TITLE: Feasibility and Efficacy of Perioperative Nivolumab With or Without Relatlimab for Patients with Potentially Resectable Hepatocellular Carcinoma (HCC)

Johns Hopkins Protocol #:	J20121/ IRB00246739
BMS Protocol #:	CA224-097
NCT #:	NCT04658147
Coordinating Center:	Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
Principal Investigator and Protocol Chair (JHU):	Mark Yarchoan, M.D. [redacted]
Co-Lead Investigator (JHU):	Won Jin Ho, M.D. [redacted]
Principal Investigator (OSU):	Anne Noonam, M.D. [redacted]
IND#:	IND 136943
IND Sponsor:	Daniel Laheru, M.D.
Research Facility:	The Johns Hopkins Oncology Center [redacted]
Bristol-Myers Squibb Supplied Agents:	Nivolumab (BMS-936558; anti-PD-1 mAb) Relatlimab (BMS-986016, anti-LAG-3 mAb)

Version:	Original/ Version 1.0/October 22, 2020 Original/ Version 1.1/January 20, 2021 Amendment 1/ Version 2.0/May 26, 2021 Amendment 2/ Version 3.0/August 23, 2021 Amendment 3/ Version 4.0/April 13, 2022 Amendment 4/ Version 5.0/December 8, 2022 Amendment 5/ Version 6.0/April 20, 2023 Amendment 6/ Version 7.0/November 13, 2023 Amendment 7/ Version 8.0/January 8, 2024 Amendment 8/ Version 9.0/March 8, 2024 Amendment 9/ Version 10.0/December 16, 2025

1. SCHEMA

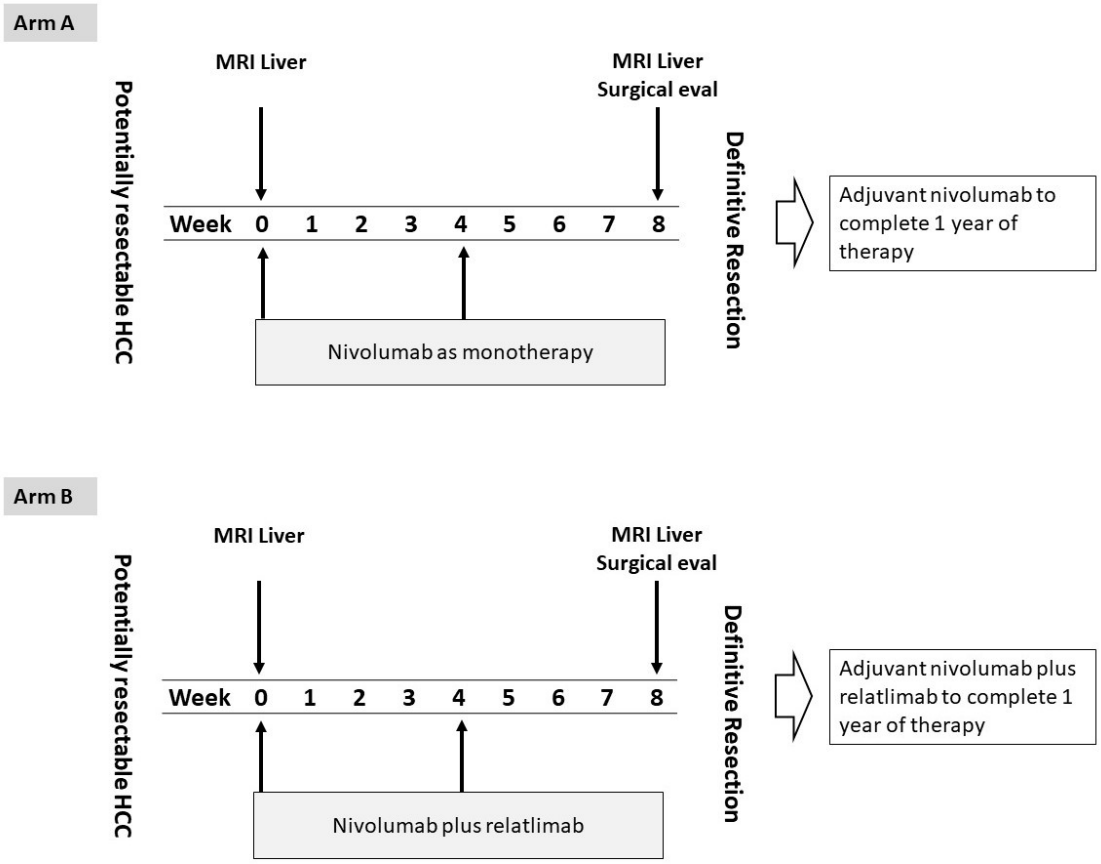


Figure 1*: Overview of the treatment plan for subjects who are enrolled in this clinical trial. Patients who are determined to be unresectable at the time of surgical evaluation must discontinue study therapy, and receive standard of care therapy at the discretion of the treating oncologist. Patients who do not undergo surgical resection due to a complete or near complete response to neoadjuvant therapy may continue to receive an additional 10 cycles of immunotherapy.*

TABLE OF CONTENTS

1. SCHEMA 3

2. OBJECTIVES and endpoints 6
   - 2.1 Primary Objective 6
   - 2.2 Secondary Objectives 6
   - 2.3 Exploratory Objectives 6
   - 2.4 Study Design 7

3. BACKGROUND 8
   - 3.1 Study Disease 8
   - 3.2 Dual Blockade of PD-1 and LAG-3 9
   - 3.3 Nivolumab/Relatlimab Dose Selection 9
   - 3.4 Rationale 12

4. PATIENT SELECTION and Randomization 12
   - 4.1 Neoadjuvant Eligibility Criteria 12
   - 4.2 Neoadjuvant Exclusion Criteria 14
   - 4.3 Adjuvant Eligibility Criteria 16
   - 4.4 Adjuvant Exclusion Criteria 17
   - 4.5 Inclusion of Women and Minorities 18
   - 4.6 Randomization 18

5. REGISTRATION PROCEDURES 18
   - 5.1 Registration Guidelines and Procedures 18

6. TREATMENT PLAN 19
   - 6.1 Agent Administration 20
   - 6.2 General Concomitant Medication and Supportive Care Guidelines 21
   - 6.3 Prohibited and Restricted Therapies 23
   - 6.4 Other Restrictions and Precautions 23
   - 6.5 Definition of an Overdose for this Protocol 24
   - 6.6 Unacceptable Toxicity 24
   - 6.7 WOCBP, Contraception, Use in Pregnancy, Use in Nursing 24
   - 6.8 Criteria for Removal from Treatment 28
   - 6.9 End of Treatment (EOT) Visit 31
   - 6.10 Duration of Follow Up 31

7. DOSING DELAYS/DOSE MODIFICATIONS 32
   - 7.1 Dose Modifications 32
   - 7.2 Dose Delays 32

8. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS 34
   - 8.1 Definitions 34
   - 8.2 Relationship and Grading 35
   - 8.3 Expectedness 36
   - 8.4 Handling of Expedited Safety Reports 37
   - 8.5 Reporting 37
   - 8.6 Special considerations for adverse events that occur during the surgery and postoperative course 40

9. Pharmaceutical Information 41
9.1 Agent Accountability 41
9.2 Mode of Action 41
9.3 Description 41
9.4 Packaging and Labeling Information 42
9.5 Preparation 42
9.6 Storage 42
9.7 Stability 42
9.8 Route of Administration 43
9.9 Subject Care Implications 43
9.10 Returns and Reconciliation 44
10. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES 44
10.1 Peripheral Blood Mononuclear Cells (PBMCs) and Whole Blood 44
10.2 Serum and Plasma Marker Studies 45
10.3 Tumor Tissue Studies 45
11. STUDY CALENDAR 46
12. STUDY ENDPOINTS 53
12.1 Primary Endpoint 53
12.2 Secondary Endpoints 53
12.3 Exploratory Endpoints 55
13. DATA REPORTING / REGULATORY REQUIREMENTS 55
13.1 Data Collection and Processing 55
13.2 Safety Meetings 56
13.3 Monitoring 56
13.4 Study Documentation 57
14. STATISTICAL CONSIDERATIONS 59
14.1 Primary Endpoint 59
14.2 Safety Endpoints 59
14.3 Sample Size/Accrual Rate 60
14.4 Stratification Factors 60
14.5 Analysis of Secondary Endpoints 60
14.6 Reporting and Exclusions 61
REFERENCES 62
APPENDIX A PERFORMANCE STATUS CRITERIA 63
APPENDIX B RECOMMENDED MANAGEMENT ALGORITHMS 64
APPENDIX C SAE REPORTING FORM 73
APPENDIX D RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) 1.1 CRITERIA FOR EVALUATING RESPONSE IN SOLID TUMORS 75

2. OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

2.1.1 To characterize the feasibility of neoadjuvant nivolumab or nivolumab plus relatlimab in resectable hepatocellular carcinoma (HCC).

2.2 Secondary Objectives

2.2.1 To characterize the safety of neoadjuvant and adjuvant nivolumab or nivolumab plus relatlimab, in resectable HCC.

2.2.2 To estimate the percentage of patients with resectable HCC who obtain an R0 resection at approximately 8-12 weeks following neoadjuvant nivolumab or nivolumab plus relatlimab.

2.2.3 To determine the percentage of evaluable patients who obtain a tumor response [including pathologic complete response (pCR), radiologic complete response or major pathologic responses (MPR)] at week 8-12 following neoadjuvant nivolumab or nivolumab plus relatlimab. Both pathologic and radiologic complete response will be counted as Complete Response (CR).

2.2.4 To determine the objective response rate (ORR) at approximately week 8 in patients with resectable HCC treated with neoadjuvant nivolumab or nivolumab plus relatlimab.

2.2.5 To determine the median overall survival (OS), 12 month OS, 18 month OS, 3 year OS, and 5 year OS, of patients with resectable HCC treated with perioperative nivolumab or nivolumab plus relatlimab.

2.2.6 To determine the median time of disease free survival (DFS), 12 month DFS, 18 month DFS, 3 year DFS, and 5 year DFS, of patients with resectable HCC treated with neoadjuvant nivolumab or nivolumab plus relatlimab. Patients who do not achieve disease-free status, including those who do not undergo surgical resection, will be excluded from disease-free survival analyses.

2.3 Exploratory Objectives

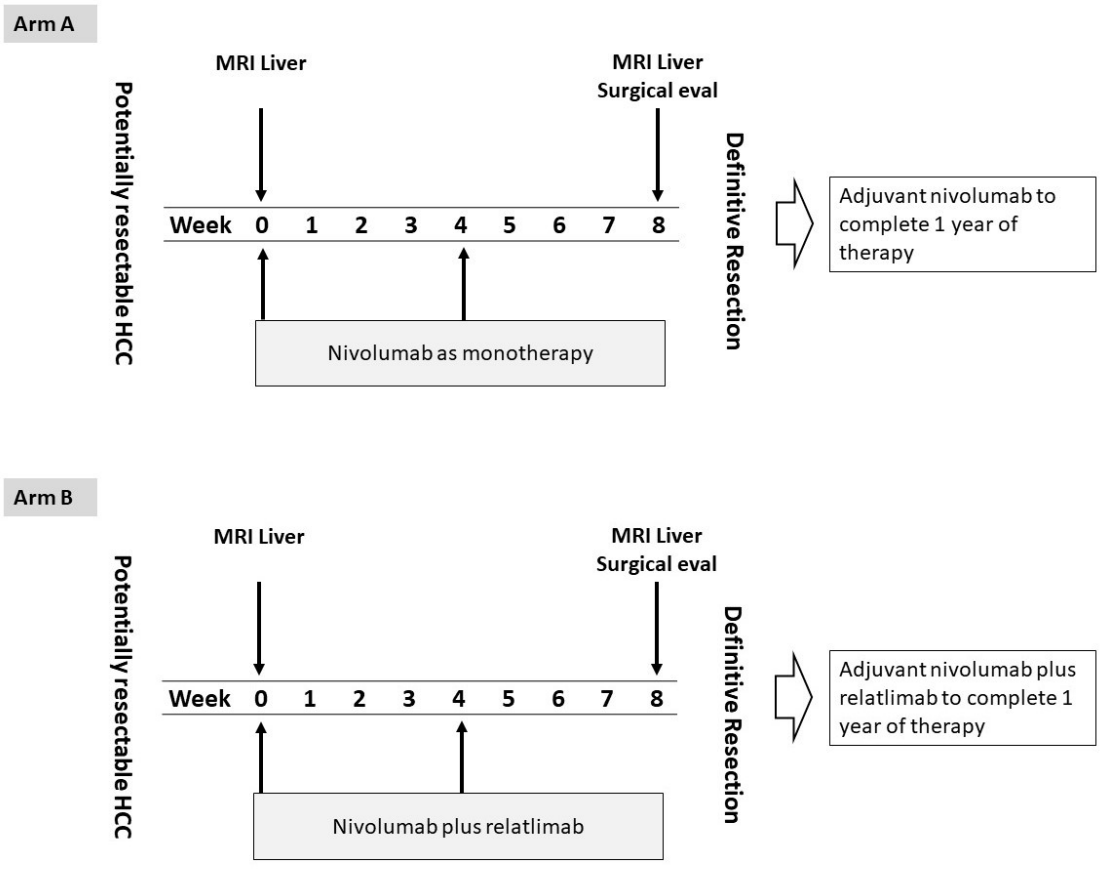
2.3.1 To collect peripheral blood mononuclear cells (PBMC), plasma, and serum to identify potential therapeutic targets, biomarkers and predictors of response (PCR/MPR, ORR, OS, and DFS) and autoimmune toxicity.

- Measure pre- and post-treatment changes in PBMCs including effector, helper, and regulatory T cells, NK cells, monocytes, and macrophages through cell phenotyping analysis and gene expression profiling.
- Proteomic approaches will be used on pre- and post-treatment sera and plasma to identify targets and biomarkers of response or toxicity.

2.3.2 To explore the effects of therapy on tumor and tumor infiltrating immune cells, and to explore potential molecular determinants of response, progression, and disease stability.

- To determine the receptor occupancy of relatlimab in tumor infiltrating lymphocytes and in the blood.
- Immunohistochemistry (IHC) and/or gene expression profiling will be used to compare the nature of tumors and immune infiltrates for responders versus non-responders.
- Next-generation sequencing of T cell receptor (TCR) genes may be used to compare the tumor infiltrating T cell repertoire in responders and non-responders.
- Up-regulation of immune inhibitory molecules (such as programmed death-ligand 1 [PD-L1]) will be evaluated in the pre- and post-treatment samples.
- Proteomic approaches to quantify protein expression and activation of specific signaling pathways in tumors from responders versus non-responders.

2.4 Study Design



This is an open-label, multi-institution, randomized phase 1b study of neoadjuvant nivolumab plus relatlimab or nivolumab monotherapy, followed by adjuvant nivolumab plus relatlimab or nivolumab monotherapy, in patients with resectable HCC. The purpose of this study is to determine the safety and tolerability of neoadjuvant/adjuvant nivolumab or nivolumab plus relatlimab in patients with HCC. Patients with HCC that is potentially resectable but at high risk

of disease recurrence are eligible for this clinical trial. Eligible patients will be randomized in a 1:1 ratio to receive either neoadjuvant nivolumab (Arm A), n=15 patients, or nivolumab in combination with relatlimab (Arm B), n=15 patients. Patients who undergo biopsy will do so prior to starting therapy. Patients will receive one infusion every 4 weeks, for a total of 2 treatment doses prior to surgery.

After completing neoadjuvant therapy, patients will receive a restaging scan and surgical evaluation. Patients who are eligible for surgical resection will proceed to a definitive surgical resection. The surgical resection should be scheduled no more than 60 days after the last dose of immunotherapy. Patients who do not undergo surgical resection due to a complete or near complete response to neoadjuvant therapy may continue to receive an additional 10 cycles of immunotherapy.

Post-surgery, patients from both treatment arms with no evidence of recurrence/progression may receive an additional 10 doses of adjuvant treatment every 28 days to complete 12 total months of IO treatment. Adjuvant therapy should begin within 90 days of surgical resection.

3. BACKGROUND

3.1 Study Disease

Hepatocellular carcinoma (HCC) is a cancer of the liver that usually develops in the setting of chronic liver disease including alcohol, chronic viral hepatitis (B or C), and non-alcoholic fatty liver disease. HCC is the second leading cause of cancer-related death in the world, and the incidence of HCC is rising in many parts of the world[1]. For all patients with HCC, the historical median overall survival is less than 2 years.

Patients with small (<5 cm), potentially resectable tumors have the potential for favorable long term survival with a partial hepatectomy or liver transplantation. However, the outcomes for patients with larger tumors that are either technically resectable or not resectable is less favorable. Some of these patients receive palliative treatments [for example, transarterial chemoembolization (TACE)]. Others receive a partial resection, but unfortunately these patients have a very high rate of intrahepatic disease relapse. For patients receiving a partial hepatectomy for HCC that is greater than 5 cm, the 5-year survival rate was 37.1% in one series[2]. The optimal management of these patients remains unclear.

We hypothesize that the use of neoadjuvant therapy patients with potentially resectable HCC will result in tumor response and downsizing, increased probability of successful surgical resection, and improved long-term outcomes. Although bevacizumab plus atezolizumab was recently established as an option for systemic therapy in the advanced or unresectable disease setting, bevacizumab has a long half life and may lead to surgical complications such as bleeding or delayed wound healing. Studies of neoadjuvant immunotherapy across multiple tumor types have thus far shown that it is safe and well tolerated. In this study, we are investigating whether neoadjuvant immunotherapy for resectable HCC is safe and feasible.

3.2 Dual Blockade of PD-1 and LAG-3

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

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

3.3 Nivolumab/Relatlimab Dose Selection

Nivolumab was recently approved for use at a dosing of 480 mg flat dosing every 4 weeks in multiple cancers, based on clinical data and population PK (PPK) simulations and exposure-response analyses suggesting no significant impact on toxicity or efficacy.

The relatlimab dose of 960 mg Q4W was selected to be evaluated in combination with 480 mg nivolumab Q4W in this study. The target dose of relatlimab 960 mg Q4W is based on the consideration that maximal target engagement will provide meaningful clinical activity.

The Relatlimab dose was selected after consideration of several factors including relatlimab pharmacokinetics, pharmacodynamics, benefit/risk assessment of relatlimab and nivolumab co-administration, and extensive nivolumab monotherapy clinical experience.

The relatlimab PK was characterized over a wide range of doses from 20 to 800 mg Q2W when administered as monotherapy or 20 to 240 mg Q2W and 160 to 1440 mg every Q4W when administered in combination with nivolumab. Relatlimab AUC(TAU) increased proportionally over a dose range of 240 mg to 800 mg Q2W or 960 mg to 1440 mg Q4W (~0.5 to 2 times of the proposed target dose of 960 mg Q4W). The different administration methods for combination therapy including single agent vial (SAV) sequential, and SAV co-administration were found to have no significant effect on PK when compared to monotherapy.

The PD measures including receptor occupancy (RO) on CD8+ effector memory T cells in

the blood and peripheral free soluble LAG-3 (sLAG-3) indicate maximal target engagement achieved at relatlimab 960 mg Q4W. At trough levels, RO was maintained above 90% and free sLAG-3 levels were below or close to the lower limit of quantification (0.626 ng/mL) for 960 mg Q4W. The target dose of 960 mg Q4W is projected to provide sustained and maximal intratumoral RO of > 90% over the entire dosing interval. Please see the Relatlimab Investigator's Brochure for more information regarding experience and safety of nivolumab/relatlimab 160/480 Q4W dose.

Safety:

In CA224020, **single-agent** relatlimab has had an acceptable safety profile at all tested doses: 20-, 80-, 240- and 800-mg flat doses. The maximum tolerated dose (MTD) was not reached up to 800-mg relatlimab Q2W.

The **combination therapy** of relatlimab + nivolumab had an acceptable safety profile among 39 participants at the 5 escalating dose levels tested up to 240 mg of each agent Q2W. Currently, the sequential administration of relatlimab up to 1440 mg and nivolumab 480 mg Q4W has been shown to be safe (zero [0] DLTs out of 7 (only 7 of 9 have completed DLT period) evaluable participants). This protocol will evaluate the combination of relatlimab 960 mg and Nivolumab 480 mg Q4W, which has also been shown to be safe (1 DLT out of 16 evaluable participants).

Both relatlimab and nivolumab have shown well-defined toxicity profiles based on a safety database comprised of participants treated with either monotherapy or double combinations across multiple tumor types. There are four ongoing studies in multiple tumor types which evaluated safety and efficacy of relatlimab in combination with nivolumab at various doses (n = 1282). Overall, the safety profile of relatlimab in combination with nivolumab is manageable. No MTD has been reached at the tested doses up to relatlimab 480 mg and nivolumab 480 mg Q4W in those studies as of a 2019 data cutoff. After that cutoff date, additional participants were enrolled into 960-mg relatlimab/480-mg nivolumab and 1440-mg relatlimab/480-mg nivolumab cohorts, as detailed below. No dose relationship between the incidence, severity, or causality of AEs and combination therapy has been demonstrated (refer to the relatlimab IB for further details). Most treatment-related AEs were Grade 1 or Grade 2. A total of 134 out of the 1282 participants (10.5%) receiving combination therapy experienced a treatment-related serious adverse event (TRSAE). Sixty-seven Grade 1 or Grade 2 infusion-related reactions were reported during infusion of study treatment and were manageable using the updated protocol guidelines. All AEs, except for 1 Grade 4 drug-induced liver injury (DILI) in a patient participating in the 80-mg relatlimab + 240-mg nivolumab dose expansion, and 1 Grade 4 myocarditis experienced by a patient dosed at 240 mg of both agents, were reversible and manageable by withholding study drug administration, providing standard medical care, and/or following immune-mediated adverse event (IMAE) algorithms.

The following safety data from a dose-escalation arm, dosed Q4W with nivolumab in CA224020, is available for 960-mg relatlimab (or higher), which will be tested in this study:

- 480-mg relatlimab/480-mg nivolumab was administered in 7 DLT-evaluable participants with 10.9 months median follow-up time. No participants reported treatment-related AEs.

Also, as of the 11-March-2020 database lock for CA224020, from preliminary information in two other escalation arms, participants were dosed with:

- 960-mg relatlimab/480-mg nivolumab was administered to 16 DLT-evaluable participants with 2.7 months median follow-up time. Two of the 16 participants reported a treatment-related Grade 3-4 event, one case of Grade 3 chronic gastritis, and one case of Grade 4 pneumonitis.

- 1440-mg relatlimab/480-mg nivolumab was tested in 9 DLT-evaluable participants with 1.7 months median follow-up time. No participants reported treatment-related AEs.

Of the DLT-evaluable participants at all Q4W doses (from 160- to 1440-mg relatlimab administered with 480-mg nivolumab, 3 developed DLTs of Grade 3 diarrhea, Grade 3 aspartate aminotransferase (AST)/alanine aminotransferase (ALT) elevations, and Grade 4 pneumonitis. All 3 DLTs are consistent with previously identified safety events in the relatlimab and Nivolumab programs and were reversible and managed with treatment algorithms.

As of Amendment 2 patients will no longer receive the 960 mg dose of relatlimab.

Based on two events of fatal myocarditis/myositis that occurred at relatlimab 960mg nivolumab 480mg Q4W dose on BMS sponsored study CA224-073, the decision was made to reduce the relatlimab dose for this study to 480mg for all newly enrolled patients and all patients who were within 8 weeks of starting treatment. Both patients on CA224-073 were patients with hepatocellular carcinoma and received only one dose of study therapy and were diagnosed with myocarditis/myositis with a rapid onset and an outcome of death despite appropriate immunosuppression and supportive management. Across all tumor types, at least 253 patients have been safely treated with relatlimab/nivolumab at the doses of 480mg/480mg Q4W or equivalent (360mg/360mg Q3W and 240mg/240mg Q2W) and higher across multiple clinical trials. One fatal myocarditis case was previously reported received relatlimab 240mg/nivolumab 240mg Q2W and had a different clinical course in comparison to the two recent cases at 960mg/480mg Q4W. No additional fatal cases occurred at this dose following institution of myocarditis management in protocols. Therefore, the decision was made to suspend relatlimab 960mg dosing and to move forward with a dose of 480mg of relatlimab with an increase in the frequency of safety monitoring for all newly enrolled patients and all patients who were within 8 weeks of starting treatment.

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

3.4 Rationale

Hepatocellular carcinoma (HCC) is an aggressive cancer and is the second leading cause of cancer-related death in the world[1]. Partial hepatectomy or liver transplantation are the only potentially curative treatments for HCC, but many patients are not eligible for curative therapy because of metastasis, local intrahepatic invasion, or comorbidities and/or poor hepatic reserve.

Even among the subset of patients who undergo a potentially curative partial hepatectomy, long-term outcomes are poor. Although estimates vary, recurrence rates of 54-100% have been reported in historical series of patients receiving a partial hepatectomy with curative intent for HCC[4-8]. The majority of recurrences (~80%) are intrahepatic. Since negative margins are usually observed at the time of surgical resection, it is believed that HCC recurrence occurs as a result of micrometastasis that persist after resection. Therefore, neoadjuvant therapies that can reduce the burden of micrometastatic disease prior to resection have the potential to improve outcomes in this disease. Neoadjuvant therapy may also improve outcomes by shrinking tumors and thereby converting patients with unresectable disease due to local invasion into surgical candidates. The use of immunotherapy in the neoadjuvant setting also offers a tremendous research opportunity to better elucidate mechanisms of response and resistance to therapy in HCC.

We have established a tissue bank of HCC resection specimens from patients receiving no neoadjuvant therapy, neoadjuvant nivolumab monotherapy, and neoadjuvant cabozantinib plus nivolumab from an ongoing clinical trial (clinicalTrials.gov Identifier: NCT03299946). Here we propose a new study in which we will treat patients with nivolumab or nivolumab/relatlimab prior to HCC resection. In addition to studying the safety and efficacy of this combination in the neoadjuvant setting, we will use multiplex IHC and single cell gene expression analysis to explore the additive effect of relatlimab on the HCC tumor microenvironment. Our unpublished experience with cabozantinib plus nivolumab was highly successful, allowing patients with classically incurable/unresectable HCC to receive a potentially curative resection. Similarly encouraging results were presented at ASCO GI 2020 by the hepatobiliary group at MD Anderson, demonstrating a 40% pathologic response rate of neoadjuvant nivolumab +/- ipilimumab.

Building on the experience of neoadjuvant immunotherapy in HCC, we hypothesize that nivolumab and nivolumab plus relatlimab will be safe and will have effects on the tumor immune microenvironment in hepatocellular carcinoma (HCC) that can be quantified.

4. PATIENT SELECTION AND RANDOMIZATION

4.1 Neoadjuvant Eligibility Criteria

4.1.1 Technically resectable HCC

- HCC may be diagnosed pathologically, or noninvasively by the American Association for the Study of Liver Diseases (AASLD) criteria or the Organ Procurement and Transplant Network (OPTN) Obligatory Diagnostic Criteria for Hepatocellular Carcinoma (HCC).

- No extrahepatic spread, no nodal disease, and no bilateral left and right branch portal vein involvement

4.1.2 Measurable disease per RECIST 1.1 as determined by the investigator

4.1.3 Age ≥ 18 years old on the day of consent

4.1.4 ECOG performance status ≤1 or Karnofsky ≥80 (**Appendix A**)

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

– White blood cell count	≥2,000/ μL
– absolute neutrophil count	≥1,500/μL
– platelets	≥100,000/μL
– hemoglobin	≥8.5 g/dL
– creatinine	Serum creatinine ≤ 1.5x ULN OR
– creatinine clearance	≥40 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal
– Lipase	≤ 1.5 x ULN OR If > 1.5 x ULN, there is no radiologic or clinical evidence of pancreatitis

4.1.6 Adequate future liver remnant, and adequate liver function, based upon meeting the following laboratory criteria:

- Child-Pugh Score of A
- Total bilirubin ≤ 2 mg/dL. For subjects with known Gilbert's disease, bilirubin ≤ 3.0 mg/dL;
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN
- Serum albumin ≥ 2.8 g/dL
- Prothrombin time (PT)/INR or partial thromboplastin time (PTT) test ≤ 1.5 x ULN

4.1.7 Patients with virally-associated or non-virally associated HCC are eligible for participation. Patients with chronic or acute HBV infection [as characterized by positive hepatitis B surface antigen (HBsAg) and/or hepatitis B core antibodies (anti-HbcAb) with detectable HBV DNA (≥10 IU/ml)] must have disease controlled (HBV DNA <500) prior to enrollment. Patients who test positive for anti-hepatitis B core (HBc) with undetectable HBV DNA (<10 IU/ml) do not require anti-viral therapy prior to enrollment, but HBV DNA levels should be monitored and antiviral therapy should be initiated if HBV DNA is detected (≥10 IU/ml).

4.1.8 LVEF assessment with documented LVEF ≥ 50% by either TTE or MUGA (TTE preferred) within 6 months from first study drug administration.

4.1.9 Women of childbearing potential (WOCBP) must have a negative urine or serum pregnancy test for the patient to be eligible for trial enrollment.

4.1.10 WOCBP must be willing to use either two adequate barrier methods or a barrier method plus a hormonal method of contraception to prevent pregnancy, or to abstain from heterosexual activity (complete abstinence) throughout the study, starting with visit 1 through 5 months after the last dose of study therapy. Approved contraceptive methods include, for example; intrauterine device, diaphragm with spermicide, cervical cap with spermicide, male condoms, female condoms with spermicide, or oral contraceptives. Spermicides alone are not an acceptable method of contraception. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

4.1.11 Male patients must agree to use an adequate method of contraception, or to abstain from heterosexual activity (complete abstinence), starting with the first dose of study drug through 7 months after the last dose of study therapy.

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

4.2 Neoadjuvant Exclusion Criteria

4.2.1 Fibrolamellar carcinoma or mixed HCC.

4.2.2 Receiving, or previously received, any systemic chemotherapy, or investigational agent for HCC.

- Note: Prior surgical resection with recurrence, or palliative local therapy (including TACE, Y-90 Resin Microspheres, etc.) would not exclude trial participation, but must have been performed at least 30 days prior to enrollment and there must be an area of viable tumor on scans.

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

4.2.4 Has a known additional malignancy that is expected to require active treatment within two years, or is likely to be life-limiting in the opinion of the treating investigator. Superficial bladder cancer, non-melanoma skin cancers, or low grade prostate cancer not requiring therapy would not exclude participation in this trial.

4.2.5 Has a known history of Human Immunodeficiency Virus (HIV)/AIDS

4.2.6 Has active co-infection with HBV and HDV.

4.2.7 Has a diagnosis of immunodeficiency, or is receiving systemic steroid therapy above physiologic replacement dose, or any other form of immunosuppressive therapy.

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

4.2.9 Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

4.2.10 Systemic or topical corticosteroids at immunosuppressive doses (> 10 mg/day of prednisone or equivalent). Inhaled or topical steroids, and adrenal replacement steroid doses ≤10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

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

4.2.12 Uncontrolled intercurrent illness including, but not limited to: Symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements

4.2.13 Uncontrolled or significant cardiovascular disease (i.e. cardiomyopathy, congestive heart failure with New York Heart Association (NYHA) functional classification III-IV, pericarditis, significant pericardial effusion, significant coronary stent occlusion), including, but not limited to any of the following:

- Myocardial infarction (MI) or stroke/transient ischemic attack within the 6 months prior to consent
- Uncontrolled Angina within the 3 months prior to consent
- Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes)
- QTc prolongation > 480 msec
- Cardiovascular disease-related requirement for daily supplemental oxygen
- History of two or more Mis OR two or more coronary revascularization procedures

- Subjects with history of myocarditis, regardless of etiology.

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

4.2.15 Moderate or severe ascites.

4.2.16 Previously identified allergy or hypersensitivity to monoclonal antibodies or any component of the study treatment formulations.

4.2.17 Pregnant or lactating females

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

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

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

4.2.21 Patient is, at the time of signing informed consent, a regular user (including "recreational use") of any illicit drugs or alcohol.

4.3 Adjuvant Eligibility Criteria

4.3.1 Patients must have had surgical resection of primary tumor

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

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

• White blood cell count	≥2,000/ μL
• absolute neutrophil count	≥1,500/μL
• platelets	≥100,000/μL
• hemoglobin	≥8.5 g/dL
• creatinine	Serum creatinine ≤ 1.5x ULN OR
• creatinine clearance	≥40 mL/min/1.73 m2 for patients with creatinine levels above institutional normal
• Lipase	≤ 1.5 x ULN OR if > 1.5 x ULN, there is no

radiologic or clinical evidence of pancreatitis

4.3.4 Adequate future liver remnant, and adequate liver function, based upon meeting the following laboratory criteria:

- Child-Pugh Score of A
- Total bilirubin ≤ 2 mg/dL. For subjects with known Gilbert's disease, bilirubin ≤ 3.0 mg/dL;
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN
- Serum albumin ≥ 2.8 g/dL
- Prothrombin time (PT)/INR or partial thromboplastin time (PTT) test ≤ 1.5 x ULN

4.3.5 Women of childbearing potential (WOCBP) must have a negative urine or serum pregnancy test for the patient to be eligible for trial enrollment.

4.3.6 WOCBP must be willing to use either two adequate barrier methods or a barrier method plus a hormonal method of contraception to prevent pregnancy, or to abstain from heterosexual activity (complete abstinence) throughout the study, starting with visit 1 through 5 months after the last dose of study therapy. Approved contraceptive methods include, for example; intrauterine device, diaphragm with spermicide, cervical cap with spermicide, male condoms, female condoms with spermicide, or oral contraceptives. Spermicides alone are not an acceptable method of contraception. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

4.3.7 Male patients must agree to use an adequate method of contraception, or to abstain from heterosexual activity (complete abstinence), starting with the first dose of study drug through 7 months after the last dose of study therapy.

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

4.4 Adjuvant Exclusion Criteria

4.4.1 More than 90 days have elapsed since surgery.

4.4.2 Patient was found to have unresectable or metastatic disease intraoperatively.

4.4.3 Patients who develop local recurrence or disease progression at any point in the study.

4.4.4 The patient has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of adjuvant study drug.

4.4.5 History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

4.4.6 History of allergic reaction to nivolumab.

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

4.5 Inclusion of Women and Minorities

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

4.6 Randomization

This study is an open-label study. As such, assignment of study treatment will not be blinded. Subjects will be randomized to Arm A (nivolumab) or Arm B (nivolumab/relatlimab) in a 1:1 fashion using permuted blocks of varying sizes. If randomization is completed for an arm based on number of evaluable patients, randomization may be halted to complete randomization to the second arm.

5. REGISTRATION PROCEDURES

5.1 Registration Guidelines and Procedures

Eligible patients will be entered on study centrally at the Sidney Kimmel Comprehensive Cancer Center at the Johns Hopkins University by the Coordinating Center. All sites should email [redacted] to ongoing study enrollment status. The Registration Form and Eligibility Checklist will be supplied to each participating site.

If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

To register a patient, the following de-identified documents should be completed by the Research Nurse or Study Coordinator at the participating site and e-mailed to [redacted]

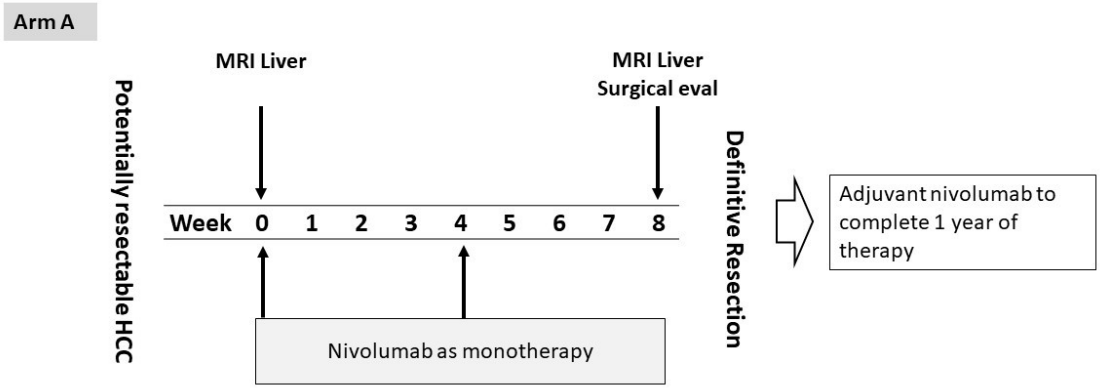
- Fax cover sheet
- Registration Form

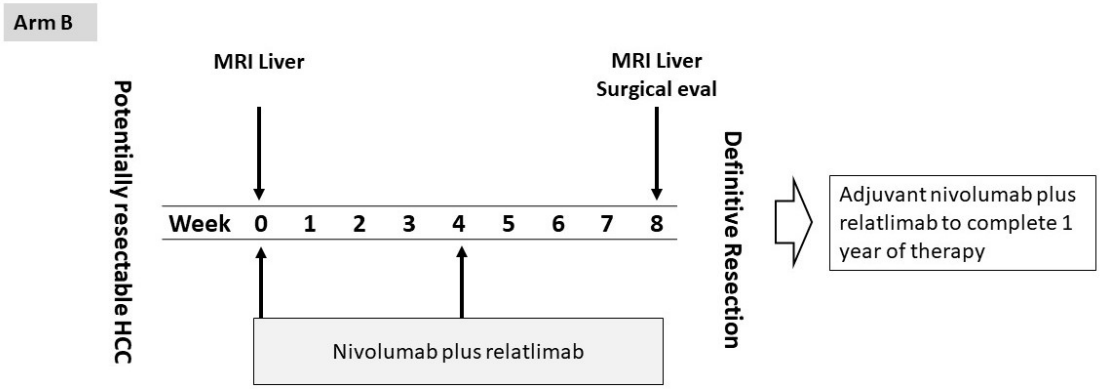
- Signed patient consent form
- Eligibility Screening Checklist
- Copy of required screening tests and scans

The Research Nurse or Study Coordinator at the participating site will then e-mail GITrialRegistration to verify eligibility. To complete the registration process, the Coordinating Center will:

- Assign a patient study number
- Register the patient on the study
- Fax or e-mail the patient study number to the participating site
- Call or e-mail the research nurse or data manager at the participating site and verbally confirm registration.

6. TREATMENT PLAN





6.1 Agent Administration

Treatment will be administered on an outpatient basis. Appropriate dosing delays are described in **Section 7.** No investigational or commercial agents or therapies other than those described below in **Table 2** may be administered with the intent to treat the patient's malignancy.

Table 2: Regimen Description

REGIMEN DESCRIPTION						
Agent	***Premedications; Precautions***	***Administration Type***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Arm A: Nivolumab	No prophylactic pre-medication will be given unless indicated by previous experience in an individual subject per **Section** Error! Reference source not found.	N/A	480 mg	IV infusion over 30 (+25/-15) min*	Day 1 of each cycle for neoadjuvant Day 1 of each cycle for 10 doses/ months (whichever occurs first) for adjuvant	28 days
Arm B: Nivolumab/ Relatlimab***		Sequential**	480mg/ 960mg	Each drug infused IV over 30 (+25/-15) min*	Day 1 of each cycle neoadjuvant Day 1 of each cycle for 10 doses/ months (whichever occurs first) for adjuvant	28 days
Arm B: Nivolumab/ Relatlimab***		Sequential**	480mg/ 480mg	Each drug infused IV over 30 (+25/-15) min*	Day 1 of each cycle neoadjuvant Day 1 of each cycle for 10 doses/ months (whichever occurs first) for adjuvant	28 days

*Infusion times are approximate and may be adjusted based on subject tolerability.
** Order of administration is nivolumab followed by relatlimab. Subjects should be observed for a minimum of 30 minutes between each infusion.
*** Patients who enrolled prior to Amendment 2 and are within 8 weeks of their first dose

will be dose reduced to 480mg/480mg, whereas patients who are past 8 weeks from their first dose may continue to receive 480mg/960mg or be dose reduced to 480mg/480mg at the discretion of the Principal Investigator. All patients enrolled after Amendment 2 will receive 480mg relatlimab.

Patients receiving combination therapy (Arm B) may discontinue either nivolumab or relatlimab and continue treatment with the remaining agent as monotherapy, at the discretion of the Investigator and with approval of the Principal Investigator, if the patient experiences an adverse event that does not meet criteria for unacceptable toxicity but, in the judgment of the Investigator, warrants discontinuation of one study drug in the best interest of the patient.

Please see **Section 7.2** for guidance regarding dosing delays.

Antiemetic medications should not be routinely administered prior to dosing of drugs. See **Section 6.2.1** for subsequent premedication recommendations following an infusion reaction.

6.2 General Concomitant Medication and Supportive Care Guidelines

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

6.2.1 Infusion Reactions

Since nivolumab and relatlimab contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce an infusion or hypersensitivity reaction. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other allergic-like reactions. All grade 3 or 4 infusion reactions should be reported within 24 hours to the IND Sponsor, Regulatory Specialist, and BMS and reported as an SAE if criteria are met. Infusion reactions should be graded according to CTCAE (version 5.0) guidelines.

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

For grade 1 symptoms (mild reaction; infusion interruption not indicated; intervention not indicated):

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

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

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

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

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

6.2.2 Nivolumab and Relatlimab-Related Adverse Events

Blocking PD-1 or LAG-3 function may permit the emergence of auto-reactive T cells and resultant clinical autoimmunity. Rash/pruritus, diarrhea/colitis, pneumonitis, hepatitis, and

hypothyroidism were drug-related, presumptive autoimmune events noted in previous nivolumab studies.

For the purposes of this study, a nivolumab- or relatlimab-related AE is defined as an AE of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes. Serological, immunological, and histological (biopsy) data should be used to support the diagnosis of an immune-mediated toxicity. Suspected nivolumab- or relatlimab-related AEs must be documented on an AE or SAE CRF. Identification and treatment of nivolumab- and relatlimab-related AEs can be found in **Appendix B**. Treatment guidelines based on CTCAE V4. Additional guidance can be found in the nivolumab and relatlimab Investigator's Brochures (IB).

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

6.3 Prohibited and Restricted Therapies

The following medications are prohibited during the study:

- Immunosuppressive agents

  NOTE: Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Immunosuppressive agents and the use of systemic corticosteroids are permitted in the context of treating AEs, prophylaxis prior to a diagnostic procedure (e.g., contrast MRI/CT scans) or as specified in **Section 6.2**. A brief course of corticosteroids for prophylaxis (e.g., contrast dye allergy) is permitted.
- Concurrent administration of any anticancer therapies (investigational or approved) with the exception of subjects in the survival period of the study.
- Use of growth factors unless prior discussion and agreement with the IND Sponsor.
- Use of allergen hyposensitization therapy

6.4 Other Restrictions and Precautions

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

It is the local imaging facility's responsibility to determine, based on subject attributes (e.g., allergy history, diabetic history and renal status), the appropriate imaging modality and contrast regimen for each subject. Imaging contraindications and contrast risks should be considered in this assessment. Subjects with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate. Specific to MRI, subjects with severe renal insufficiency (i.e., estimated glomerular filtration rate (eGFR) < 30

mL/min/1.73m2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this subject population. In addition, subjects are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc.

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

6.5 Definition of an Overdose for this Protocol

Overdose of nivolumab or relatlimab is defined as:

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

All reports of overdose (with and without an AE) must be reported within 24 hours to the IND Sponsor [redacted] Regulatory [redacted]), and Bristol-Myers Squibb (BMS) as an SAE per **Section 8**.

6.6 Unacceptable Toxicity

Unacceptable toxicities are defined as any adverse event requiring permanent discontinuation per **Section 6.8.1** (exceptions for permanent discontinuation must be approved by the IND Sponsor).

If more than 1 of the first 6 patients experiences an unacceptable toxicity within the first cycle, then enrollment will be halted, and the overall risk-benefit ratio of the study will be reconsidered. At any time thereafter, if more than 33% of patients are observed to experience unacceptable toxicity within the first cycle (e.g. 3/9), then enrollment will be suspended until further review and consideration by the IND Sponsor. There will be no dose reductions for nivolumab or relatlimab.

Events meeting unacceptable toxicity criteria should be reported via email to the IND Sponsor [redacted]

6.7 WOCBP, Contraception, Use in Pregnancy, Use in Nursing

6.7.1 Definition of Women of Childbearing Potential

WOCBP is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a documented serum follicle stimulating hormone (FSH) level > 40mIU/mL to confirm menopause.

Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic

FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels.

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

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

6.7.2 Contraception

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 24 weeks after the end of study treatment.*****

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)[c] • Intrauterine device (IUD)[c] • Bilateral tubal occlusion

- Vasectomized partner

  A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

- Sexual abstinence

  Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

- It is not necessary to use any other method of contraception when complete abstinence is elected.
- WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in **Section 9**.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence

NOTES:

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

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

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

Unacceptable Methods of Contraception*

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

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

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

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

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until end of relevant systemic exposure defined as 33 weeks after the end of study treatment.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 33 weeks after the end of study treatment.

Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of study treatment.

6.7.3 Use in Pregnancy

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

Pregnancy in female subjects throughout the study or within 24 weeks of completing treatment as well as any pregnancy in partners of male subjects throughout the study or within 33 weeks of completing the study should be reported initially as a serious adverse event (see SAE reporting procedures in **Section 8.5**) by the investigator within 24 hours of learning of its occurrence. Pregnancy information must be reported on the Pregnancy Form.

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

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

partner.

6.7.4 Use in Nursing Women

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

6.8 Criteria for Removal from Treatment

A subject must be discontinued from the trial for any of the following reasons:

- The patient or legal representative (such as a parent or legal guardian) withdraws consent for treatment and follow-up,
- Termination of the study, and
- Patient is lost to follow up.

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

- Patients who have completed either 10 doses or 10 months (whichever comes first) of adjuvant therapy, or an equivalent treatment period for patients who do not undergo surgery
- The patient or legal representative (such as a parent or legal guardian) withdraws consent for treatment but not follow-up,
- Development of local recurrence or distant metastatic disease,
- Treatment of nivolumab/relatlimab is delayed or interrupted for > 3 weeks during neoadjuvant portion of trial or > 6 weeks during adjuvant portion of the trial (either continuous or cumulatively) the subject must permanently discontinue study treatment and move directly to surgery.
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable toxicity (see **Section 6.6/6.8.1**) or specific delay criteria listed in **Section 7.2**,
- If in the opinion of the Investigator, a change or temporal or permanent discontinuation of therapy would be in the best interest of the patient (The IND Sponsor should be included in this decision),
- Noncompliance with trial treatment or procedure requirements,

- Patient becomes pregnant. All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation, and

- Patient is lost to follow-up.

6.8.1 Nivolumab- and Relatlimab-Related Adverse Events

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

1. Severe or life-threatening related AEs, including, but not limited to, any of the following (the IND Sponsor and BMS must be notified in the event of these AEs):
    - Any grade 2 treatment-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to ≤ Grade 1 severity within the re-treatment period OR requires systemic treatment

    - Any grade 3 non-skin, drug-related AE lasting > 7 days or recurs, with the following exceptions:

        - Grade 3 treatment-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation

        - Grade 3 treatment-related endocrinopathies adequately controlled with only physiologic hormone replacement such as hyper- or hypothyroidism, or glucose intolerance, do not require discontinuation. Grade 3 adrenal insufficiency does require discontinuation.

        - Grade 3 treatment-related laboratory abnormalities do not require treatment discontinuation except:

            - Grade 3 treatment-related thrombocytopenia > 7 days OR that is associated with bleeding requires discontinuation

            - Any treatment-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
                - ALT or AST > 8 x ULN, regardless of duration, or
                - ALT or AST > 5 x and ≤ 8 x ULN, that fails to return to ≤ Grade 1 within 2 weeks despite medical intervention, or
                - Total bilirubin > 5 × ULN, or
                - Potential drug-induced liver injury (DILI) event **(Section 8.5.5)**

- Elevated troponin ≥ Grade 3 requires discontinuation (except Grade 3 elevation without other signs of cardiac toxicity as determined by cardiac evaluation)

- Any grade 4 treatment-related AE or laboratory abnormality, except for the following events which do not require discontinuation:

  - Grade 4 neutropenia ≤ 7 days

  - Grade 4 lymphopenia and leukopenia.

  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations.

  - Isolated grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.

  - Grade 4 treatment-related endocrinopathy adverse events, such as hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the IND Sponsor. Grade 4 adrenal insufficiency does require discontinuation, however.

- Any dosing interruption lasting > 6 weeks with the following exceptions:

  - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the IND Sponsor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

  - Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the IND Sponsor. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the IND Sponsor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab or relatlimab dosing.

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

6.9 End of Treatment (EOT) Visit

All subjects will return to the study site 30 days (± 7 days) after the final study treatment (or within 7 days prior to initiation of a new anti-cancer treatment, whichever comes first) for an EOT evaluation. Procedures and assessments performed at this visit and beyond should follow the respective guidelines described in **Sections 6.10 and 11** as appropriate. If the patient is unable to return for an EOT visit (e.g. disease/clinical progression, poor health, intercurrent illness, or initiation of a new anti-cancer therapy), an assessment of adverse events should be made by telephone or telemedicine visit on day 30 (±7) after the last study drug dose in place of the PE/PS/vitals. Clinical laboratory values should still be collected.

6.10 Duration of Follow Up

6.10.1 Safety Follow-Up

Subjects who discontinue treatment will be contacted by telephone, telemedicine visit, in-person visit, or email at 100 days (+14 day reporting window) from the last dose of study drug or within 7 days before initiation of a new antineoplastic treatment (whichever comes first) to monitor drug toxicity. In addition, all SAEs occurring during this time should be reported as well.

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

6.10.2 Clinical Follow-Up

Treated subjects will begin the follow-up period after they complete the EOT visit. Subjects who complete or discontinue from treatment without local recurrence or disease progression will be contacted (by phone, telemedicine, email, medical record search or in person visit) per standard of care for 5 years or study closure (whichever comes first) to monitor overall survival and disease free survival. Information of other cancer therapies after discontinuation from the study treatment will also be collected. After disease progression or start of a new antineoplastic therapy, subjects will enter the survival follow-up portion of the trial (**Section 6.10.3**).

6.10.3 Survival Follow-Up

Subjects who discontinue treatment and have disease progression will enter the survival follow-up portion of the trial. Subjects will be contacted (by phone, telemedicine, email, medical record search, or in person visit) per standard of care to monitor overall survival. Information of other cancer therapies after discontinuation from the study treatment will also be collected.

7. DOSING DELAYS/DOSE MODIFICATIONS

7.1 Dose Modifications

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

Due to safety concerns at 960mg relatlimab (myocarditis/myositis/myasthenia), patients who enrolled prior to Amendment 2 and are within 8 weeks of their first dose will be dose reduced to 480mg relatlimab, whereas patients who are past 8 weeks from their first dose may continue to receive 960mg relatlimab or be dose reduced to 480mg relatlimab at the discretion of the Principal Investigator.

7.2 Dose Delays

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

Guidance for Investigators is provided in the current relatlimab and nivolumab Investigator's Brochures. Additionally, management algorithms have been developed to assist Investigators with select toxicities and can be found in **Appendix B.** Management algorithms based on CTCAE V4. Toxicities for which management algorithms have been developed include:

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

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

- Select drug-related AEs and drug-related laboratory abnormalities:
  - Grade ≥ 1 pneumonitis
  - Increase from baseline of ≥ one grade (to at least grade 2) of AST, ALT, and/or total bilirubin
  - Grade ≥ 2 creatinine
  - Grade ≥ 2 diarrhea or colitis
  - Grade ≥ 2 neurological AE
  - Grade 4 amylase and/or lipase abnormalities regardless of symptoms or clinical manifestations

- Troponin >ULN requires dose delay for confirmatory repeat level within 24 hours and prompt cardiac evaluation
    - If troponin elevation in an asymptomatic patient that is not confirmed on repeat, dose delay may not be required, provided that a cardiac evaluation is completed
    - Otherwise if symptomatic and/or troponin elevation is confirmed, dosing may only resume when AE resolves to baseline

- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study drug.

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

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

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

Patients receiving combination therapy may discontinue either nivolumab or relatlimab and continue treatment with the remaining agent as monotherapy, at the discretion of the Investigator and with approval of the Principal Investigator, if the patient experiences an adverse event that does not meet criteria for unacceptable toxicity but, in the judgment of the Investigator, warrants discontinuation of one study drug in the best interest of the patient.

During the neoadjuvant portion of the study, if study treatment is delayed > 3 weeks, the investigator should be contacted to determine if it is in the patient's best interest to discontinue

therapy and proceed to surgical evaluation.

8. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

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

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

8.1 Definitions

8.1.1 Adverse Events (AEs)

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

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

8.1.2 Serious Adverse Event (SAE)

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

- Results in death
- Is life threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions) for >24 hours
- Results in persistent or significant disability/incapacity

- Is a congenital anomaly/birth defect (note: reports of congenital anomalies/birth defects must also be reported on the Pregnancy Form)
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Potential drug induced liver injury (DILI) is also considered an important medical event.
- Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.
- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose
- Is a pregnancy or pregnancy outcome of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, or stillbirth.

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

- a visit to the emergency room or other hospital department <24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- Admissions as per protocol for a planned medical/surgical procedure or to facilitate a procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

8.2 Relationship and Grading

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

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

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

The following factors should also be considered:

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

Assessment of Grade:

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

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

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

8.3 Expectedness

Unexpected AE: An AE, which varies in nature, intensity or frequency from information on the investigational drug/agent provided in the product IB, package insert or safety reports. Any AE

that is not included in the IB, package insert, safety reports or informed consent is considered "unexpected". An expected AE with a fatal outcome should be considered unexpected unless the IB specifically states that the AE might be associated with a fatal outcome.

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

8.4 Handling of Expedited Safety Reports

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

8.5 Reporting

8.5.1 Adverse Events and Serious Adverse Events

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

A non-serious adverse event is an AE not classified as serious. All non-serious AEs (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days (+14 day reporting window) following the last dose of study treatment or before initiation of a new antineoplastic treatment (whichever comes first). Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. Non-serious AEs are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [e.g., IND US trial] as part of an annual reporting requirement.

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

Report AEs to the IND Sponsor within 24 hours once identified as an unacceptable toxicity (defined in Section 6.6).

IND Sponsor:
Regulatory: [redacted]

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

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

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

IND Sponsor: [redacted]
Regulatory: [redacted]
BMS: [redacted]

8.5.2 Follow-up of Adverse Events and Serious Adverse Events

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

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

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

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

8.5.3 Reconciliation of SAEs

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

8.5.4 Overdose

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

8.5.5 Potential Drug Induced Liver Injury (DILI)

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

1) ALT or AST elevation > 10 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.

8.5.6 Pregnancy Reporting

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial or within 24 weeks following cessation of the study drugs, or pregnancy of a partner of a male subject within 33 weeks of cessation of the study drugs, must be reported by the investigator using the Pregnancy Surveillance Form. All subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported to the IND Sponsor and BMS.

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

8.5.7 Institutional Review Board

Participating sites will be responsible for reporting to their IRB. SAEs will be reported to the IRB per institutional guidelines. Follow-up information will be submitted to the IRB as soon as relevant information is available per institutional standards.

8.5.8 Food and Drug Administration (FDA)

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

8.5.8.1 Expedited IND Safety Reports:

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

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

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

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

8.5.8.2 IND Annual Reports

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

8.6 Special considerations for adverse events that occur during the surgery and postoperative course

Surgical resection for HCC is a high risk procedure that requires prolonged hospitalization, has significant toxicities, and is commonly associated with complications and comorbidities. It is a standard of care, therefore, is not part of this research study. From the day of surgery throughout the postoperative course day 30, participants will be primarily followed by their primary surgeons for monitoring and managing the complications and comorbidities attributable to the surgery. Expected surgical AEs will not be routinely collected as part of this study protocol as surgery is

considered standard of care, however, we will collect AEs in the perioperative period that may be related to study therapy.

9. PHARMACEUTICAL INFORMATION

9.1 Agent Accountability

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

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

9.2 Mode of Action

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

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

9.3 Description

Nivolumab injection, 100 mg/vial (10 mg/mL) is a clear to opalescent, colorless to pale, yellow liquid, light (few) particulates may be present. The drug product is a sterile, nonpyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriamine pentacetic acid (pentetic acid) and polysorbate 80 (Tween™ 80), pH 6.0 and includes a 0.7-mL overfill to account for vial, needle, and syringe (VNS) holdup. It is supplied in 10-cc type I flint glass vials, stoppered with butyl rubber stoppers and sealed with aluminum seals.

Relatlimab injection, 80mg/vial (10mg/mL) 8mL, is a clear to opalescent, colorless to pale, yellow liquid, with light (few) particulates that may be present. There are two drug formulations that are available. The same excipients are used for both formulations, except for pentetic acid: Relatlimab, L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate 80, water for injection, and pH 5.0 to 6.0. It is supplied in 10-cc type I flint glass vials, stoppered with fluoropolymer film-

laminate rubber stopper and sealed with aluminum seal.

9.4 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements. Open-label cartons will be supplied with 4 vials per carton.

9.5 Preparation

Care must be taken to assure sterility of the prepared solution, as the products do not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between the nivolumab and polyolefin or PVC bags, or non-DEHP or PVC infusion sets have been observed. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves. Detailed instructions on the preparation of nivolumab alone or for sequential administration with relatlimab will be provided in the Pharmacy Manual.

Treatment Arm A and B: Nivolumab injection can be diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection (D5W), USP to protein concentrations as low as 0.35 mg/mL. When the dose is fixed (e.g., 240 mg, 360 mg, or 480 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 160 mL. **For patients weighing less than 40 kilograms (kg), the total volume of infusion must not exceed 4 mL per kg of patient weight.**

Treatment Arm B: Relatlimab injections can be diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection (D5W), USP to protein concentrations no lower than 0.2 mg/mL. **Maximum infusion volume should not exceed 160 mL. For subjects weighing less than 40 kg, the total volume of infusion must not exceed 4 mL per kg of subject weight.**

9.6 Storage

Clinical supplies must be stored in a secure, limited-access location. Nivolumab vials must be stored at a temperature of 2°C to 8°C (36°F to 46°F) and should be protected from light and freezing. If stored in a glass front refrigerator, vials should be stored in the carton. Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.7 Stability

Treatment Arm A: The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°-8°C, 36°-46°F) for up to 24 hours, and a maximum of 8 hours of the total 24 hours can be at room temperature (20°-25°C, 68°-77°F) and room light. The maximum 8-hour period under room temperature and room light conditions includes the product administration period.

Treatment Arm B: The administration of nivolumab and relatlimab (sequential administration)

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 (20°C to 25°C; 68°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.

9.8 Route of Administration

Treatment Arm A: Nivolumab is to be administered as a 30 minute IV infusion, using a volumetric pump with a 0.2-micron to 1.2-micron pore size, low-protein binding (polyethersulfone membrane) in-line filter at the protocol-specified dose. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline (approximately 15-20mL).

Treatment Arm B: When using Relatlimab injection 80mg/vial (10mg/mL) 8mL, Nivolumab and relatlimab are to be sequentially administered. Nivolumab is administered as a 30 minute IV infusion, followed by at least a 30 minute break, followed by Relatlimab IV infusion over 30 minutes using a volumetric pump with a 0.2 micron to 1.2 micron pore size, low protein binding (polyethersulfone membrane) in-line filter at the protocol-specified dose. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline (approximately 15-20 mL).

9.9 Subject Care Implications

The overall safety experience with nivolumab is based on experience in approximately 1500 subjects as either a monotherapy or in combination with other therapeutics. In general for monotherapy, the safety profile is similar across tumor types. The one exception is pulmonary inflammation AEs which may be numerically greater in subjects with NSCLC possibly because in some cases it can be difficult to distinguish between nivolumab-related and unrelated causes of pulmonary symptoms and radiographic changes. The most frequently reported treatment related AE is fatigue, which is almost always low grade.

Most related AEs are thought to be due to the effects of inflammatory cells on specific tissues. A variety of PTs have been used to describe similar kinds of organ-related AEs with the result being that AE frequency tables organized by PTs can lead to underestimation of the frequency of similar kinds of organ-related AEs. To address this issue, select AE categories were created. Select AE categories group together the most common and impactful PTs by organ category. These categories include the following: pulmonary, gastrointestinal, hepatic, dermatologic, endocrine, and renal AEs. It is also useful to consider the management of nivolumab-related AEs by organ category as the diagnostic workup often requires excluding other potential diagnoses and when appropriate instituting specific management principles as outlined in this protocol and **Appendix B**.

The safety of relatlimab has been well characterized and the clinical safety is being assessed in a cohort of 25 subjects treated with escalating doses of relatlimab monotherapy followed by 243 subjects treated with escalating doses of relatlimab in combination with nivolumab. Of the 212

subjects receiving the combination at a dose of every 2 weekly relatlimab 80mg plus nivolumab 480mg, 44.8% percent developed treatment-related AEs, primarily fatigue, diarrhea, pruritus and infusion related reaction. Treatment-related SAEs occurring in the 243 combination-treated patients were reported as similar to those of nivolumab monotherapy, and included 3 cases of G3-4 colitis, 2 cases each of aseptic meningitis and mucosal inflammation, and 1 case each of arthritis, dyspnea, hepatitis, pancreatitis, pericarditis, pneumonitis, and ventricular fibrillation (VF). One patient experienced fatal myocarditis. Subjects should be informed to report any signs or symptoms of developing autoimmune or inflammatory disease.

In animals, lymphoplasmacytic infiltration of the choroid plexus and spinal cord was observed with anti-PD-1 antibody and anti-PD-1 plus anti-LAG-3 therapy but not anti-LAG-3 alone. Aseptic meningitis has also been observed in 3 human subjects receiving the combination and all were successfully treated with immunosuppressive therapy. Vigilance is recommended for potential symptoms.

Additionally, severe cardiac toxicities have been reported as stated above, including 1 case of G5 myocarditis and 1 case of G4 VF. Subsequent cardiac monitoring with troponins revealed 3 cases of G1 myocarditis. Patients at risk for cardiac toxicities will be excluded and vigilance is recommended for potential symptoms and abnormalities detected on laboratory monitoring.

9.10 Returns and Reconciliation

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

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

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

10.1 Peripheral Blood Mononuclear Cells (PBMCs) and Whole Blood

PBMCs will be collected per the study calendar. Post-treatment changes in PBMCs including effector, helper, and regulatory T cells, NK cells and macrophages will be measured by FACs. Post-treatment expression of PD-1 and other lymphocyte activation markers will be measured and correlated with OS. Relatlimab receptor occupancy in the blood will be quantified by a flow cytometry-based receptor occupancy assay.

10.2 Serum and Plasma Marker Studies

Sera and plasma will be collected per the study calendar to identify potential therapeutic targets, biomarkers, and predictors of response and autoimmune toxicity through proteomic approaches. This will include molecules of close interest to Lag3 (soluble Lag3, soluble FGL1, etc.).

10.3 Tumor Tissue Studies

For patients who undergo baseline biopsy 4-6 core tumor biopsies will be collected prior to treatment initiation. Additional tumor tissue, including adjacent normal tissue when clinically appropriate, will be collected from surgical resection samples for patients who continue to a surgical resection. Archival tumor samples may also be collected for every patient (slides and/or blocks) if available. Archival tumor samples may be used in lieu of the baseline biopsy for patients who have sufficient archival tumor tissue. Fine needle aspiration samples do not contain sufficient tissue contextual information and will not be obtained.

The purpose of these tumor tissue studies is to determine the effect of nivolumab monotherapy, and in combination therapy with relatlimab, on tumor infiltrating lymphocytes as well as immune activation pathways, immune suppressive pathways, and cytokine/chemokine signaling. Relatlimab receptor occupancy on tumor infiltrating lymphocytes will also be determined. In situ tissue assays will include immunohistochemistry (including multiplexed platforms, e.g. imaging mass cytometry/CODEX) and RNAscope.

Table 3: Proposed Biomarker Table

Biomarker	Assay	Use (Integral, Integrated, or Exploratory)AND Purpose [b]	Tissue/Body Fluid Tested and Timing of Assay
CD8+ T effector cells and CD4+FoxP3+ T regulatory cells	IHC	To explore changes in the tumor microenvironment that may impact response to therapy.	Tumor tissue Pre-treatment, and at surgical resection
PD-L1 expression on tumor and tumor infiltrating lymphocytes (TILs)	IHC	To explore changes in the tumor microenvironment that may impact response to therapy	Tumor tissue Pre-treatment, and at surgical resection
MHC I and II expression	IHC	To explore changes in MHC I and II expression on anti-PD1 +/- anti-Lag3 treatment, in order to provide a mechanistic rationale for the combination	Tumor tissue Pre-treatment, and at surgical resection
Lag3 and FGL1 expression	IHC	To explore baseline expression and changes in molecules of interest for Lag3 inhibition	Tumor tissue Pre-treatment, and at surgical resection
ADAM10 and ADAM17 expression	RNAscope	To explore baseline expression and changes in regulatory molecules of Lag3 function	Tumor tissue Pre-treatment, and at surgical resection

Genomic sequencing library construction, whole genome/exome sequencing, whole transcriptome sequencing, T cell receptor and B cell receptor sequencing, neoepitope prediction, mutation burden, CITE-seq, ChIP-seq, ATAC-seq, and MBD-seq, and bioinformatic analysis will be performed either at an on-campus laboratory or at an off-campus sequencing service. These assays will allow us to explore the effects of therapy on tumor and tumor infiltrating immune cells.

All the samples will be de-identified before sending to any laboratory for sequencing. The FASTQ files, BAM files and VCF files will be generated and analyzed. Genomic sequencing data will be stored and computations conducted using a JH IT managed subscription of Azure.

Results from the sequencing studies will not be released to the patients. These studies are for research purposes only and are not using a clinically validated platform.

11. STUDY CALENDAR

Following neoadjuvant therapy with nivolumab ± relatlimab, patients will undergo surgical evaluation. The timing of the surgical evaluation is at the discretion of the surgical oncologist, but will generally occur after completion of 2 cycles of immunotherapy. Surgery will generally occur at approximately 30 days after the last dose of immunotherapy, but the optimal date of surgery is at the discretion of the surgical oncologist. For patients determined to be candidates for surgery, the surgical resection should be performed within 60 days of the last dose of immunotherapy. Patients who do not undergo surgical resection due to a complete or near complete response to neoadjuvant therapy may continue to receive an additional 10 cycles of immunotherapy. Such patients do not need to complete the Adjuvant Eligibility Checklist.

Post-surgery, patients from both treatment arms with no evidence of recurrence/progression may receive an additional 10 doses of adjuvant therapy every 28 days to complete 12 months of IO treatment. Adjuvant therapy should begin within 90 days of surgical resection.

	Pre-study	Neoadjuvant Cycles[19] (Cycles 1 & 2)				Surgical Evaluation [18]
		Day 1	Day 8[24]	Day 15[24]	Day 22[24]	
Visit Window[1]	-28 to -1	±3	±4	±4	±4	+7
Nivolumab		X				
Relatlimab (Arm B only)[21]		X				
Surgical evaluation	X					X[18]
Informed consent	X					
Inclusion/exclusion criteria	X					
Randomization	X					
Demographics	X					
Medical and Cancer History[2]	X					
Concurrent medications	X	X	X	X	X	X
Vital Signs and pulse ox[3]	X	X				X
Physical exam[4]	X	X				X
Performance status	X	X				X
Height[5]	X					
Weight	X	X				X
CBC with differential[6,7]	X	X				X
CMP[6,7]	X	X				X
TSH[6,8]	X	X				X
Troponin, CPK/CK-MB[6, 9]	X	X	X	X	X	X
EKG[10]	X	X				
Echocardiogram[11]	X					
Serum/Urine Preg[6, 12]	X	X				
AFP[6]	X	X				X
PT /INR and pTT[6]	X					X
Lipase[6]	X					
Hepatitis C[13]	X					
Hepatitis B[13]	X					
Viral quantitation[13]	X					
Adverse event evaluation[23]	X	X	X	X	X	X
Whole blood for PBMCs and RO (Up to 100 CCs) [14, 20]		X				X
Whole blood for serum (up to 5 CCs) [14, 20]		X				X
Whole blood for plasma (up to 10 CCs) [14, 20]		X				X
RECIST[22]		X				X
Radiographic evaluation[15]	X					X
Tumor biopsy[16, 20]	X					
Surgical Specimen[17, 20]						X
Archival tumor tissue[16]	X					

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

1) Longer delays to be approved by the principal investigator.
2) Includes history of lung disease, HIV, hepatitis B or C infection, and complete cancer history.
3) Temperature, blood pressure, pulse, and pulse oximetry should be taken prior to and at the end of the study drug infusion.
4) Complete physical exam will be completed at baseline; focused physical examinations will be conducted thereafter. Exams, concomitant medication, AE assessments can be made up to 3 days prior to infusion. Additional weekly visits (in person, telemedicine, or by telephone) with AE assessment will occur through Week 8 for patients that received relatlimab
5) Height will be taken at or prior to screening only.
6) Labs may be collected within a window of 7 days prior to C1D1 and C3D1 and 4 days prior to all other visits. Unexpected Grade 3 or greater laboratory abnormalities should be repeated within 24-72 hours if clinically indicated and monitored as necessary to determine if event meets toxicity criteria.
7) Clinical hematology: CBC with differential ANC, ALC, AEC, and platelet count; serum chemistry: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
8) T3/FT4 to be checked reflexively if clinically indicated because TSH is abnormal
9) T(cTnt) or I (cTnI) to be obtained at baseline during Pre-Study screening visit for all patients prior to randomization. For patient randomized to Arm B, T(cTnt) or I (cTnI) and CPK/CK-MB will be obtained weekly (±4 day window) starting with C1D1 through surgical evaluation (week 8). T(cTnt) or I (cTnI) and CPK/CK-MB will be obtained during adjuvant Cycles 3 & 4 for Arm B patients. Troponin elevations will require the participant to undergo a cardiac evaluation per **Section 7.2**. Following this evaluation, determination of further treatment will be based on the discussion with the IND Sponsor.
10) EKG should be performed within 7 days prior to initiating therapy (C1D1 EKG only needs to be completed if screening EKG was more then 7 days prior to C1D1 dosing), if clinically indicated, or at elevation of troponin levels per **Section 7.2**
11) LVEF assessment with documented LVEF >50% by either TTE or MUGA (TTE preferred test) within 6 months from first study drug administration.
12) Serum or urine bHCG for women of childbearing potential only. Women with modestly elevated bHCG must obtain a negative transvaginal ultrasound in order to enroll on this protocol.
13) All screened patients should receive qualitative HBsAg, anti-HBc, anti-HBs, and anti-HCV. Patients found to have hepatitis B infection (positive anti-HBc and/or anti-HBsAg) should receive quantitative hepatitis B Virus (HBV) DNA testing, and patients with hepatitis C infection (positive anti-HCV) should receive quantitative HCV RNA testing at screening.

Patients who test positive for hepatitis B infection should have monitoring and treatment for hepatitis B according to institutional treatment practices throughout the entire study period.

14) Pre-study research blood will be collected after eligibility is confirmed, but prior to first dose of therapy. During adjuvant immunotherapy, research blood will be collected every 3 cycles beginning with Cycle 3, and at the EOT visit at participating sites.
15) Radiographic evaluation will be performed with a CT chest/abdomen/pelvis, or MRI liver plus CT chest (preferred). Patients will preferably have the same imaging modality used at baseline and prior to surgical evaluation. CT scans of the chest/abdomen/pelvis with IV contrast that were performed as part of SOC care prior to consenting may be used if the scans were performed within 28 days of C1D1. During adjuvant immunotherapy, patients should receive a CT chest/abdomen/pelvis, or MRI liver plus CT of the chest every 3 months (± 1 month) to evaluate for disease recurrence. The EOT scans do not need to be repeated if one has been done within the past 6 weeks.
16) A baseline biopsy should be attempted for all subjects unless determined to be unsafe by the study PI or if the subject has sufficient archival tumor tissue. Biopsy should be performed after eligibility is confirmed but prior to initiation of therapy.
17) Only for subjects who undergo surgical resection. Refer to laboratory manual for details.
18) Surgical evaluation is standard of care and the timing is at the discretion of the treating surgical oncologist. Window provided for surgical evaluation is a recommendation only and is not mandated per protocol.
19) Cycle length is 28 days
20) Research samples will be collected at the discretion of the PI based on availability of supplies and safety of patient and staff
21) Order of administration is nivolumab followed by relatlimab. Subjects should be observed for a minimum of 30 minutes between each infusion.
22) RECIST to be completed at C1D1 and surgical evaluation only during neoadjuvant phase
23) AE assessment will be made weekly (via in-person visit, telemedicine, or telephone) through Cycle 4 for patients who received relatlimab.
24) Additional visits on Days 8, 15, and 22 are for Cycles 1-4 only for patients that received relatlimab

	Adjuvant Cycles (Cycles 3-12)[14]				EOT Visit[16]	100 Day Safety FU[17]	Clinical FU[18]	Survival FU[19]
	Day 1	Day 8[15]	Day 15[15]	Day 22[15]				
Visit Window[1]	±7	±4	±4	±4	±7	±14		
Nivolumab	X							
Relatlimab (Arm B only)[2]	X							
Inclusion/exclusion criteria	X[20]							
Concurrent medications	X	X	X	X	X	X		
Vital Signs and pulse ox[3]	X				X			
Physical exam[4]	X				X			
Performance status	X				X			
Weight	X				X			
CBC with differential[5,6]	X				X			
CMP[5,6]	X				X			
TSH[5,7]	X							
Troponin, CPK/CK-MB[5, 8]	X	X	X	X				
Serum/Urine Preg[5, 9]	X							
AFP[5]	X[21]				X			
Lipase	X[22]							
PT/INR and PTT	X[22]							
Adverse event evaluation[10]	X	X	X	X	X	X		
Whole blood for PBMCs and RO (Up to 100 CCs)[11]	X				X			
Whole blood for serum (up to 5 CCs)[11]	X				X			
Whole blood for plasma (up to 10 CCs)[11]	X				X			
Radiographic evaluation[12]	X						X	
Archival tumor tissue[13]	X							
Survival Follow-Up								X

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

1) Longer delays to be approved by the principal investigator.
2) Order of administration is nivolumab followed by relatlimab. Subjects should be observed for a minimum of 30 minutes between each infusion.
3) Temperature, blood pressure, pulse, and pulse oximetry should be taken prior to and at the end of the study drug infusion.
4) Complete physical exam will be completed at baseline; focused physical examinations will be conducted thereafter. Exams, concomitant medication, AE assessments can be made up to 3 days prior to infusion. Additional weekly visits (in person, telemedicine, or by telephone) with AE assessment will occur through Cycle 4 for patients that received relatlimab.
5) Labs may be collected within a window of 7 days prior to C1D1 and C3D1 and 4 days prior to all other visits . The EOT labs maybe be collected within a window of 7 days of the visit. Unexpected Grade 3 or greater laