must be completed, unless previously completed ≤ 7 days prior to a patient's first dose of protocol-indicated treatment:

- Physical Exam.
- ECOG performance status.
- Complete Blood Count (CBC) with differential (including white blood cell count with differential, hemoglobin, hematocrit, and platelet count).
- Blood Chemistry [including sodium, potassium, chloride, bicarbonate or carbon dioxide, blood urea nitrogen (BUN), creatinine, glucose, total bilirubin, AST, ALT, alkaline phosphatase (ALP), calcium, albumin, total protein; magnesium and phosphorus].
- Additional labs: LDH, TSH (and if TSH is abnormal, then free T3 and free T4), cortisol, CK, CK-MB, and troponin-I. If clinically indicated: ACTH, amylase and lipase.

On Cycle 1, Day 1, the following procedures will be completed prior to first dose of protocol-indicated treatment:

- Vital Signs: Heart rate (HR), blood pressure (BP), and temperature.
- Weight.
- Concomitant medication and Adverse Event review.
- Serum or urine Pregnancy Test in women of childbearing potential (as defined in Appendix 4) – unless serum pregnancy test during screening was previously completed ≤ 72 hours prior to a patient's first dose of protocol-indicated treatment.
- Peripheral blood sample for correlative research.

On Cycle 1, Day 1, the following procedures will be completed in association with Arm B dosing:

- Pre-Dose Vital Signs (≤30 minutes prior to START of nivolumab infusion):
  - Heart rate (HR), blood pressure (BP), and temperature.
- Nivolumab infusion:
  - On Cycle 1, Day 1, all patients in Arm B are scheduled to receive nivolumab as a 30 minute (±10 minutes) intravenous infusion.
- Post-Dose Vital Signs (≤30 minutes after the END of the nivolumab infusion):
  - Heart rate (HR), blood pressure (BP), and temperature.
- Ipilimumab infusion:
  - On Cycle 1, Day 1, all patients in Arm B are scheduled to receive ipilimumab as a 90 minute (±10 minutes) intravenous infusion.
  - Note: Nivolumab and ipilimumab are to be administered as SEPARATE intravenous treatments. On days when both drugs are administered, the nivolumab infusion must be completed BEFORE initiation of intravenous ipilimumab – see Section 9.7.
- Post-Dose Vital Signs (≤30 minutes after the END of ipilimumab):
  - Heart rate (HR), blood pressure (BP), and temperature.

7.11. Assessments, Arm B: Cycle 1, Day 8 and Day 15

On Cycle 1, Day 8 and Day 15, the following procedures will be completed:

- Physical Exam.
- Weight
- Vital Signs: Heart rate (HR), blood pressure (BP), and temperature.
- ECOG performance status.
- Concomitant medication and Adverse Event review.
- Complete Blood Count (CBC) with differential (including white blood cell count with differential, hemoglobin, hematocrit, and platelet count).
- Blood Chemistry [including sodium, potassium, chloride, bicarbonate or carbon dioxide, blood urea nitrogen (BUN), creatinine, glucose, total bilirubin, AST, ALT, alkaline phosphatase (ALP), calcium, albumin, total protein; magnesium and phosphorus].
- Additional labs: LDH, TSH (and if TSH is abnormal, then free T3 and free T4), cortisol, troponin-I, CK, and CK-MB. If clinically indicated: ACTH, amylase and lipase.

On Cycle 1, Day 15, the following will also be completed:

- Peripheral blood sample for correlative research.

7.12. Assessments, Arm B: Cycles 2-4, Day 1

Beginning with Cycle 2, Day 1: Up to 3 days delay (i.e. plus 1 to 3 days; but not minus 1 to 3 days) in the initiation of Day 1 of a new cycle, will be permitted in order to facilitate holidays, weekends, bad weather, scheduling, or other unforeseen circumstances not including adverse events. Such administrative delay – not to be used for adverse event management – will not be considered a protocol deviation.

Also, in order to facilitate scheduling flexibility for on-study laboratory items: For all cycles, beginning with Cycle 2, Day 1: Laboratories designated as Hematology, Serum Chemistries or as "Additional Labs" in Section 7.3 (Arm B) need not be repeated on days of treatment, if already resulted ≤ 3 days prior to treatment.

On Day 1 of Cycles 2, 3 and 4, the following procedures will be completed prior to protocol-indicated treatment:

- Physical Exam.
- Weight
- Vital Signs: Heart rate (HR), blood pressure (BP), and temperature.
- ECOG performance status.
- Concomitant medication and Adverse Event review.
- Complete Blood Count (CBC) with differential (including white blood cell count with differential, hemoglobin, hematocrit, and platelet count).
- Blood Chemistry [including sodium, potassium, chloride, bicarbonate or carbon dioxide, blood urea nitrogen (BUN), creatinine, glucose, total bilirubin, AST, ALT, alkaline phosphatase (ALP), calcium, albumin, total protein; magnesium and phosphorus].
- Additional labs: LDH and TSH (and if TSH is abnormal, then free T3 and free T4). If clinically indicated: ACTH, amylase and lipase.
- **On Cycle 2, Day 1:** Cortisol, troponin-I, CK, and CK-MB.
- **On Cycle 3, Day 1:** Peripheral blood sample for correlative research, and Fresh tumor biopsy (±7 days).

On Day 1 of Cycles 2, 3 and 4, the following procedures will be completed in association with Arm B dosing:

- Pre-Dose Vital Signs (≤30 minutes prior to START of nivolumab infusion):
  - Heart rate (HR), blood pressure (BP), and temperature.
- Nivolumab infusion:
  - On Cycles 2-4, Day 1, all patients in Arm B are scheduled to receive nivolumab as a 30 minute (±10 minutes) intravenous infusion.
- Post-Dose Vital Signs (≤30 minutes after the END of the nivolumab infusion):
  - Heart rate (HR), blood pressure (BP), and temperature.
- Ipilimumab infusion:
  - On Cycles 2-4, Day 1, all patients in Arm B are scheduled to receive ipilimumab as a 90 minute (±10 minutes) intravenous infusion.
  - Note: Nivolumab and ipilimumab are to be administered as SEPARATE intravenous treatments. On days when both drugs are administered, the nivolumab infusion must be completed BEFORE initiation of intravenous ipilimumab – see Section 9.7.
- Post-Dose Vital Signs (≤30 minutes after the END of ipilimumab):
  - Heart rate (HR), blood pressure (BP), and temperature.

7.13. Assessments, Arm B: Cycles 5+, Day 1

On Cycles 5+, Day 1, the following procedures will be completed prior to protocol-indicated treatment:

- Physical Exam.
- Weight
- Vital Signs: Heart rate (HR), blood pressure (BP), and temperature.
- ECOG performance status.
- Concomitant medication and Adverse Event review.
- Complete Blood Count (CBC) with differential (including white blood cell count with differential, hemoglobin, hematocrit, and platelet count).
- Blood Chemistry [including sodium, potassium, chloride, bicarbonate or carbon dioxide, blood urea nitrogen (BUN), creatinine, glucose, total bilirubin, AST, ALT, alkaline phosphatase (ALP), calcium, albumin, total protein; magnesium and phosphorus].
- Additional labs: LDH and TSH (and if TSH is abnormal, then free T3 and free T4). If clinically indicated: ACTH, amylase and lipase.
- **On Cycle 5, Day 1:** Peripheral blood sample for correlative research.
- **On Cycle 15, Day 1:** Peripheral blood sample for correlative research.

On Cycles 5+, Day 1, the following procedures will be completed in association with Arm B dosing:

- Pre-Dose Vital Signs (≤30 minutes prior to START of nivolumab infusion):
  - Heart rate (HR), blood pressure (BP), and temperature.
- Nivolumab infusion:
  - On Cycles 5+, Day 1, all patients in Arm B are scheduled to receive nivolumab as a 30 minute (±10 minutes) intravenous infusion.
- Post-Dose Vital Signs (≤30 minutes after the END of the nivolumab infusion):
  - Heart rate (HR), blood pressure (BP), and temperature.

7.14. Imaging Assessments: Every 12 Weeks

CT/MRI re-scanning:

- Ideally performed every 12 weeks after Cycle 1, Day 1, but for the purpose of scheduling flexibility: Scan completion also permitted with minus 1 to minus 7 day window. The minus 1-7 day scan window is intended for flexibility in scheduling re-scans *between Days 22-28 of Cycles 3, 6, 9, etc of every third cycle in Arm A; between Days 15-21 of Cycle 4 in Arm B; and then between Days 22-28 of Cycles 7, 10, 13, etc of every third cycle in Arm B*.
- Scanning on the same day as Day 1 of a new cycle is discouraged but allowed, provided scan results receive appropriate RECIST review prior to initiating the new cycle of study treatment.
- Evaluation of disease status by CT/MRI including imaging coverage of anatomical

regions as outlined in Section 8.11.

- Additional disease evaluations or increased scan frequency may be performed according to the medical judgment of the patient's study physician, in accordance with the following: In the event of suspected Progressive Disease (PD), a CT/MRI is to be performed as soon as possible. In the event of a Complete or Partial Response (CR/PR), a confirmatory CT/MRI is to be performed no earlier than 28 days after the first assessment of CR/PR.

7.15. End-of-Treatment / Withdrawal Assessments

Reasonable effort should be made to complete End-of-Treatment (EOT) / Withdrawal procedures on the day it is decided that a patient will no longer receive protocol-indicated treatment.

The following EOT procedures must be completed subsequent to and not later than 14 days after study physician decision to permanently discontinue protocol-indicated treatment with nivolumab, relatlimab or ipilimumab (whichever treatment occurs last) and prior to any subsequent anti-cancer therapy:

- Physical Exam.
- Vital Signs: Heart rate (HR), blood pressure (BP), and temperature.
- ECOG Performance Status.
- Weight.
- Concomitant medication and Adverse Event review.
- Complete Blood Count (CBC) with differential (including white blood cell count with differential, hemoglobin, hematocrit, and platelet count).
- Blood Chemistry [including sodium, potassium, chloride, bicarbonate or carbon dioxide, blood urea nitrogen (BUN), creatinine, glucose, total bilirubin, AST, ALT, alkaline phosphatase (ALP), calcium, albumin, total protein; magnesium and phosphorus].
- Additional labs: LDH and TSH; and, if TSH is abnormal, then also free T3 and free T4.
- Serum or urine Pregnancy Test in women of childbearing potential (as defined in Appendix 4).
- Disease evaluation by CT/MRI (only if the previous CT/MRI was done > 28 days before).
- Biomarker and pharmacodynamic (PD) blood samples.

7.16. 30-Day and 100-Day Follow-Up Visit Assessments

Documented attempt(s) should be made for patient return to the study clinic. It will not be considered a protocol deviation if the patient is physically unable to return for the 30-day and 100-day follow-up visits; such circumstance should be recorded in the study documents, and as much of the follow-up information as possible should be obtained via feasible patient contact and from local and outside facilities.

A follow-up clinic visit is to be completed 30-37 days after patient's final protocol-indicated treatment with nivolumab, relatlimab or ipilimumab (whichever occurs last), in order to undergo the following assessments:

- Physical Exam.

- Vital Signs: Heart rate (HR), blood pressure (BP), and temperature.
- ECOG Performance Status.
- Weight.
- Concomitant medication and Adverse Event review.
- Complete Blood Count (CBC) with differential (including white blood cell count with differential, hemoglobin, hematocrit, and platelet count).
- Blood Chemistry [including sodium, potassium, chloride, bicarbonate or carbon dioxide, blood urea nitrogen (BUN), creatinine, glucose, total bilirubin, AST, ALT, alkaline phosphatase (ALP), calcium, albumin, total protein; magnesium and phosphorus].
- Additional labs: LDH and TSH; and, if TSH is abnormal, then also free T3 and free T4.
- Serum or urine Pregnancy Test in women of childbearing potential (as defined in Appendix 4).
- Biomarker and pharmacodynamic (PD) blood samples.

A follow-up clinic visit is to be completed 100-114 days after patient's final protocol-indicated treatment with nivolumab, relatlimab or ipilimumab (whichever occurs last), in order to undergo the following assessments:

- Physical Exam.
- Vital Signs: Heart rate (HR), blood pressure (BP), and temperature.
- ECOG Performance Status.
- Weight.
- Adverse Event review.

If a patient discontinues the study for reason other than progressive disease confirmed by CT or MRI (e.g. adverse event), then CT or MRI scans involving sites of known or suspected disease must be continued (if clinically feasible) every 12 weeks (± 7 days) for 12 months and then approximately every 24 weeks (± 4 weeks) thereafter, relative to date(s) of prior scanning, until disease progression is confirmed by imaging. (Note: If the patient initiates treatment in another clinical trial, then any continuing scans done for this trial may terminate.)

7.17. Survival and Long-Term Follow-Up

Each patient will be followed for survival and information about subsequent anticancer therapy every 12 weeks (3 months) ±14 days after patient's final protocol treatment with nivolumab, relatlimab or ipilimumab (whichever occurs last) until death, termination of the study, patient withdraws consent, or for a maximum of 2 years after the patient's final protocol-indicated treatment – whichever comes first. Contact can be made via clinic visit, chart review, obituary or similar observation (e.g. Social Security death index), or by telephone. Outside of this intended schedule, the sponsor-investigator and/or BMS may also request that survival data be collected on all treated subjects. At that time of this request, each subject will be contacted by similar means to determine their survival status unless the subject had withdrawn consent for all contact.

8. STUDY PROCEDURES

8.1. Informed Consent

Informed consent must be obtained before any study-specific screening assessments are performed. Screening assessments are to be performed within 14 days prior to Day 1 of Cycle 1 unless otherwise noted (e.g. baseline CT or MRI scan allowed up to 28 days prior to initiating Cycle 1, Day 1 treatment). Assessments performed as standard of care within the screening window may be used for screening. Baseline characteristics include but are not limited to: demographics, medical and surgical history, extent of disease, prior anti-cancer treatment, and tumor histology.

8.2. Physical Examination and ECOG Performance Status

Physical examination and assessment of Eastern Cooperative Oncology Group (ECOG) performance status to be performed within 14 days prior to initiating protocol treatment; on Cycle 1, Day 1 (unless previously completed ≤ 7 days prior to a patient's first dose of protocol-indicated treatment), and at additional time points as outlined in Section 7.

8.3. Vital Signs

Vital signs to include: Heart rate (HR), blood pressure (BP), and temperature (oral or tympanic).

On each day of treatment with nivolumab/relatlimab or nivolumab/ipilimumab, Pre-Dose and Post-Dose vitals must be respectively recorded ≤30 minutes prior to the start treatment, and ≤30 minutes after the end of each separate treatment; thus:

- On Day 1 of each cycle in *Arm A*, a minimum of 3 sets of vital signs are scheduled to be recorded: Pre-nivolumab, Post-nivolumab and Post-relatlimab.
- In *Arm B*, on Day 1 of each of the first four cycles, a minimum of 3 sets of vital signs are scheduled to be recorded: Pre-nivolumab, Post-nivolumab and Post-ipilimumab. For Arm B cycles 5 onward, a minimum of 2 sets of vital signs are scheduled to be recorded: Pre-nivolumab and Post-nivolumab.

8.4. Body Weight

Weight is measured at screening, prior to every dose of study treatment; and at the EOT, 30-day and 100-day Follow-up visits.

Patient's body weight must be measured *at least* on the *same day* in which every dose of nivolumab, relatlimab, or ipilimumab is administered to the patient.

In Arm B: Each of the first 4 doses of nivolumab and ipilimumab (scheduled for administration on Day 1 of Cycles 1-4) must be adjusted if patient's body weight changes > ±10% from the weight used to calculate the dose.

8.5. Review of Concomitant Medications and Adverse Events

Review and capture of all concomitant medications will be performed at each visit as indicated in Section 7. Concomitant medications include prescription medications and over-the-counter preparations used by a patient within at least 14 days prior to first dose of protocol-defined

treatment and continuing through at least the 30-day Follow-Up study visit (or until initiation of subsequent anticancer therapy). Adverse events will be collected as detailed in protocol Section 13.

8.6. Complete Blood Count (CBC) with Differential

Local hematology results at time points indicated in Section 6.1 to include white blood cell count with differential, hemoglobin, hematocrit, and platelet count.

8.7. Blood Chemistry

Local blood chemistry results at time points indicated in Section 7 to include sodium, potassium, chloride, bicarbonate or carbon dioxide, blood urea nitrogen (BUN), creatinine, glucose, total bilirubin, AST, ALT, alkaline phosphatase (ALP), calcium, albumin, total protein; magnesium and phosphorus.

8.8. Additional Labs

Blood draws for additional local laboratory assessment of LDH, TSH, free T3, free T4, cortisol, troponin-I, CK, and CK-MB at time points indicated in Section 7. Designation of "reflexive" in Section 7 indicates assessment of free T3 and free T4 only when TSH is not within normal range. ACTH, amylase and lipase done as clinically indicated per judgment of the investigator.

8.9. ECG

For patients in Arm A: Standard 12-lead electrocardiogram (ECG), single tracing, using local site equipment completed during screening for all patients. Additional single tracing ECGs done prior to treatment on days as indicated in Section 7.2. Additional ECGs as clinically indicated per patient's study physician.

The corrected QT interval (QTc) will be calculated using the method[13] of Fridericia (QTcF), where QTcF equals the QT interval divided by the cube root of the RR interval:

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

Note: During screening, as part of eligibility verification, QTcF > 480 msec is an exclusionary criterion (Section 5).

8.10. Pregnancy Test

For women of childbearing potential (WOCBP): Serum pregnancy test required during screening; and either serum or urine pregnancy test required ≤ 72 hours prior to first dose of protocol-indicated treatment (unless serum pregnancy test during screening was already done ≤ 72 hours prior to initiating c1d1 treatment), and at the EOT and 30-day Follow-up visits.

See Appendix 4 for study required contraception and definition of WOCBP.

8.11. Disease Assessment by CT/MRI

Baseline evaluation of disease status by Computed Tomography (CT) and/or Magnetic Resonance Imaging (MRI) ≤ 28 days prior to initiating protocol treatment on Cycle 1, Day 1.

Baseline and subsequent scans to include imaging of the chest, abdomen, and pelvis and CT and/or MRI of the brain. Additional sites of known or suspected disease should be imaged during screening and subsequent scans.

Re-scanning to occur every 12 weeks (minus 1-7 days) after initiating protocol treatment on Cycle 1, Day 1. The minus 1-7 day scan window is intended for flexibility in scheduling.

Additional disease evaluations or increased scan frequency may be performed according to the medical judgment of the patient's study physician, in accordance with the following: In the event of suspected Progressive Disease (PD), a CT/MRI is to be performed as soon as possible. In the event of a Complete or Partial Response (CR/PR), a confirmatory CT/MRI is to be performed no earlier than 28 days after the first assessment of CR/PR.

At End-of-Treatment, CT/MRI required only if the previous CT/MRI was done >28 days before.

At the 1M F/U Follow-Up visit, CT/MRI required only if disease progression was not already documented by CT/MRI done before, during or after the prior EOT visit.

If a patient discontinues the study for reason other than progressive disease confirmed by CT or MRI (e.g. adverse event), then CT or MRI scans involving sites of known or suspected disease must be continued (if clinically feasible) every 12 weeks (± 7 days) for 12 months and then approximately every 24 weeks (± 4 weeks) thereafter, relative to date(s) of prior scanning, until disease progression is confirmed by imaging.

If the patient initiates treatment in another clinical trial, then any continuing scans done for this trial may terminate.

8.12. Required Baseline Tumor Tissue

Archival tissue [paraffin block(s) or unstained slides from paraffin block(s)] from the primary tumor and/or a metastatic site must be available prior to initiating treatment, or patient must be willing to undergo a fresh pre-treatment standard of care tumor biopsy. Within 28 days prior to initiating treatment, the screening team must have documentation that an archival or fresh tumor specimen has been requested from a local or outside facility. Physical possession and centralized testing of requested tissue is required prior to initiating study treatment because all patients in this study are being stratified by MHC-II status, based on centralized testing performed at Vanderbilt.

8.13. Fresh Tumor Biopsy

Fresh biopsy of lesion amenable to safe biopsy from a primary lesion or metastatic site, performed approximately 6 weeks following initiation of protocol-indicated treatment:

- Arm A: Fresh biopsy on Cycle 2, Day 15 (±7 days)
- Arm B: Fresh biopsy on Cycle 3, Day 1 (±7 days).

Note that research blood is also scheduled for collection on these days, and with similar ±7 day flexibility, in order that the research blood draws are ideally obtained on the same day as the on-study fresh biopsy (and ideally PRIOR to the biopsy procedure).

8.14. Biomarker and Pharmacodynamic (PD) Blood Samples

Peripheral blood samples for exploratory analysis including biomarker and possible PD research to be obtained at time points indicated in Section 7.

Note that 2 of these time points also correspond to days when fresh tumor biopsy is also intended (i.e. Cycle 2, Day 15 in Arm A; and Cycle 3, Day 1 in Arm B). To accommodate scheduling, a ±7 day window for the fresh on-study biopsy is allowed; therefore, a similar ±7 day window is also applicable to the research blood draws scheduled for these two time points, in order for the research blood to be collected ideally on the same day as the fresh biopsy (and ideally PRIOR to the biopsy procedure).

8.15. Handling of Biological Samples

All biological samples to be analyzed locally will be collected and handled according to local institutional practices. All biological samples to be analyzed centrally will be collected and handled according to a provided laboratory manual. Retention time for biologic specimens will be specified in the laboratory manual.

9. PROTOCOL TREATMENT

9.1. Dose Summary

This is a phase 2, open-label, two-arm study in patients with locally advanced/unresectable or metastatic melanoma, evaluating the efficacy of either nivolumab plus relatlimab against MHC-II positive tumors (Arm A); or nivolumab plus ipilimumab against MHC-II negative tumors (Arm B). The dose summary for each respective study arm is presented below in **Table 3** and **Table 4**:

TABLE 3: Dose Summary, Arm A, MHC-II Positive

ARM A: MHC-II (+)	*4 week cycles*	**Comments: Arm A**
	Cycles 1+ DAY 1	*All Cycles = 28 days (4 weeks) per cycle*
Nivolumab	480 mg	30 minute i.v. infusion
Relatlimab	160 mg	60 minute i.v. infusion *Relatlimab infusion to be started AFTER completion of nivolumab infusion.*

TABLE 4: Dose Summary, Arm B, MHC-II Negative

ARM B: MHC-II (-)	*3 week cycles*	*4 week cycles*	**Comments: Arm B**
	Cycles 1, 2, 3, and 4 DAY 1	**Cycles 5+ DAY 1**	*Cycles 1-4 = 21 days (3 weeks) per cycle* *Cycles 5+ = 28 days (4 weeks) per cycle*
Nivolumab	1 mg/kg	480 mg	30 minute i.v. infusion
Ipilimumab	3 mg/kg		90 minute i.v. infusion *Ipilimumab infusion to be started AFTER completion of nivolumab infusion.*

Stratified by MHC-II status (either positive or negative) of baseline tumor tissue, participants will receive one of the following regimens:

- **Arm A (MHC-II positive):**
  - nivolumab 480mg IV + relatlimab 160mg IV q4w.
- **Arm B (MHC-II negative):**
  - nivolumab 1mg/kg IV + ipilimumab 3mg/kg IV q3w x4 (i.e. 4 total doses of nivolumab, and 4 total does of ipilimumab); then
  - nivolumab 480mg IV q4w.

Every effort should be made to target infusion timings to be as close as possible to the scheduled duration. But given the variability of infusion pumps, time windows of ±10 minutes for the scheduled duration of infusions are permitted. (Additionally, prolongation of infusion duration for the purpose of managing suspected or actual adverse event such as infusion reaction will not be considered a protocol deviation.)

In Arm B, doses of nivolumab and ipilimumab administered on a mg/kg basis (i.e. all those given prior to initiation of flat-dose nivolumab scheduled to begin in Cycle 5 of Arm B) will be determined by measuring the patient's weight in kilograms on the day of dosing, prior initiation of nivolumab/ipilimumab.

If the patient's weight on the day of dosing differs by > ±10% from the weight used to calculate a dose based on mg/kg, then doses of nivolumab and ipilimumab must be recalculated prior to administration.

In Arm B, unless otherwise specified (e.g. by established institutional practice), all calculated doses based on mg/kg may be rounded up (or down) to the nearest milligram; and a ±5% variance in the calculated total dose will be allowed for ease of dose administration.

9.2. Antiemetic Premedication

Administration of established institutional standard premedication prior to infusion is allowed, however it is recommended that antiemetic medications should not be routinely administered prior to dosing of drugs. See Section 11.5 for subsequent premedication recommendations following a study drug-related infusion reaction.

9.3. Nivolumab Infusion

The study will supply nivolumab to the site.

All patients in this study will receive nivolumab:

- Patients in Arm A will receive nivolumab in combination with relatlimab.
- Patients in Arm B will receive nivolumab in combination with ipilimumab.

Each patient receiving nivolumab will be treated at the assigned dose as specified in Section 9.1. Nivolumab will be administered intravenously consistent with the product label[14], as a 30 minute (±10 minutes) intravenous infusion.

In Arm A, all nivolumab administrations are scheduled as a flat-dose of 480mg.

In Arm B, a patient's first 4 doses of 1mg/kg nivolumab will be determined by measuring the patient's weight in kilograms on the day of dosing, prior to each nivolumab dose. If the patient's weight on the day of nivolumab dosing differs by > ±10% from the weight used to calculate the dose, then doses of nivolumab (and ipilimumab) must be recalculated prior to administration.

Patients should be carefully monitored for infusion reactions during nivolumab administration. If an infusion-related reaction (IRR) is noted, patients should be managed according to established local procedures consistent with the product label[14] and Section 11.5.

For purpose of adverse event management, doses of nivolumab may be held/delayed for up to 42 days (6 weeks) from time of the last nivolumab dose (e.g. Section 11.2).

9.4. Relatlimab (BMS-986016) Infusion

The study will supply relatlimab to the site.

Patients stratified to Arm A of the study (i.e. tumor tissue MHC-II positive) will receive relatlimab in combination with nivolumab.

On Day 1 of each 4 week cycle, patients in Arm A are scheduled to receive SEPARATE intravenous infusions of nivolumab and relatlimab: **The relatlimab infusion will be started AFTER completion of the nivolumab infusion**.

Each patient receiving relatlimab will be treated at the assigned dose as specified in Section 9.1. Relatlimab will be administered consistent with the investigator's brochure[15], as a 60 minute (±10 minutes) intravenous infusion.

For all relatlimab administrations, an appropriate dosing history will be recorded, e.g.:

- Total dose administered.
- Infusion start and stop time.
- Dose interruption or termination and reason for such actions.

Patients should be carefully monitored for infusion reactions during relatlimab administration. If an infusion-related reaction (IRR) is noted, patients should be managed according to established local procedures consistent with the investigator brochure[15] and Section 11.5.

For purpose of adverse event management, doses of relatlimab may be held/delayed for up to 6 weeks from time of the last relatlimab dose (e.g. Section 11.2).

9.5. Ipilimumab Infusion

The study will supply ipilimumab to the site.

Patients stratified to Arm B of the study (i.e. tumor tissue MHC-II negative) will receive ipilimumab in combination with nivolumab.

In Arm B, combinatorial treatment with nivolumab and ipilimumab is scheduled to be administered on Day 1 of four initial cycles lasting 3-weeks per cycle.

Every patient in Arm B of the study is scheduled to receive 4 total doses of nivolumab and 4 total doses of ipilimumab in a combinatorial setting. (In Arm B, after 12 weeks of combinatorial treatment with nivolumab + ipilimumab, all patients in Arm B are then scheduled to continue nivolumab alone, as monotherapy, in lengthened cycles lasting 4 weeks per cycle.)

After receiving 4 infusions of ipilimumab, ipilimumab treatment will be complete.

Each patient receiving ipilimumab will be treated at the assigned dose as specified in Section 9.1. Ipilimumab will be administered intravenously consistent with the product label[16], as a 90 minute (±10 minutes) intravenous infusion.

In Arm B, on Day 1 of Cycles 1-4: Patients in Arm B are scheduled to receive SEPARATE intravenous infusions of nivolumab and ipilimumab: **The ipilimumab infusion will be started AFTER completion of the nivolumab infusion**.

In Arm B, a patient's 4 doses of 3mg/kg ipilimumab will be determined by measuring the patient's weight in kilograms on the day of dosing, prior to each ipilimumab dose. If the patient's weight on

the day of ipilimumab dosing differs by > ±10% from the weight used to calculate the dose, then doses of ipilimumab (and nivolumab) must be recalculated prior to administration.

Patients should be carefully monitored for infusion reactions during ipilimumab administration. If an infusion-related reaction (IRR) is noted, patients should be managed according to established local procedures consistent with the product label[16] and Section 11.5.

For purpose of adverse event management, doses of ipilimumab may be held/delayed for up to 6 weeks from time of the last ipilimumab dose (e.g. Section 11.2).

9.6. Nivolumab and Relatlimab (Arm A): Separate Infusions

When both nivolumab and relatlimab are to be administered on the same day, separate infusion bags and filters must be used for each infusion.

Nivolumab is to be administered first.

The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the relatlimab infusion.

The second infusion will be relatlimab and will start after the infusion line has been flushed, filters changed, and patient has been observed to ensure no infusion reaction has occurred.

Relatlimab infusion will start within 60 minutes after completion of the nivolumab infusion.

9.7. Nivolumab and Ipilimumab (Arm B): Separate Infusions

When both nivolumab and ipilimumab are to be administered on the same day, separate infusion bags and filters must be used for each infusion.

Nivolumab is to be administered first.

The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion.

The second infusion will always be ipilimumab and will start no sooner than 30 minutes after completion of the nivolumab infusion.

9.8. Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of patients treated with immunotherapy may derive clinical benefit despite initial evidence of PD[10]. Patients will be permitted to continue treatment beyond initial RECIST 1.1 defined PD as long as they meet the following criteria:

1) Investigator-assessed clinical benefit, and do not have rapid disease progression
2) Tolerance of study drug
3) Stable performance status
4) Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g. CNS metastases)
5) Patient provides written informed consent prior to receiving any additional nivolumab treatment, or nivolumab in combination with ipilimumab treatment, or nivolumab in combination with relatlimab treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options.

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

All decisions to continue treatment beyond initial progression must be discussed with the sponsor-investigator and documented in writing in advance within the study records. Patients will be re-consented with an ICF describing any reasonably foreseeable risks or discomforts.

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

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

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

9.9. Discontinuation of Protocol-Indicated Treatment

In this trial, combinatorial treatment with relatlimab and nivolumab (Arm A) or ipilimumab and nivolumab (Arm B) shall be considered separable: Relatlimab and nivolumab or ipilimumab and nivolumab may be permanently discontinued simultaneously; or relatlimab treatment may be discontinued before discontinuing nivolumab; or ipilimumab may be discontinued before discontinuing nivolumab treatment.

The visit schedule for protocol treatment will apply until permanent discontinuation of both nivolumab and relatlimab (in Arm A), or both nivolumab and ipilimumab (in Arm B). Once permanent discontinuation of both drugs has occurred, an End-of-Treatment (EOT) visit will be performed within 14 days after the decision to permanently discontinue the last of the two treatments (nivolumab and/or relatlimab; or nivolumab and/or ipilimumab), prior to any subsequent anti-cancer therapy.

After the EOT visit, the patient will continue to be followed until 30 to 37 days after the last dose of protocol-indicated treatment, at which time the one month Follow-Up visit must be completed.

Reasons for permanent discontinuation of a patient's protocol-indicated treatment include any of the following:

- Inability to tolerate nivolumab and/or relatlimab (Arm A).
- Inability to tolerate nivolumab and/or ipilimumab (Arm B).
- Patient withdraws consent to participate.
- Occurrence of an AE considered by the investigator to require treatment discontinuation.
- Toxicity requiring discontinuation as outlined in Section 11.4.
- Progressive Disease (PD), verified by CT/MRI according to RECIST v1.1.

- Treatment failure not meeting the criteria for PD, but considered by the investigator to require treatment discontinuation (e.g. clinical progression).
- Requirement for a significant surgical procedure. Note: Patients requiring a minor surgical procedure (e.g. port placement, skin abscess drainage) may continue at the investigator's discretion following discussion with the sponsor-investigator or designee. A brief interruption in therapy may be considered.
- An intercurrent illness which, in the opinion of the investigator, would prevent completion of trial-related evaluations.
- The investigator judges it necessary due to medical reasons (e.g. significant deterioration in performance status).
- Required use of a prohibited concomitant medication, as defined in Section 10.2. Note: subject to discussion with and approval by the sponsor-investigator, inadvertent isolated receipt of a prohibited concomitant medication (e.g. incidental to acute management of an adverse event) does not require permanent discontinuation.
- The patient becomes pregnant during treatment. (Cases of pregnancy that occur during maternal or paternal exposures to study treatment should be reported as SAEs. Data on fetal outcome and breast-feeding may be collected for regulatory reporting and drug safety evaluation.)
- Significant deviation from the protocol or eligibility criteria. Such patients will be considered protocol violations and may be discontinued from treatment after discussion with the sponsor-investigator.
- Noncompliance with trial procedures may require discontinuation after discussion with the sponsor-investigator.
- Termination of the trial by the sponsor-investigator or regulatory authority.

9.10. Duration of Follow-Up

In general, it intended that patients will be treated until disease progression or intolerable toxicity; or up to a maximum of 2 years of study treatment. Criteria for patient discontinuation include those listed in Section 11.4. Patients should be assessed when it is decided the patient will no longer receive protocol-indicated treatment; and assessed again 30-37 days after patient's final protocol-indicated treatment with nivolumab, relatlimab or ipilimumab (whichever treatment occurs last).

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

Subsequently, each patient will be followed for survival every 3 months (± 14 days) after patient's final protocol-indicated treatment until death, end of the study, until patient withdraws consent, or for a maximum of 2 years after the patient's final protocol-indicated treatment with relatlimab/nivolumab/ipilimumab – whichever comes first. Contact can be made via clinic visit, chart review, obituary or similar observation (e.g. Social Security death index), or by telephone.

The sponsor-investigator and/or BMS may request that survival data be collected on all treated subjects outside of the protocol-defined window. At that time of this request, each subject will be contacted to determine their survival status unless the subject had withdrawn consent for all contact.

9.11. Withdrawal from Study

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor-investigator for safety or behavioral reasons; or the inability of the patient to comply with the protocol-required schedule of study visits or procedures; or an inability to maintain voluntary informed consent. The EOT and the Follow-Up visits should be performed to the extent possible and the Investigator should ensure any SAE is followed as described in Section 13.

Reasons for withdrawal from the study might include but are not limited to any of the following:

- The patient withdraws consent to participate in treatment, follow-up, or survival monitoring.
- The investigator judges it necessary due to medical reasons.
- Subject is lost to follow-up.
- A maximum of 2 years of survival monitoring elapses after patient's last dose of protocol-indicated nivolumab/relatlimab/ipilimumab.
- Study is terminated for any reason.

10. CONCOMITANT TREATMENT

10.1. Supportive Care Guidelines

Patients may receive their current concomitant medication (CM) and any medication considered necessary by the patient's study physician for the welfare of the patient during the trial, except as otherwise restricted or prohibited (for example, if the CM is listed in Section 5 Inclusion/Exclusion Criteria, or in Section 10.2). Furthermore, when used within established institutional guidelines (when existent) and/or at study physician's discretion, the following medications and procedures are permitted during the trial:

- Palliative radiotherapy for localized pain control against non-target lesions, as long as it is not anticipated to significantly influence systemic bone marrow function, Section 10.3.

All concomitant medications should be recorded throughout the patient's participation in the study, including medications taken within at least 14 days prior to first dose of protocol-defined treatment.

Concomitant medications and supportive care therapies must also be documented at the time of study discontinuation and at the 30-day follow-up visit.

Appropriate documentation for all forms of premedications, supportive care, and concomitant medications (for example, medications such as sedatives, antibiotics, analgesics, antihistamines, corticosteroids, erythropoietin; procedures such as paracentesis, thoracentesis; or blood products such as blood cells, platelets, fresh frozen plasma transfusions) must be captured on the eCRF.

10.2. Prohibited Therapies and Procedures

The following therapies and procedures are not allowed from first visit (Screening) after signing consent, or as specified in the inclusion/exclusion criteria (Section 5) until completion of the EOT Visit:

- Other than nivolumab/relatlimab or nivolumab/ipilimumab, any other anti-cancer treatment, including cytotoxic or cytostatic agents, or hormonal therapy (except as otherwise

permitted by protocol – e.g. corticosteroids initiated during the study to manage adverse events associated with immunotherapy; or stable doses of corticosteroids established prior to study entry for stable CNS metastasis; or anti-estrogen/androgen therapy for select *in situ* malignancies in remission).

- Hematopoietic growth factors or transfusions used to meet hematologic criteria for study inclusion (Section 5).
- Radiotherapy against target lesion(s), Section 10.3.
- Although bisphosphonate osteoclast inhibitors (e.g. zoledronic acid or pamidronate) for treatment of bone metastases are permitted during study treatment, the osteoclast inhibitor denosumab is a monoclonal antibody, which could confound safety analysis in the study if the patient experiences a hypersensitivity reaction to denosumab. Therefore, concomitant use of denosumab will not be permitted.
- Major surgery that would preclude the patient from complying with the protocol requirements.

If any of the above listed medications/procedures becomes necessary during the trial, the patient must be withdrawn from treatment and the EOT Visit should be performed. The 30-day and 100-day Follow-up visits should then be conducted according to Section 7.4 after the patient's final treatment with nivolumab/relatlimab/ipilimumab (whichever occurs last), and the patient will be followed for survival.

10.3. Concomitant Radiotherapy

Per study eligibility criteria, prior therapeutic or palliative radiation therapy must be completed > 2 weeks prior to first dose of study treatment.

After beginning trial treatment, palliative radiotherapy must be discussed in advance of receipt, in writing, with the sponsor-investigator.

Local radiotherapy of isolated lesions with palliative intent (e.g. bleeding, pain, compression, etc.) will be permitted if considered medically necessary by the study physician. The irradiated area should be as small as possible, and the total dose delivered must be in a palliative range according to institutional standards. Irradiated lesions will be followed for disease progression but will not be accounted for in the evaluation of the response. Radiotherapy other than palliative radiotherapy for symptom control is not allowed concomitantly with the administration of protocol-indicated treatment.

Patients requiring palliative radiotherapy should be assessed for disease progression. If palliative radiotherapy is needed to control pain, the site(s) of disease causing pain should be present at baseline; otherwise, painful lesion(s) requiring radiotherapy should be considered as a sign of disease progression.

If palliative radiotherapy is required, then patients should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs considered related to radiotherapy should resolve to Grade ≤1 prior to resuming study treatment.

If a treatment cycle is interrupted for palliative radiation, then the decision to possibly resume study treatment will be made by the study physician, with written advance agreement from the investigator and the sponsor-investigator. Continuous interruption of >42 days due to palliative radiotherapy will not be allowed.

Only non-target lesions may receive palliative radiotherapy while on trial treatment. Details of palliative radiotherapy should be documented in the source records and eCRF. Details in the

source records should include: dates of treatment, anatomical site, dose administered and fractionation schedule, and AEs.

11. ADVERSE EVENT MANAGEMENT

Patients should be instructed to notify their study team at the first occurrence of any adverse symptom. In addition to dose delays according to protocol guidance, investigators are encouraged to employ best supportive care according to local institutional clinical practice.

Recognizing that new knowledge will be acquired and unforeseen safety issues may arise in the course of the study, the management guidelines are not exhaustive and do not represent a full spectrum of care or treatment options.

In general, an adverse event related to study treatment that results in a dose delay should be present on the day of intended study treatment (i.e. a delayed toxicity that develops mid-cycle, but which is no longer present or has resolved to an acceptable grade on the day of intended dosing, generally does not require a delay in treatment – unless, for example, the occasion involves retrospective detection of a prior event of sufficient grade to, regardless of duration, require delay or discontinuation).

Each adverse event will be graded according to the NCI's Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0, dated November 27, 2017; the therapy modifications described in this section are applied according to this severity grading.

In the event of multiple concurrent adverse events, treatment modification should be based on toxicity with the most severe grade. Each treatment delay must be documented, including the respective reason.

For purpose of any necessary definition with respect to adverse event management, "baseline value" is defined as the documented value in place most immediately prior to patient's first receipt of nivolumab, relatlimab or ipilimumab on Cycle 1, Day 1.

Nivolumab and/or relatlimab, and nivolumab and/or ipilimumab, may be delayed for any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the study physician, warrants delaying the dose for purpose of increased patient safety.

In the event of an adverse event deemed by the study physician as *not related* or *unlikely related* to protocol-indicated treatment, the study physician may nevertheless optionally choose to precautionarily interrupt nivolumab/relatlimab (either or both drugs), or nivolumab/ipilimumab (either or both drugs), for up to 42 days from the last respective dose.

In the event of treatment interruption, the study records should reflect treatment was withheld; other visit assessments and procedures however, including re-scanning for monitoring disease progression, must continue per protocol according to the timeline in place prior to the dose interruption.

11.1. Dose Modifications

There will be no dose reductions for nivolumab, ipilimumab, or relatlimab. Adverse events requiring dose modification will be managed by dose delay.

11.2. Criteria for Dose Delays

Dose delay criteria apply for all adverse events deemed by the investigator to be possibly, probably or definitely drug-related, regardless of whether or not the event is attributed to nivolumab, ipilimumab, relatlimab, or combinations.

All study drugs (i.e. nivolumab, ipilimumab and relatlimab) must be delayed until treatment can resume (see Section 11.3).

Treatment delays up to 6 weeks from the last dose are allowable.

ARM A: Nivolumab and relatlimab should be delayed for the following:

- Select drug-related AEs and drug-related laboratory abnormalities:
  - ≥ Grade 3 skin.
  - ≥ Grade 1 pneumonitis.
  - ≥ Single grade increase shift in abnormality in AST, ALT, and total bilirubin.
  - ≥ Grade 2 creatinine.
  - ≥ Grade 2 diarrhea or colitis.
  - ≥ Grade 2 neurological AE.
  - Grade 4 amylase and/or lipase abnormalities regardless of symptoms or clinical manifestations.
- Myocarditis (any grade).
- All troponin elevations require a dose delay to allow for prompt cardiac evaluation. Following this evaluation, determination of further treatment will be based on the discretion of the investigator.
- Any AE, laboratory abnormality, or concurrent illness that, in the judgment of the investigator, warrants delaying the dose of study drug.

ARM B: Nivolumab and ipilimumab should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following **exceptions**:
  - Grade 2 drug-related fatigue or laboratory abnormalities **do not require** a treatment delay.
- Any Grade 3 skin, drug-related adverse event.
- Any Grade 3 drug-related laboratory abnormality, with the following **exceptions** for asymptomatic amylase or lipase, AST, ALT, or total bilirubin:
  - Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis **do not require** a dose delay. It is recommended to consult with the sponsor-investigator for Grade 3 amylase or lipase abnormalities.
  - If a patient has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity.
  - If a patient has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity.

11.3. Criteria to Resume Treatment

When a patient's treatment with study drug is interrupted due to adverse event, the patient's treatment may be resumed when the drug-related AE(s) resolve to Grade ≤1 or baseline value, with the following exceptions:

- Patients may resume treatment in the presence of Grade 2 fatigue.
- Patients who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Patients with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin.
- Patients with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 11.4) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed. Patients with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month are eligible for retreatment at the discretion of the investigator.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.
- Patients in Arm A may resume treatment with relatlimab when troponin levels return to normal.

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled time point per protocol. However, if the treatment is delayed past the scheduled time point per protocol, the scheduled study treatment administration will be delayed, but not skipped, until dosing resumes. In particular, this is to ensure that subjects in Arm B will receive 4 administrations of combined nivolumab and ipilimumab treatment if toxicity allows.

If dose delay is necessary for subjects in Arm B during Weeks 1-12 (i.e. Cycles 1 thru 4), then both nivolumab and ipilimumab must be delayed until treatment can resume. However, if a nivolumab-related infusion reaction prevents subsequent infusion of ipilimumab on the same day, the dose of ipilimumab should be replaced as soon as possible. In such instances, at least 19 days must elapse between the replacement dose of ipilimumab and the administration of the next dose of nivolumab combined with ipilimumab.

If treatment is delayed or interrupted for > 6 weeks, the subject must be permanently discontinued from study therapy, except as otherwise specified (e.g. in Section 11.4).

11.4. Criteria to Permanently Discontinue Treatment

Treatment with nivolumab, ipilimumab, and/or relatlimab (BMS-986016) should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment.

- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, endocrinopathies, uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reactions, and infusion reactions:
    - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration **requires** discontinuation.
    - For Grade 3 endocrinopathy adverse events such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidosis, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (steroids, thyroid hormones) or glucose controlling agents, respectively, **do not require** treatment discontinuation.
    - Grade 3 drug-related laboratory abnormalities **do not require** treatment discontinuation **except**:
        - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding **requires** discontinuation.
        - Any drug-related liver function test (LFT) abnormality that meets the following criteria **requires** discontinuation:
            - AST or ALT > 5 x ULN.
            - Total bilirubin > 3 x ULN.
            - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN.

- Any Grade 3 myocarditis.

- Any Grade 4 drug-related adverse event or laboratory abnormality, **except for the following events** which do not require discontinuation:
    - Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. It is recommended to consult with the sponsor-investigator for Grade 4 amylase or lipase abnormalities.
    - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.

- Any dosing interruption lasting > 6 weeks from the last dose **with the following exceptions**:
    - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks from the last dose, the sponsor-investigator must be consulted in writing. Tumor imaging assessments should continue as per protocol even if dosing is interrupted.

— Dosing interruptions > 6 weeks from the last dose that occur for non-drug-related reasons may be allowed if approved by the sponsor-investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks from the last dose, the sponsor-investigator must be consulted. Tumor imaging assessments should continue as per protocol even if dosing is interrupted.

Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the patient with continued study drug dosing should discontinue the study drugs.

The consideration to re-initiate study therapy in selected cases at any time point after discontinuation could be made on a case-by-case basis after considering the overall benefit/risk profile and in consultation between the investigator and the sponsor-investigator. The selected patients will need to meet eligibility criteria. The original dose and schedule and protocol rules would apply accordingly (Section 11.4).

In this trial, combinatorial treatment with relatlimab and nivolumab (Arm A) or ipilimumab and nivolumab (Arm B) shall be considered separable (see also Section 9.9):

- **Arm A:** The assessment for discontinuation of drug should be made separately considering each drug component in the nivolumab + relatlimab combination (Arm A). If discontinuation criteria are attributed to only one drug used in this combination, once the patient meets criteria to resume therapy, the subject may continue dosing with nivolumab (if nivolumab was not attributed to criteria for discontinuation) and/or with relatlimab (if relatlimab was not attributed to criteria for discontinuation).

- **Arm B:** The assessment for discontinuation of drug should be made separately considering each drug component in the nivolumab + ipilimumab combination (Arm B). If discontinuation criteria are attributed to only one drug used in this combination, once the patient meets criteria to resume therapy, the subject may continue dosing with nivolumab (if nivolumab was not attributed to criteria for discontinuation) and/or with ipilimumab (if ipilimumab was not attributed to criteria for discontinuation).

If a patient meets criteria for discontinuation and the investigator is unable to determine whether the event is related to both or one study drug, the patient should discontinue all study drugs and be taken off the treatment phase of the study.

11.5. Treatment of Nivolumab, Ipilimumab, and Relatlimab Related Infusion Reactions

If infusion reaction or hypersensitivity were to occur, manifestation might include fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms.

According to the relatlimab investigator brochure[15], the all-combination group of study CA224020 includes 1166 subjects treated with relatlimab and nivolumab. The all-combination group includes Parts B+C+D. In combination therapy (Parts B, C, and D), 22 Grade 1 and 37 Grade 2 infusion-related reactions were reported. There were no Grade 3 or higher infusion reactions reported. The overall frequency (5.1%) observed in Study CA224020 is similar to the frequency observed for nivolumab monotherapy: In patients receiving nivolumab as a 60-minute intravenous infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients; and in a trial assessing the pharmacokinetics and safety of a more rapid infusion, in which patients received nivolumab as a 60-minute intravenous infusion or a 30-minute intravenous infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Refer to Section 5.9 of the

nivolumab label[14] for further details. All events were manageable per updated protocol guidelines, and only 2 subjects required treatment discontinuation, in each case due to recurrent Grade 2 infusion related reactions.[15]

Data regarding serious adverse reactions (i.e. "Serious Adverse Reactions for relatlimab monotherapy and relatlimab + nivolumab Considered Expected for Safety Reporting Purposes *(N=1401)*" in Table 1-2 of Appendix 1 of the relatlimab investigator brochure lists (serious) infusion related reaction as an uncommon event [i.e. n=4 (0.29%)] with no occurrence of life-threatening or fatal serious adverse reactions.[15]

All Grade 3 or 4 infusion reactions should be reported within 24 hours to the Coordinating Center and reported as an SAE if criteria are met (Section 13). Infusion reactions should be graded according to NCI CTCAE (version 5.0) guidelines.

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

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

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

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

- Stop the study drug infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate.
- If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further study drug will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF).
- The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional study drug administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

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

- Immediately discontinue infusion of study drug.

- Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed.
- Subject should be monitored until the investigator is comfortable that the symptoms will not recur.
- Study drug will be permanently discontinued.
- Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms.
- In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

11.6. Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with adverse events (AEs) which in severity and duration can differ from AEs caused by other therapeutic classes. In this protocol, nivolumab, ipilimumab, and relatlimab are considered immuno-oncology agents. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity.

Management Algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological
- Myocarditis.

For the above events deemed by the investigator as possibly, probably or definitely related to nivolumab, ipilimumab, and/or relatlimab, Management Algorithms are found in Appendix 6.

While safety management algorithms for similar adverse events may be presented elsewhere (e.g. ipilimumab investigator brochure), the recommendations for the combinatorial treatments outlined in this study protocol are to follow the nivolumab-based algorithms for immuno-oncology agents, in order to standardize safety management in this protocol. For individual cases, adverse event treatment management algorithms included in the nivolumab IB or ipilimumab IB might be considered.

The guidance provided in these algorithms should not replace the investigator's medical judgment but should complement it.

12. DRUG FORMULATION, SUPPLY AND STORAGE

12.1. Description of Nivolumab

Nivolumab (OPDIVO) is a programmed death receptor-1 (PD-1) blocking antibody that is currently approved for a variety of indications including melanoma with lymph node involvement or metastatic disease after complete resection, in the adjuvant setting; unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab; metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy; metastatic small cell lung cancer with progression after platinum-based chemotherapy and at least one other line of therapy; advanced renal cell carcinoma after prior anti-angiogenic therapy; intermediate or poor risk, previously untreated advanced renal cell carcinoma, in combination with ipilimumab; classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or 3 or more lines of systemic therapy that includes HSCT; recurrent or metastatic squamous cell carcinoma of the head and neck with progression on or after platinum-based therapy; locally advanced or metastatic urothelial carcinoma with progression (during or following platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy); adult and pediatric metastatic colorectal cancer (microsatellite instability-high or mismatch repair deficient) after progression on a fluoropyrimidine, oxaliplatin, and irinotecan, as a single agent or in combination with ipilimumab; and hepatocellular carcinoma after sorafenib treatment.[14]

12.2. Packaging of Nivolumab

The study will supply nivolumab to the site.

Nivolumab is typically available as nivolumab injection: 40 mg/4 mL (10 mg/mL), 100 mg/10 mL (10 mg/mL), and 240 mg/24mL (10 mg/mL) clear to opalescent, colorless to pale-yellow solution in a single-dose vial.

Nivolumab drug product should be visually inspected for particulate matter and discoloration prior to administration. Discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial.[14]

12.3. Handling and Storage of Nivolumab

Nivolumab product does not contain a preservative. Nivolumab will be prepared according to the product label. After preparation, the diluted nivolumab solution should be stored either[14]:

- At room temperature for no more than 8 hours from the time of preparation to end of the infusion. Discard diluted solution if not used within 8 hours from the time of preparation; or
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of preparation to end of infusion. Discard diluted solution if not used within 24 hours from the time of preparation.

Do not freeze.

12.4. Description of Ipilimumab

Ipilimumab (YERVOY) is a recombinant human monoclonal antibody that binds to the cytotoxic T-lymphocyte-associated-antigen 4 (CTLA-4), a negative regulator of T-cell activity. An IgG1 kappa immunoglobulin, ipilimumab is approved for treatment of unresectable or metastatic melanoma; adjuvant treatment of cutaneous melanoma with involvement of regional lymph nodes after resection; intermediate or poor risk, previously untreated advanced renal cell carcinoma, in combination with nivolumab; and under accelerated approval for microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, in combination with nivolumab.[16]

12.5. Packaging of Ipilimumab

The study will provide ipilimumab to the site.

Ipilimumab is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution for intravenous infusion, which may contain a small amount of visible translucent-to-white, amorphous ipilimumab particulates. It is typically supplied in single-use vials of 50 mg/10 mL (5 mg/mL) and 200 mg/40 mL (5 mg/mL). Each milliliter contains 5 mg of ipilimumab and the following inactive ingredients: diethylene triamine pentaacetic acid (DTPA) (0.04 mg), mannitol (10 mg), polysorbate 80 (vegetable origin) (0.1 mg), sodium chloride (5.85 mg), tris hydrochloride (3.15 mg), and water for injection, USP at a pH of 7.[16]

12.6. Handling and Storage of Ipilimumab

Store ipilimumab under refrigeration at 2°C to 8°C (36°F to 46°F). Protect ipilimumab from light by storing in the original carton until time of use. Do not freeze or shake.[16]

12.7. Description of Relatlimab (BMS-986016)

Relatlimab (also known as BMS-986016) is a fully human antibody against the lymphocyte activation gene 3 (LAG-3) product. LAG-3 (CD223) is a negative regulatory T-cell receptor implicated in the control of T-cell function in conventional and regulatory T cells. An immunoglobulin G4 (IgG4) isotype antibody including a stabilizing hinge mutation (S228P), relatlimab binds to the LAG-3 receptor on T cells with high affinity, thus blocking LAG-3 interactions with its ligand, the major histocompatibility complex (MHC) Class II, the peptide antigen presentation molecule recognized by CD4+ T-cells. When administered alone or in combination with other therapeutic immuno-oncology monoclonal antibodies, it is hoped that relatlimab may enhance the anti-tumor immune response via blocking the downregulatory pathway otherwise involved in maintaining T-cell quiescence.[15]

12.8. Packaging of Relatlimab

The study will supply to each site relatlimab injection drug product for intravenous (IV) administration.

Two formulations of relatlimab injection for IV administration are currently available as 100 mg/vial (10 mg/mL) in 10-cc vials. The same excipients are used for both formulations, except for one formulation with and the other without pentetic acid. A third relatlimab formulation (with pentetic acid) for IV administration is also currently available as 80mg/vial.

All three relatlimab formulations for IV administration are a colorless to pale yellow liquid, clear to

slightly opalescent, and light (few) particles (consistent in appearance to protein particulates) may be present. All three formulations are pH 5.0 to 6.0, with a container closure system of a 10cc Type1 flint glass vial stoppered with fluoropolymer film-laminate rubber stoppers and sealed with aluminum seals. The components of the 3 relatlimab formulations for IV administration are[15]:

- Relatlimab injection (100mg/vial) without pentetic acid: Relatlimab, histidine, histidine hydrochloride monohydrate, sucrose, polysorbate 80, water for injection.
- Relatlimab injection (100mg/vial or 80mg/vial) with pentetic acid: Relatlimab, histidine, histidine hydrochloride monohydrate, sucrose, pentetic acid, polysorbate 80, water for injection.

Note: In addition to the three relatlimab formulations for IV administration mentioned above, two additional relatlimab products are also available for subcutaneous administration (e.g. see Table 3.2.1-1 of the investigator brochure[15]). However, under this clinical study protocol as presently configured, there are no current plans for subcutaneous administration of relatlimab (which will continue to be administered as an intravenous infusion consistent with above protocol Section 9).

12.9. Handling and Storage of Relatlimab

Relatlimab drug product for intravenous administration should be stored at 2°C to 8°C (36°F to 46°F) with protection from light. Do not freeze the drug product.

The intravenous administration of relatlimab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours and a maximum of 4 hours of the total 24 hours can be at room temperature (15°C to 25°C; 59°F to 77°F) and exposed to room light. The maximum 4-hour period under room temperature and room light conditions includes the product administration period.[15]

12.10. Relatlimab Drug Accountability and Compliance Check

The investigator is responsible for ensuring accountability for relatlimab, including maintenance of drug accountability records.

Drug accountability records will appropriately document a full inventory relatlimab including:

- Confirmation of relatlimab delivery to the trial site
- A record of each dose of relatlimab dispensed
- The return of relatlimab provided by the study to the sponsor-investigator or designee, or documentation of destruction at the site (if drug destruction at the site is authorized in advance in writing by the sponsor-investigator or designee).

Records will specify relevant dates, quantities, batch numbers, use-by dates and patient numbers, as applicable.

The investigator, or designee, should maintain records that adequately document:

- That patients were provided the doses specified by the clinical trial protocol, and
- That all relatlimab provided by the study was fully reconciled.

13. SAFETY REPORTING OF ADVERSE EVENTS

13.1. General

Adverse events will be graded according to the NCI's Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0, dated November 27, 2017, currently locatable via the following URL:
<https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf>.

If events are not listed in the CTCAE, severity may be designated as mild, moderate, severe, life-threatening, or fatal which respectively correspond to Grades 1, 2, 3, 4, and 5 on the NCI CTCAE, with the following definitions:

- **Mild:** Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- **Moderate:** Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) such as preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc;
- **Severe:** Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL such as bathing, dressing and undressing, feeding self, using the toilet, taking medications;
- **Life-threatening:** Urgent intervention indicated to prevent risk of death present at the time of the event;
- **Fatal:** An event that results in the death of the patient.

Information on adverse events, whether serious or not, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported as described in the following sections.

Non-serious adverse events experienced by a participant will be collected and reported from initiation of nivolumab/relatlimab/ipilimumab, throughout the study; and until 100 days after patient's final study-indicated treatment with nivolumab, relatlimab or ipilimumab (whichever occurs last) or until initiation of another anticancer therapy – whichever occurs first. Participants who experience an ongoing adverse event possibly, probably or definitely related to a study procedure and/or study medication beyond 100 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible or not clinically significant by the investigator.

After informed consent but prior to initiation of nivolumab/relatlimab or nivolumab/ipilimumab, non-serious adverse events should be reported only if possibly, probably or definitely attributed by the patient's study physician to a protocol-mandated procedure or intervention.

After informed consent, any Serious Adverse Event (SAE) that occurs during the clinical study or within 100 days after a patient's last dose of protocol-indicated nivolumab, relatlimab or ipilimumab, regardless of causality to study drug, must be reported to the Coordinating Center in an expedited fashion as directed below (Reporting Procedures).

During the 30-day follow-up period, new onset, non-serious adverse events should only be recorded if, in the opinion of the investigator, there is a reasonable possibility the event is attributable to the investigational product. Non-serious adverse events related to the next phase of the patient's treatment should NOT be recorded. All serious adverse events occurring within

the 30-day follow-up period must be reported, regardless of suspected causality.

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB and the Coordinating Center of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

13.2. Risks Associated with Nivolumab

The most common adverse reactions (≥20%) in patients were:

- Nivolumab as a single agent: fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia, headache, abdominal pain, and vomiting.
- Nivolumab in combination with ipilimumab: fatigue, rash, diarrhea, nausea, pyrexia, vomiting, dyspnea, musculoskeletal pain, pruritus, abdominal pain, cough, arthralgia, decreased appetite, and upper respiratory infection.

A more detailed safety profile of nivolumab is provided in the investigator's brochure[17]; and in the product label[14], currently locatable online via the following:

Nivolumab (OPDIVO):
< https://packageinserts.bms.com/pi/pi_opdivo.pdf >.

13.3. Risks Associated with Relatlimab (BMS-986016)

- The current industry-sponsored clinical program is evaluating advanced solid tumors (advanced melanoma after previous progression on prior anti-PD1 therapy) in Study CA224020; relapsed-refractory hematological malignancies (Hodgkin lymphoma) in Study CA224022; advanced solid tumors (special focus in a Japanese population) in Study CA224034; and, in Study CA224048, 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).

  As of the respective clinical data cutoff dates (CA224020: 03-Jun-2019; CA224022: 26-Jun-2019; CA224034 and CA224048: 15-May-2019): 1348 subjects in total (1191 in study CA224020, 104 in CA224022, 29 in CA224034 and 24 in CA224048) have been treated with relatlimab in 4 ongoing Phase 1 and Phase 2a Bristol-Myers Squibb Company (BMS)-sponsored studies assessing the PK, efficacy, and safety of relatlimab alone or in combination with nivolumab or ipilimumab or BMS 986205 (IDO-1 inhibitor) in subjects with advanced solid tumors and hematological malignancies.[15]

- Across the 4 studies (CA224020, CA224022, CA224034 and CA224048), 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 maximum administered dose (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. 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).[15]

- The all-combination group of study CA224020 includes 1166 subjects treated with relatlimab and nivolumab. Drug-related AEs were reported in 739 (63.4%) subjects, with the most commonly reported (≥ 5% of subjects) being fatigue (14.5%), pruritus (9.1%), diarrhea (8.4%), asthenia (6.5%), rash (6.4%), nausea (6.2%), arthralgia (6.2%), hypothyroidism (6.3%) and increased lipase (5.9%).

  Grade 3 drug-related AEs were reported in 132 (11.3%) subjects, Grade 4 in 30 (2.6%) subjects, and Grade 5 in 1 (0.1%) subject. Grade 3 to 4 drug-related AEs were reported in at least 162 (13.9%) subjects and included increased lipase (3.2%), colitis, increased amylase (1.3% each), increased ALT (1.0%), pneumonitis (0.8%), diarrhea (0.9%), increased AST (0.5%), autoimmune hepatitis (0.4%), myocarditis, type 1 diabetes mellitus, gastritis, maculo-papular rash, hypophysitis, hepatitis, anaemia, asthenia, fatigue and mucosal inflammation (0.3% each).

  Drug-related SAEs were reported in 119 of the 1166 (10.2%) subjects treated with relatlimab and nivolumab in Parts B, C, and D. Grade 3 to 4 drug-related SAEs occurring in 3 or more subjects included pneumonitis, colitis, myocarditis, aspartate aminotransferase increase, autoimmune hepatitis, immune-mediated hepatitis, diarrhea, gastritis, hypophysitis, increased lipase, and type 1 diabetes mellitus. All SAEs, (all at a dose level of 80 mg relatlimab/240 mg nivolumab Q2W), were reversible and manageable by withholding study drug administration providing standard medical care, and/or following immune-related AE algorithms.

  In combination therapy (Parts B, C, and D), 22 Grade 1 and 37 Grade 2 infusion-related reactions were reported. There were no Grade 3 or higher infusion reactions reported. The overall frequency (5.1%) observed in Study CA224020 is similar to the frequency observed for nivolumab monotherapy. In patients receiving OPDIVO as a 60-minute intravenous infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. Refer to Section 5.9 of (OPDIVO USPI) for further details.[14] All events were manageable per updated protocol guidelines, and only 2 subjects required treatment discontinuation, in each case due to recurrent Grade 2 infusion related reactions.[15]

- A more detailed safety profile of relatlimab is provided in the investigator's brochure.[15]

13.4. Risks Associated with Ipilimumab

- The most common adverse reactions (≥5%) with ipilimumab as a single agent are fatigue, diarrhea, pruritus, rash, and colitis. Additional common adverse reactions at the 10 mg/kg dose (≥5%) include nausea, vomiting, headache, weight loss, pyrexia, decreased appetite, and insomnia.
- The most common adverse reactions (≥20%) with ipilimumab in combination with nivolumab are fatigue, rash, diarrhea, musculoskeletal pain, pruritus, nausea, cough, pyrexia, arthralgia, decreased appetite, abdominal pain, vomiting, and dyspnea.
- A more detailed safety profile of ipilimumab is provided in the product label[16], currently

locatable online via the following:

Ipilimumab (YERVOY):
< https://packageinserts.bms.com/pi/pi_yervoy.pdf >.

13.5. Potential Drug Induced Liver Injury (DILI)

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

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

AND

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

AND

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

13.6. Pregnancy

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

Via SAE reporting procedures (Section 13.9), the investigator must immediately report this event using either the MedWatch or appropriate Pregnancy Surveillance Form (provided upon request from BMS), or approved site SAE form.

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 MedWatch, Pregnancy Surveillance Form, or approved site SAE form.

Any pregnancy that occurs in a female partner of a male study participant (until such time that any protocol-required contraception is no longer required by protocol) should be reported using the MedWatch, Pregnancy Surveillance Form, or approved site SAE form via SAE reporting procedures (Section 13.9). In order for the sponsor-investigator 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.

13.7. Overdose

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

13.8. Definitions

13.8.1 **Adverse Event (AE)**
An adverse event is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

13.8.2 **Serious Adverse Event (SAE)**
A serious adverse event is an undesirable sign, symptom or medical condition which:

- Is fatal or life-threatening;
- Requires or prolongs inpatient hospitalization;
- Results in persistent or significant disability/incapacity;
- Constitutes a congenital anomaly or birth defect; or
- Jeopardizes the participant and requires medical or surgical intervention to prevent one of the outcomes listed above.

Events **not** considered to be serious adverse events are hospitalizations for:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures.
- Elective or pre-planned treatment for a pre-existing condition that did not worsen.
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in an inpatient admission.
- Respite care.

13.8.3 **Expectedness**
Expected: Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Unexpected: An adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

13.8.4 **Attribution**
Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely – The AE is doubtfully related to the study treatment.
- Unrelated – The AE is clearly NOT related to the study treatment.

13.9. Reporting Procedures

13.9.1 General Considerations

All adverse events will be captured on a centralized electronic case report form called ON-line Clinical Oncology Research Environment = Oncore:
< http://www.vicc.org/ct/research/oncore.php >.

Oncore is a highly secure, web based, cancer specific, and customizable system that provides fully integrative clinical data management and study administration capabilities developed in an ongoing collaborative effort with NCI designated Comprehensive Cancer Centers. It fully integrates study administration functionality including protocol tracking, patient registration, NCI reporting, review committee tracking, and SAE tracking, with clinical data management functionality including electronic case report forms (eCRF) design, clinical data capture, protocol and regulatory compliance monitoring. Specified members at each participating site will submit all regulatory documents to the Coordinating Center.

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs, and avoid colloquialisms and abbreviations. If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g. record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death." Deaths that occur during the protocol specified adverse event reporting period that are attributed by the investigator solely to progression of disease should be recorded only in the study eCRF and not reported as an SAE.

A pre-existing medical condition is one that is present prior to initiation of protocol specified treatment. Such conditions should be reported as medical and surgical history. A pre-existing medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a patient is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a patient is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for pre-existing conditions; or
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study; or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

13.9.2 **Serious Adverse Events**

All serious adverse events, regardless of causality to study drug, will be reported to the Principal Investigator and/or the Study Coordinator at each institution, and also to the Coordinating Center.

All serious adverse events must be reported to the Coordinating Center within 24 hours of the investigator becoming aware of the event. Events should be reported using the Vanderbilt SAE form, located in the packet of supplemental forms. This form must be fully completed and emailed (preferred), faxed, or scanned to:

ATTN: VICC CTSR Personnel
EMAIL: Coordinating.Center@vumc.org
FAX: (615) 875-0040

If SAE documents are faxed, the Coordinating Center must be notified via email as well. Follow-up information must also be reported within 24 hours of receipt of the information by the investigator.

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 material new information becomes available, a follow-up SAE report should be sent. All SAEs should be followed to resolution or stabilization.

The Coordinating Center will disseminate information regarding serious adverse events to the participating sites as described in FDA guidance only in the case that the event(s) is/are unexpected, and is/are believed to be related (i.e., possibly, probably or definitely) to the study device/medication.

All Serious Adverse Events (SAEs), whether related or not related to study drug, that occur following the patient's written consent to participate in the study through 100 days after the patient's last dose of protocol-indicated nivolumab, relatlimab or ipilimumab must be reported to the Coordinating Center (which will report such event also to BMS Worldwide Safety).

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

Vanderbilt University Medical Center acting as the Coordinating Center will be responsible for reporting of events to BMS and the FDA as appropriate (outlined below).

13.9.3 **Institutional Review Board**

All adverse events and serious adverse events will be reported to the IRB per current institutional standards. If an adverse event requires modification of the informed consent, these modifications will be provided to the IRB with the report of the adverse event. If an adverse event requires modification of the study protocol, these modifications will be provided to the IRB as soon as is possible.

13.9.4 **Food and Drug Administration (FDA)**

In this trial, unexpected serious adverse events believed to be definitely, probably, or possibly related to study treatment (as determined by the sponsor-investigator) will be reported to the FDA via MedWatch 3500A, currently available at:
< https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf >.
Submissions by the sponsor can be submitted via fax or email and must be addressed to the Regulatory Project Manager in the FDA review division that has responsibility for review of the IND. The Coordinating Center will be responsible for correspondence regarding adverse events with the FDA for all participating sites.

13.9.5 Bristol-Myers Squibb (BMS)

Vanderbilt University Medical Center acting as the coordinating center will be responsible for reporting to BMS any Serious Adverse Event (SAE), whether related or not related to study drug, that occurs during the SAE reporting period (as defined above in Section 13.9.2).

Within 24 hours after the sponsor-investigator (or designee) initially receives the safety information, the Coordinating Center will report the SAE to BMS on the MedWatch, Pregnancy Surveillance Form (provided upon request from BMS), or site SAE form approved by BMS; via email or facsimile to the following:

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: 609-818-3804

Follow-up SAE reports received by the Coordinating Center should be sent within 24 hours or 1 Business Day to BMS using the same procedure used for transmitting the initial SAE report.

The Sponsor will reconcile the SAE 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.

14. CORRELATIVE STUDIES

14.1. Overview

Patients with MHC-II expressing melanomas, defined as those with ≥5% expression on tumor cells by pathologist assessment using immunohistochemistry analysis of MHC-II/HLA-DR, will be assigned to nivolumab and relatlimab, whereas those who are negative (<5%) are assigned to nivolumab and ipilimumab. This will be assessed from fresh or archival tissue obtained since any other systemic therapy. Additional tissue for correlative assessment will be collected or requested according to **Table 5**:

TABLE 5: Samples to be Requested/Collected for Correlative Studies

Tissue type	Screening	On-Treatment							Follow-up	
	Pre-treatment (≤28d)	**Arm A: MHC-II positive** Nivolumab + Relatlimab (cycle = 28 days[1])		**Arm B: MHC-II negative** Nivolumab + Ipilimumab (4 initial cycles = 21 days[2]) Nivolumab monotherapy (Subsequent cycles = 28 days[3])					**Arm A and Arm B**	
		4 week cycles		**3 week cycles**				**4 week cycles**		
		Cycles 1+	Cycles 1&2	Cycle 1			Cycles 2, 3 & 4	Cycles 5+	EOT (</-14d)	30d F/U (30-37d)
		Day 1 (+1-3d)	Day 15	D 1	D 8	D 15	Day 1 (+1-3d)	Day 1 (+1-3d)		
Archival or fresh tumor tissue[4]	X									
Fresh tumor biopsy[5]			c2d15 (+/-7d)				c3d1 (+/-7d)			
Peripheral Blood[6]		c1d1, c4d1, c14d1	c1d15, c2d15	X		X	c3d1	c5d1, c15d1	X	X

[1] Arm A cycle (28 days): On Day 1 of each 28-day cycle, all patients are scheduled to receive nivolumab and relatlimab intravenously.

[2] Arm B 4 initial cycles (21 days): On Day 1 of cycles 1-4, all patients are scheduled to receive nivolumab and ipilimumab intravenously.

[3] Arm B subsequent cycles (28 days): Starting with cycle 5, patients will receive nivolumab only, intravenously every 4 weeks.

[4] Archival or fresh tumor tissue: Mandatory tissue at baseline required for analysis of tumor for MHC-II status (</= 28d prior to c1d1). Tumor tissue must be received at VUMC for MHC-II testing in order for the participant to be enrolled in the correct arm of the study. (Note the Tissue Requisition Form in the Lab Manual.) Archival tissue [paraffin block(s) or unstained slides from paraffin block(s)] from the primary tumor and/or a metastatic site must be available prior to initiating treatment, or patient must be willing to undergo a fresh pre-treatment standard of care tumor biopsy. Within 28 days prior to initiating treatment, the screening team must have documentation that an archival or fresh tumor specimen has been requested from a local or outside facility. Physical possession and centralized testing of requested tissue is required prior to initiating study treatment because all patients in this study are being stratified by MHC-II status, based on centralized testing performed at Vanderbilt.

[5] Fresh biopsy of lesion amenable to safe biopsy from a primary lesion or metastatic site, performed approximately 6 weeks following initiation of protocol-indicated treatment: Arm A: Fresh biopsy on Cycle 2, Day 15 (±7 days); Arm B: Fresh biopsy on Cycle 3, Day 1 (±7 days).

[6] Peripheral blood samples for exploratory analysis including biomarker and possible PD research to be obtained at time points indicated, consistent with Section 7. Note that 2 of these time points also correspond to days when fresh tumor biopsy is also intended (i.e. Cycle 2, Day 15 in Arm A; and Cycle 3, Day 1 in Arm B). To accommodate scheduling, a ±7 day window for the fresh on-study biopsy is allowed; therefore, a similar ±7 day window is also applicable to the research blood draws scheduled for these two time points, in order for the research blood to be collected ideally on the same day as the fresh biopsy (**and ideally PRIOR to the biopsy procedure**).

14.2. Tumor Tissue

MHC-II testing for treatment assignment will be tested using archival tissue obtained since last systemic therapy or using fresh biopsies. Fresh biopsies prior to treatment will be obtained whenever possible, even if archival tissue is available. Available tissue will also be tested for RNA sequencing, immunofluorescence testing (including PD-L1, CD8, CD4, and others).

When at all reasonably possible, the same archival tissue originally used for initial screening should also be used for additional correlative analysis. Fresh biopsies are still encouraged even if sufficient archival tissue for MHC-II testing is available.

If residual archival tumor tissue is unavailable or insufficient from the time point previously used for initial MHC-II testing, then alternative tissue from the most recent biopsy/specimen should be used for correlative research.

Every reasonable effort should be made to obtain additional pre-treatment archival slides to assess tumor heterogeneity and dynamic changes over time.

14.3. Peripheral Blood

Blood from each patient at Pre-Treatment (C1D1), On-Treatment (as specified in section 7), and at EOT/Progression is **required**. Subjects who discontinue study related therapy can continue to have correlative blood samples collected.

Approximately 47mL of peripheral blood is anticipated to be drawn for correlative research at each of 7 time points in Study Arm A and Study Arm B: c1d1, c1d15, c2d15, c4d1, c14d1, EOT, and 30d F/U (Arm A); and c1d1, c1d15, c3d1, c5d1, c15d1, EOT, and 30d F/U (Arm B).

14.4. Specimen Banking

Any leftover study tissue or blood samples may be stored for future research studies. The subjects will consent to the future use of samples in the consent form for the study. All future use as part of residual or repository specimens collected in this trial for purposes not prospectively defined will require review and approval by the Institutional Review Board according to its established policies, whether the specimens are stored in a central site or at a local institution or in a virtual repository.

15. DATA SAFETY AND MONITORING

15.1. Data Management and Reporting

Participating institutions will be collaborating with Vanderbilt for patient accrual. Data will be collected using a centralized electronic case report form called ON-line Clinical Oncology Research Environment = Oncore (http://www.vicc.org/ct/research/oncore.php). Oncore is a highly secure, web based, cancer specific, and customizable system that provides fully integrative clinical

data management and study administration capabilities developed in an ongoing collaborative effort with NCI designated Comprehensive Cancer Centers. It fully integrates study administration functionality including protocol tracking, patient registration, NCI reporting, review committee tracking, and SAE tracking, with clinical data management functionality including electronic case report forms (eCRF) design, clinical data capture, protocol and regulatory compliance monitoring. Also the system is capable of storing basic protocol information (e.g., IRB approval dates, dates for annual renewals) and clinical trial research data. Oncore allows the investigator to define specific protocol requirements and generate data collection forms. Creation of the data collection form is done with a single button click after the parameters of an individual protocol have been specified. Oncore permits specification of study protocols, management of patient enrollment, clinical data entry and viewing, and the generation of patient or study-specific reports based on time stamping. OnCore is embedded with a comprehensive domain repository of standard reference codes and forms to promote standardization. The sources for the repository include CDUS, CTC, CDEs from NCI, ICD, MedDRA and various best practices from contributing NCI-designated Comprehensive Cancer Centers. OnCore provides several reporting features specifically addressing NCI Summary 3 and Summary 4 and other reporting requirements. Data may also be exported in a format suitable for import into other database, spreadsheets or analysis systems (such as SPSS). This system will be used to manage all VICCC clinical trials data. OnCore is maintained and supported in the VICC Clinical and Research Informatics Resource.

15.2. Meetings

This study will be monitored by the VICC melanoma research team, which includes medical oncologists, research nurses, data managers, and regulatory specialists. The team meets on a regular basis to discuss AEs/SAEs, accrual, compliance, safety issues, adherence to protocol, etc. pertaining to cancer studies conducted by the team. In addition, meetings between the Coordinating Center and research teams at participating sites may be scheduled as necessary, in order to discuss relevant issues related to the trial (e.g. AEs/SAEs, accrual, compliance, safety issues, adherence to protocol, reviews).

15.3. Monitoring

The Vanderbilt-Ingram Cancer Center (VICC) oversees patient safety and data monitoring for its investigator-initiated and NIH-NCI funded clinical trials through its Data and Safety Monitoring Committee (DSMC). The purpose of the DSMC is to ensure the efficient implementation and management of the VICC Data and Safety Monitoring Plan (DSMP). The Committee maintains authority to intervene in the conduct of studies as necessary to ensure clinical research performed at VICC achieves the highest quality standards.

The VICC DSMC meets on a quarterly basis and ad hoc to discuss data and safety monitoring of clinical trials and to oversee the VICC DSMP. Internal audits for compliance with adverse event reporting, regulatory and study requirements, and data accuracy and completion are conducted according to the VICC DSMP according to study phase and risk. The committee reviews all serious adverse events (SAE) on Vanderbilt sponsored investigator-initiated studies on a quarterly basis and provides DSMC SAE review reports to the Vanderbilt IRB.

15.4. Data Handling and Record Keeping

An electronic case report form (eCRF) is required and must be completed for each included participant. The completed dataset should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from Vanderbilt.

To enable evaluations and/or audits from health authorities and Vanderbilt, each site investigator agrees to keep records including: The identity of all participants (sufficient information to link

records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. To comply with international regulations, the records should be retained by the investigator in compliance with regulations.

Queries resulting from review of the eCRFs will be generated for the site and corrections will be made by the study site personnel. This will be done on an ongoing basis.

16. REGULATORY CONSIDERATIONS

16.1. Protocol Review and Amendments

Information regarding study conduct and progress will be reported to the Institutional Review Board (IRB) per current institutional standards at each participating study site.

The trial will not be initiated until there is approval by the local IRB of the protocol, informed consent document and any other material used to inform the patient about the nature of the trial. The IRB should be duly constituted according to local regulatory requirements. The investigator will inform the IRB of the progress of the trial at least yearly.

Any changes to the protocol will be made in the form of a written amendment and must be approved by the sponsor-investigator and the IRB of each institution prior to local implementation. All amendments will also be submitted as necessary to the FDA by the sponsor-investigator (or designee).

Protocol changes to eliminate an immediate hazard to a trial patient may be implemented by the investigator immediately. The investigator must then immediately inform the local IRB; and the sponsor-investigator (or designee), who will communicate as appropriate with the FDA.

The sponsor-investigator (or designee) is responsible for the coordination and development of all protocol amendments. Once approved by the sponsor-investigator, Vanderbilt will disseminate this information to the participating centers.

16.2. Informed Consent

The investigator (or designee) will explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary, that s/he may withdraw from the study at any time, and that withdrawal of consent will not affect subsequent medical treatment or relationship with the treating physician(s) or institution. The informed consent will be given by means of a standard written statement, written in non-technical language, which will be IRB approved. The subject should read and consider the statement before signing and dating it, and will be given a copy of the document. No subject will enter the study or have study-specific procedures done before his/her informed consent has been obtained.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the written informed consent document (or a separate document to be given in conjunction with the consent document) will include a subject authorization to release medical information to the study sponsor and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the study, including subjects' medical history.

16.3. Ethics and GCP

This study will be carried out in compliance with the protocol and Good Clinical Practice, as described within:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees to adhere to the instructions and procedures described within the above and thereby to adhere to the principles of Good Clinical Practice with which the above conform.

16.4. Confidentiality

It is the responsibility of the investigator to ensure that the confidentiality of all patients participating in the trial and all of their medical information is maintained. Case report forms (CRFs) and other documents submitted to regulatory authorities must not contain the name of a trial patient. All patients in the trial will be identified by a unique identifier which will be used on all CRFs and any other material submitted to regulatory authorities. All case report forms and any identifying information must be kept in a secure location with access limited to the study staff directly participating in the trial.

16.5. Study Termination

The sponsor-investigator reserves the right to terminate the study at any site and at any time. Reasons for study termination may include, but are not limited to, the following:

- Investigator non-compliance with the protocol, GCP or regulatory requirements.
- Insufficient enrollment.
- Safety concerns.
- Decision by suppliers to modify or discontinue the availability, development or manufacture of protocol-indicated treatment.
- A request to discontinue the study by the IRB or FDA.

The sponsor-investigator will promptly notify investigators, the IRB and FDA if the study is terminated for any reason.

17. STUDY COORDINATION

17.1. Trial Compliance

This is an investigator-initiated study. The Principal Investigator, Elizabeth Davis, M.D. (who may also be referred to as the Sponsor-Investigator), is conducting the study as acting as the sponsor. Therefore, the legal and ethical obligations of the Principal Investigator include both those of a sponsor and those of a principal investigator.

Vanderbilt is the Coordinating Center for this study. All aspects of the study will be carefully monitored by the Coordinating Center for compliance with applicable government regulations with respect to current GCP and standard operating procedures.

17.2. Changes to Protocol and Informed Consent Document

Any change to the protocol and informed consent document must be reviewed and approved by the Coordinating Center before being submitted to the Institutional Review Board/Independent Ethics Committee at participating institutions. Amendments should not be implemented until all necessary approvals have been obtained, except when necessary to eliminate an immediate hazard to study subjects.

17.3. Protocol Deviations

The Coordinating Center is responsible for implementing and maintaining quality assurance and quality control to ensure that studies are conducted according to the protocol, GCP, and all applicable regulatory requirements. A protocol deviation is any noncompliance with the protocol. Noncompliance can be on the part of the study participant, the investigator, or the study site staff. Deviations to the protocol are not permitted except when necessary to eliminate an immediate hazard to study subjects.

17.4. Monitoring and Quality Assurance

As the Coordinating Center, Vanderbilt has responsibilities to health authorities to take all reasonable steps to ensure the proper conduct of the study with regard to ethics, protocol adherence, integrity, validity of the data recorded on the CRFs, and adherence to regulations regarding Good Clinical Practice (GCP) and the protection of human subjects.

In accordance with applicable regulations, GCP, and Coordinating Center procedures, sites will be contacted prior to the start of the study to review with site staff the protocol, study requirements, and site responsibilities to satisfy regulatory, ethical, and Coordinating Center requirements.

During the course of the study, the Coordinating Center will routinely monitor the sites for protocol compliance, compare CRFs with original source documents from individual subjects, assess drug accountability, and ensure that the study is being conducted according to the pertinent regulatory requirements. The review of subject medical records will be performed in a manner to ensure that subject confidentiality is maintained. Monitoring visits will primarily be conducted remotely, and sites are required to provide the appropriate source documentation in order to allow for proper oversight per GCP. Investigators must agree to cooperate with the Coordinating Center to ensure that any problems detected are resolved.

17.5. Data Verification

Data will be collected via eCRFs and entered into the database per Coordinating Center guidelines. The Coordinating Center will check data accuracy by performing source data verification. Source data verification is a direct comparison of the entries made on the CRFs against the appropriate source documentation. This will be conducted remotely, with the possibility of on-site verification periodically. Discrepancies in the data will be brought to the attention of the investigator and/or the investigator's staff. Any necessary corrections will be made directly to the eCRFs or via queries by the investigator and/or the investigator's staff.

17.6. Study Documentation

Each participating site is responsible for submitting copies of all relevant regulatory documentation to the Coordinating Center. The required documents include, but are not limited to the following: local IRB approvals (i.e., protocol, consent form, amendments, patient brochures, recruitment material, etc.), each participant's informed consent, enrollment form, eligibility checklist, summary of unanticipated problems or protocol deviations, and documentation of expertise of the investigators. The Coordinating Center will provide each participating site with a comprehensive list of the necessary documents. Specified members at each participating site will submit all pertinent regulatory documents to the Coordinating Center, for storage in a secure location. It is the responsibility of the participating sites to maintain copies of all documentation submitted to the Coordinating Center.

17.7. Closure of the Study

The Coordinating Center reserves the right to discontinue a site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

17.8. Records Retention

U.S. FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by each Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the study is discontinued and the U.S. FDA and the applicable national and local health authorities are notified.

Following closure of the study, each participating center will maintain a copy of all site study records in a safe and secure location. The Coordinating Center will inform the investigator at each site at such time that the records may be destroyed.

17.9. Publication

It is understood that any manuscript or releases resulting from the collaborative research must be approved by the sponsor-investigator and will be circulated to applicable participating sites/investigators prior to submission for publication or presentation.

18. STATISTICAL CONSIDERATIONS

18.1. Primary Endpoint

To evaluate the efficacy, measured by change in activated GZMB+ CD8+ T-cell density intratumorally, of two immunotherapy regimens in patients with advanced melanoma. Patients with MHC-II (+) melanoma receive nivolumab plus relatlimab treatment. Patients with MHC-II (-) melanoma receive nivolumab plus ipilimumab treatment.

18.2. Sample Size and Power

The primary endpoint for this study is change in GZMB+ CD8+ T cell infiltration. A total sample size of 36 with 18 in each arm will provide 83% power to detect a difference in mean activated CD8+ T cell density change of one standard deviations (e.g., 1 SD=1000 counts/mm^2 is roughly the effect size for doubling T cell count), with a two-sided significance level of 0.05. Assuming a 10% dropout rate, a total number of 40 patients is planned for enrollment in the study to ensure the study has adequate statistical power for the primary analysis.

18.3. Secondary Endpoints

Efficacy for each arm: response rate as measured by RECIST 1.1, progression free survival, and overall survival. Survival statistics will be assessed descriptively for each arm and summarized with median, 1 year, and 2 year landmark analyses.
Safety: safety and tolerability of nivolumab plus relatlimab in patients with MHC-II (+) melanoma, and of nivolumab plus ipilimumab in patients with MHC-II (-) melanoma.

18.4. Statistical Analysis Plan

Patient demographics/other baseline characteristics will be listed by patient and/or summarized descriptively by each arm. Categorical data will be presented as frequencies and percentages. For continuous data, summary statistics will be presented. Between-group differences will be assessed with t-test based on a continuous variable. Nonparametric counterparts, Wilcoxon rank sum test, will be used when assumptions for parametric methods are not met. Binary and categorical data will be analyzed with chi-squared test or Fisher's exact test. Multivariable analysis will be performed using linear regression model, where the outcome variable is the density of activated CD8+ T cell post-treatment and the explanatory variable is the MHC-II status, adjusted for baseline T cell density. Median PFS and median OS will be estimated with 95% confidence intervals. If the median has not be reached by the end of the follow-up, mean survival will be reported instead. Kaplan-Meier curves will be constructed by MHC-II status. Multiple comparison issues will be corrected using the Bonferroni's approach. All statistical analysis will be performed using R 3.4.2 or a newer version.

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APPENDIX 1

Cockcroft-Gault Formula

The following may be used for calculating the estimated creatinine clearance rate (eC_{CR}) using the Cockcroft-Gault formula[18]. Additionally, the use of on-line calculators or formulas which are institutional standards for eC_{CR} and differ slightly may also be used consistently throughout the study. The calculations and results must be documented in the patient's chart or research record.

When serum creatinine is measured in mg/dL:

$$eC_{CR} = \frac{(140 - \text{Age in years}) \cdot \text{Weight (in kilograms)} \cdot [0.85 \textit{ if Female}]}{72 \cdot \text{Serum Creatinine (in mg/dL)}}$$

When serum creatinine is measured in µmol/L:

$$eC_{CR} = \frac{(140 - \text{Age in years}) \cdot \text{Weight (in kilograms)} \cdot \text{Constant}}{\text{Serum Creatinine (in µmol/L)}}$$

Where Constant is 1.23 for men and 1.04 for women.

APPENDIX 2

ECOG Performance Status[19]

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

APPENDIX 3

New York Heart Association (NYHA) Functional Classification[20]

NYHA Class	Symptoms
I	No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

Abbreviations: NYHA = New York Heart Association

APPENDIX 4
Acceptable Contraception

For purpose of this study, acceptable birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective and include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[1]:
  - oral
  - injectable
  - implantable[2]
- Intrauterine device (IUD)[2]
- Intrauterine hormone-releasing system (IUS)[2]
- Bilateral tubal occlusion[2]
- Vasectomised partner[2,3]
- Sexual abstinence[4]

For purpose of this study, acceptable birth control methods which may not be considered as highly effective that result in a failure rate of more than 1% per year include:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide[5]
- Cap, diaphragm or sponge with spermicide[5]

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[1] Hormonal contraception may be susceptible to interaction with the investigational medicinal product (IMP), which may reduce the efficacy of the contraception method.
[2] Contraception methods that in the context of this guidance are considered to have low user dependency.
[3] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
[4] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.
[5] A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

Source: Clinical Trial Facilitation Group[21] (CTFG), 2014.

A woman of childbearing potential (WOCBP) must agree to use 2 methods of acceptable contraception (that are included in the above table in this Appendix 4) with one method highly effective and the other method either highly effective or less highly effective, from the time she signs consent, and until at least 165 days (24 weeks) after her final dose of nivolumab, relatlimab or ipilimumab.

A man able to father children who has a female partner of childbearing potential must agree to use 2 methods of acceptable contraception (that are included in the above table in this Appendix 4) with one method highly effective and the other method either highly effective or less highly effective, from the time he signs consent, and until at least 225 days (33 weeks) after his final dose of nivolumab, relatlimab or ipilimumab.

A woman of childbearing potential participating in the study must have a negative serum pregnancy test during screening and a negative serum or urine pregnancy test ≤ 72 hours prior to her first dose of protocol-indicated treatment on Cycle 1, Day 1.

A female is considered to be a "woman of childbearing potential" (WOCBP) following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP:

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

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

A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause (if menopausal status is considered with respect to contraception required by the study).

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

- 1 week minimum for vaginal hormonal products (rings, creams, gels);
- 4 week minimum for transdermal products;
- 8 week minimum for oral products.

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

Male patients able to father children are defined as those who are not surgically sterile (i.e. patient has not had a vasectomy).

If able to father children, male participants with a female partner of childbearing potential must agree to the following:

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Inform female partner(s) to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 225 days after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 225 days after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 225 days after the end of study treatment.

A trial physician or clinical designee shall counsel female patients of childbearing potential, and male patients able to father children who have a female partner of childbearing potential, regarding the importance of pregnancy prevention, the implications of an unexpected pregnancy, and the use of acceptable contraception. At a minimum, applicable patients must agree to the consistent and correct use of at least one method of acceptable contraception, as listed in the above table in Appendix 4.

APPENDIX 5

Response Evaluation Criteria in Solid Tumors (RECIST v1.1)[22]

Measurability of tumor at baseline

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

Measurable:

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

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

Malignant lymph nodes: To be considered pathologically enlarged *and* measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable:

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

Special considerations regarding lesion measurability:

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

- "Cystic lesions" thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment

- Tumor lesions situated in a previously irradiated area, or other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Specifications by methods of measurements

Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.
- Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.
- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following CR or surgical resection is an endpoint.
- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response.

- Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or SD in order to differentiate between response (or SD) and progressive disease.

Tumor response evaluation
To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. Response criteria are listed in **Table 6** and **Table 7**:

TABLE 6: Response Criteria for Evaluation of *TARGET* Lesions

	Evaluation of Target Lesions
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression.)
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

TABLE 7: Response Criteria for Evaluation of *NON-TARGET* Lesions

	Evaluation of Non-target Lesions
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis)
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression.)
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Evaluation of Best Overall Response

It is assumed that at each protocol specified time point, a response assessment occurs. **Table 8** provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

TABLE 8: Overall Response Status for Patients with Baseline Measurable Disease

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

Abbreviation: CR, complete response; NE, non-evaluable; PD, progressive disease; PR, partial response; SD, stable disease

The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of CR or PR IS NOT required:

Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Best response determination in trials where confirmation of CR or PR IS required:

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as shown in **Table 9**.

TABLE 9: Best Overall Response when Confirmation of CR and PR Required

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[1]
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

Abbreviation: CR, complete response; NE, non-evaluable; PD, progressive disease; PR, partial response; SD, stable disease

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

APPENDIX 6

Guidelines for the Management of Immune-Related Adverse Events (irAEs)

The following adverse event management algorithms in this appendix are obtained from Version 18 of the Nivolumab Investigator Brochure, dated 25 June 2019.

These general guidelines constitute guidance to the Investigator. The guidance applies to all immuno-oncology (I-O) agents and regimens.

Where applicable the Approved Label should be used in combination with the protocol and IB for guidance around dose modifications and discontinuation.

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

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

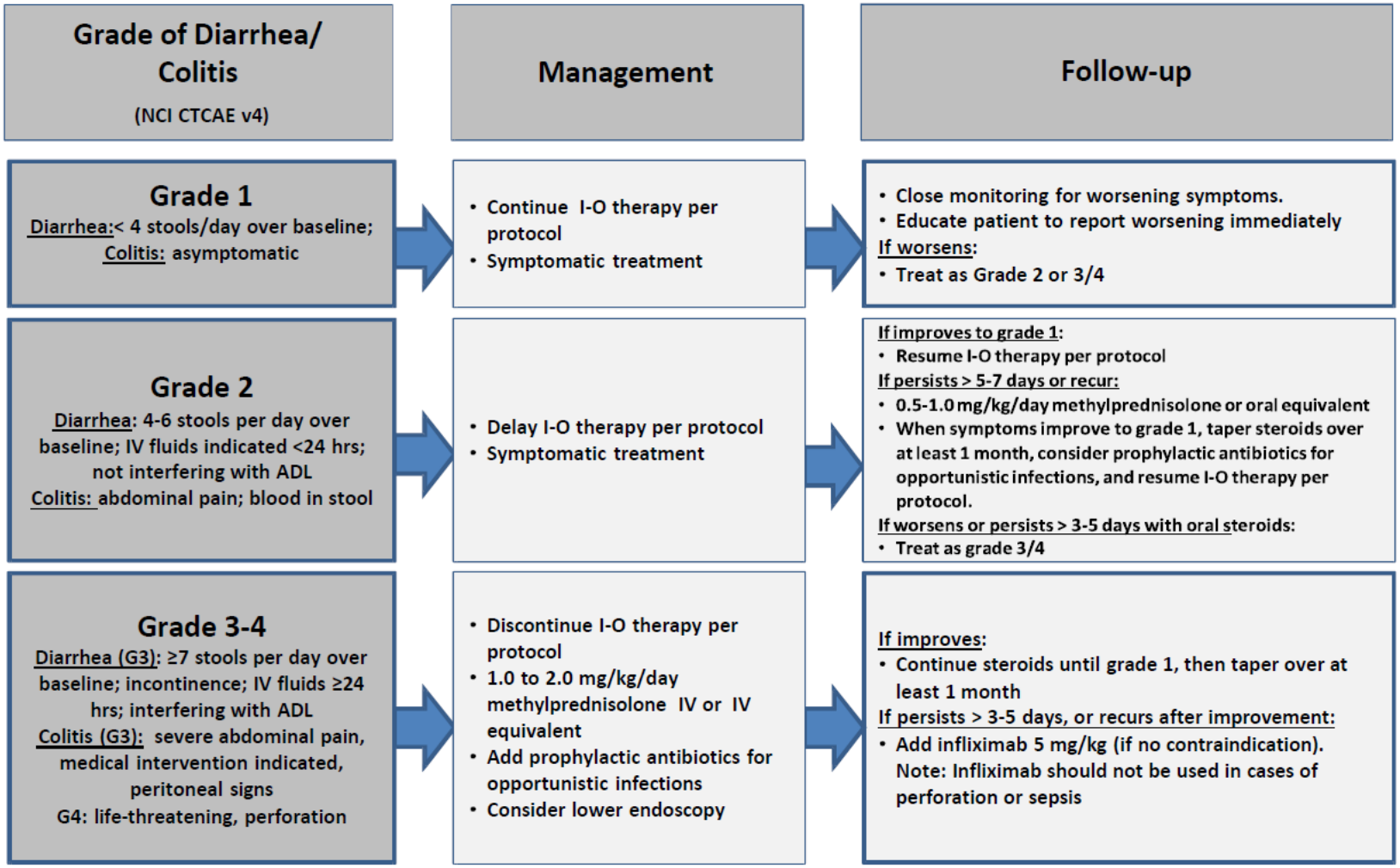
Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

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

Investigators should refer to the most current version of the IB or Approved Label for current recommendations for management of a specific Adverse Event of interest.

GI Adverse Event Management Algorithm

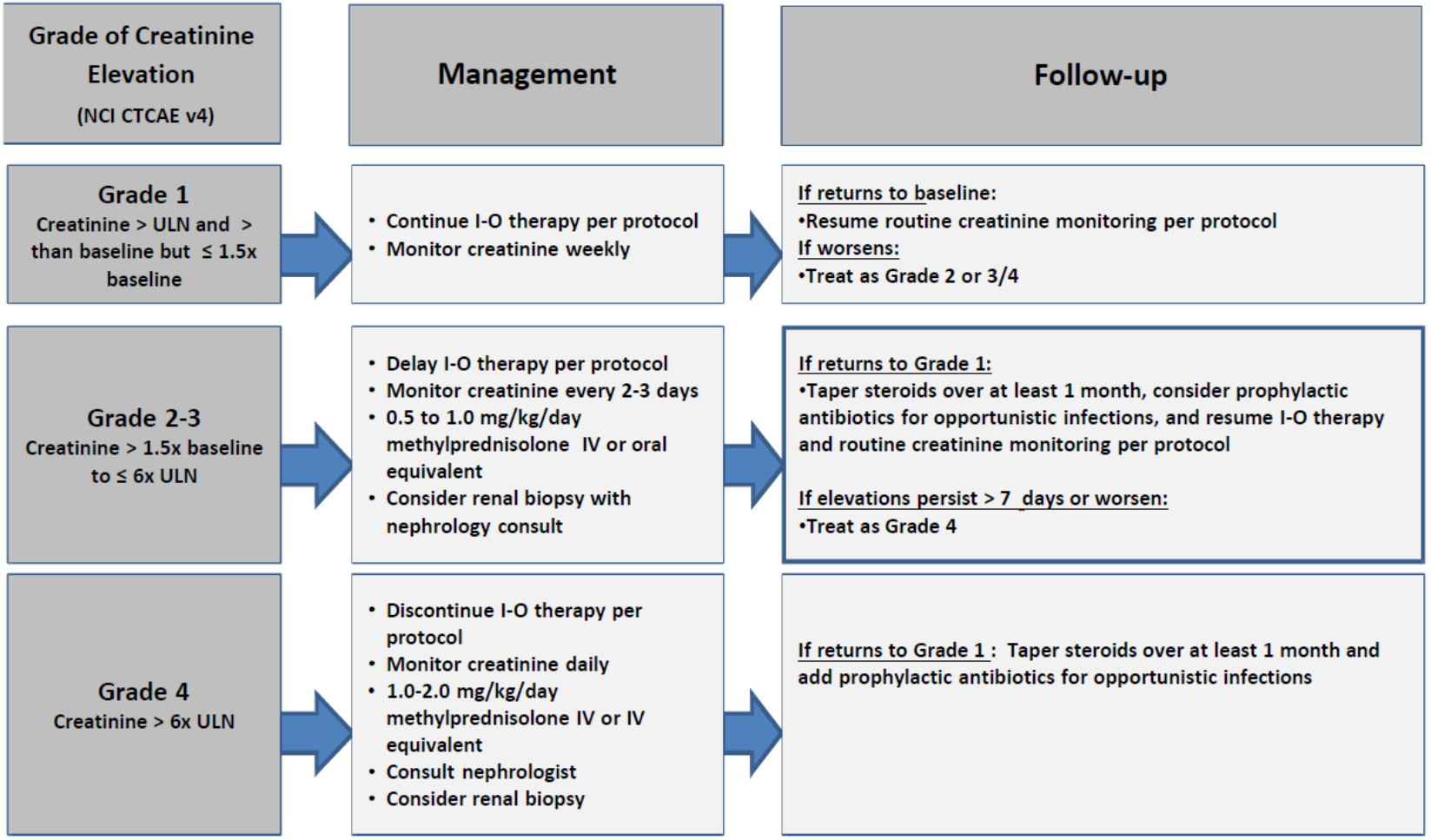
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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

Renal Adverse Event Management Algorithm

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



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

Pulmonary Adverse Event Management Algorithm

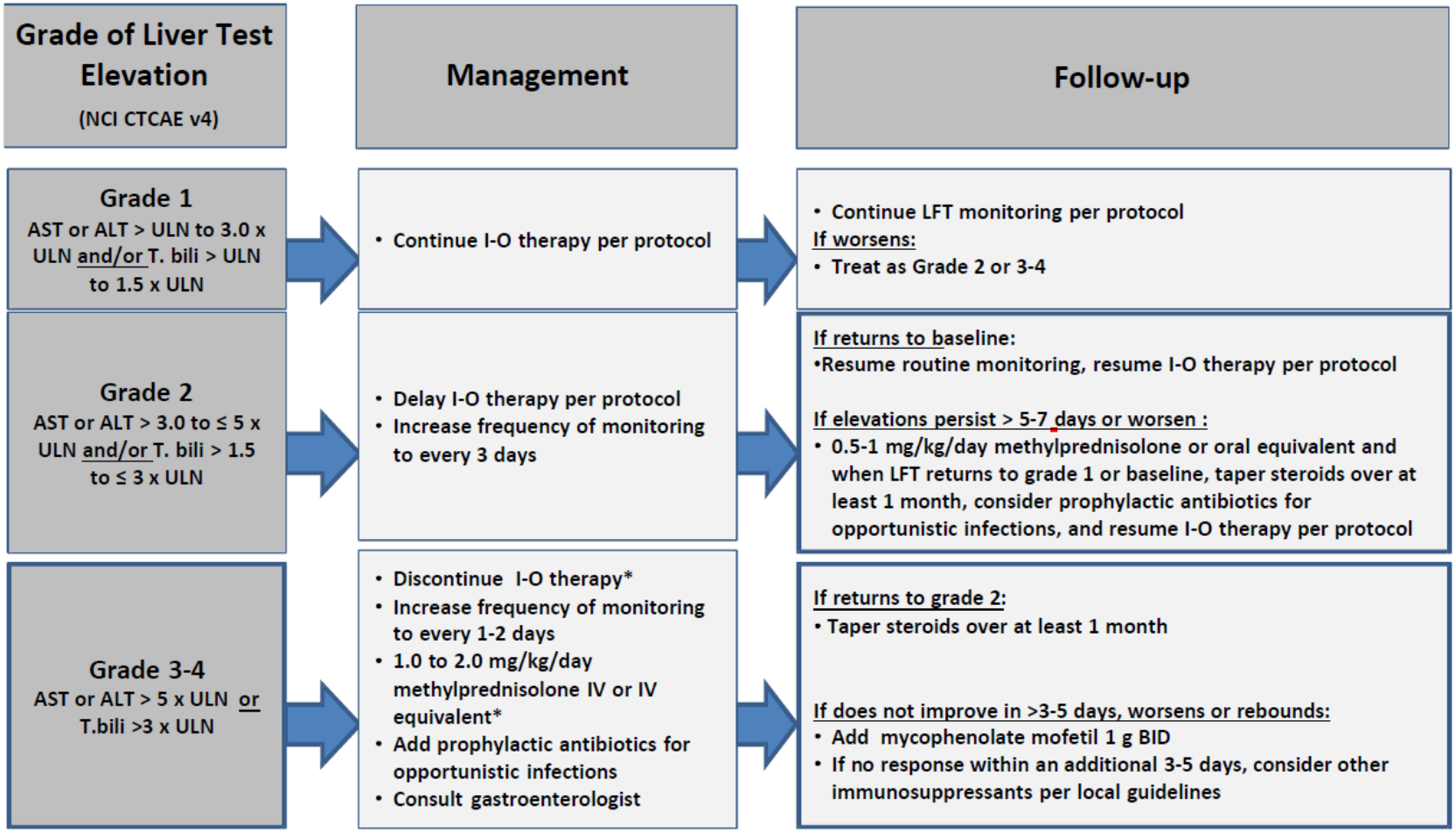
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy , lung biopsy	• Re-image every 1-3 days If improves: • When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics If not improving after 2 weeks or worsening: • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression

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

Hepatic Adverse Event Management Algorithm

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

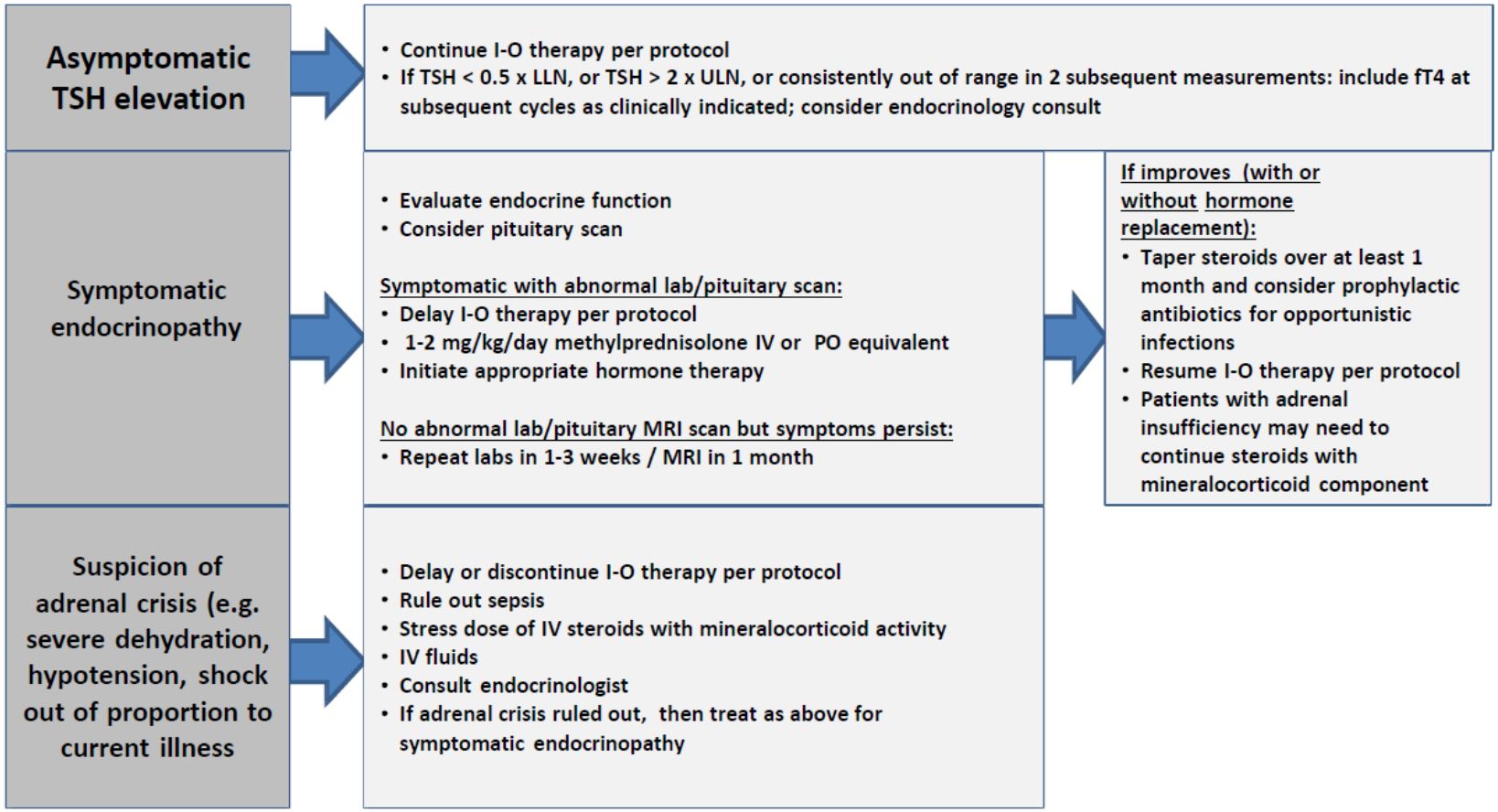


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

Endocrinopathy Adverse Event Management Algorithm

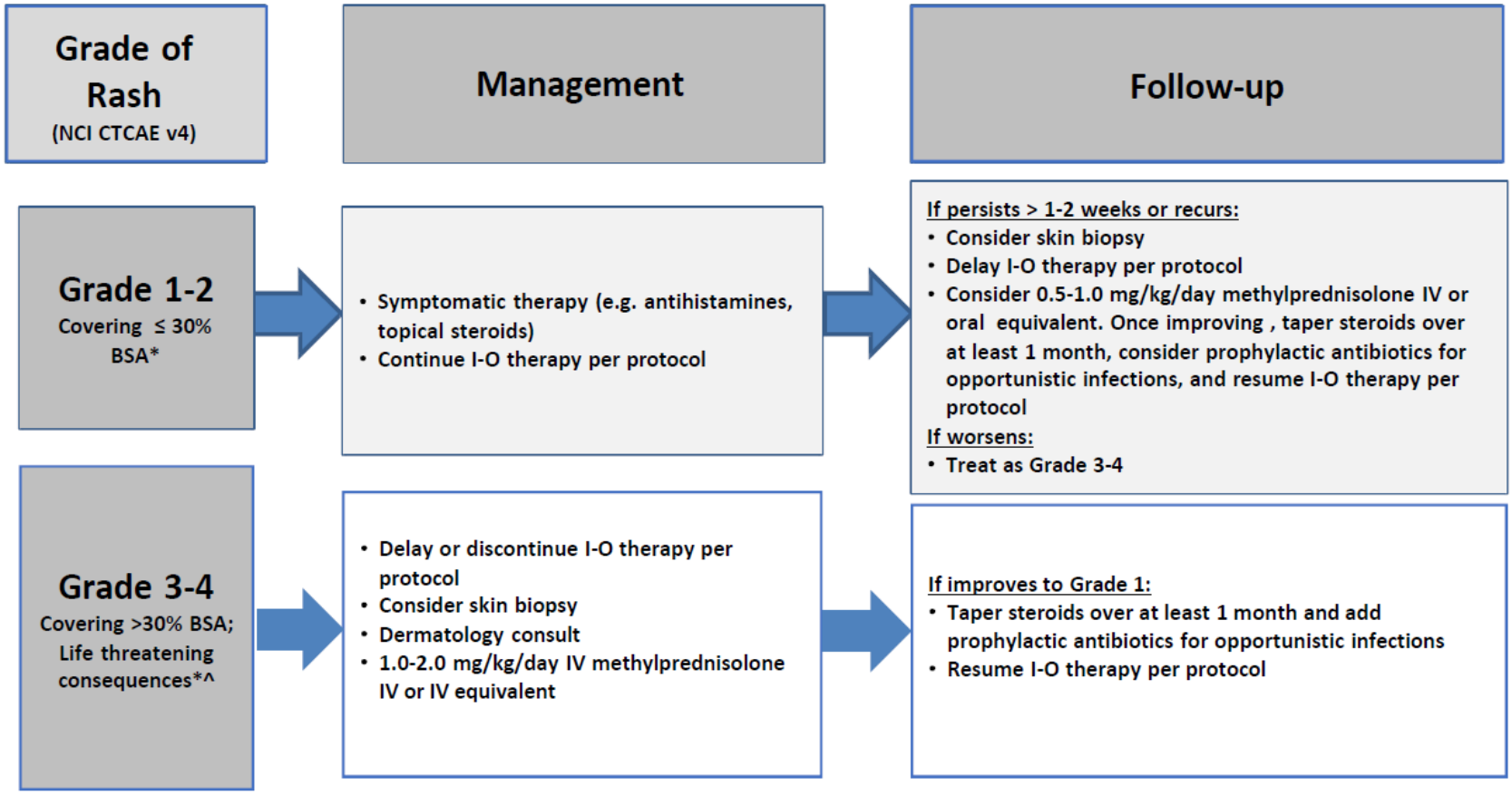
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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

Skin Adverse Event Management Algorithm

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



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

*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

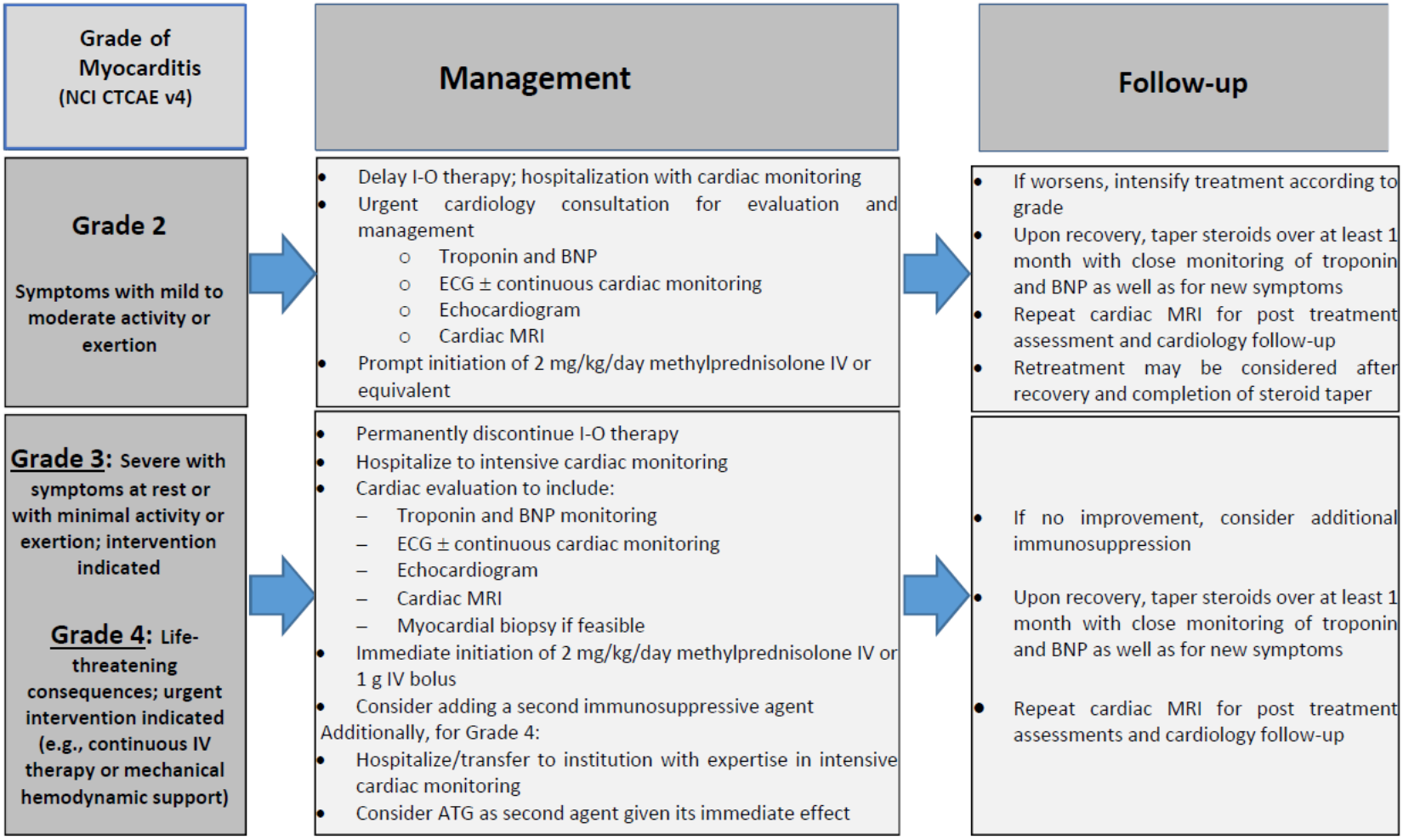
Neurological Adverse Event Management Algorithm

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

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

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

Myocarditis Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.
ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging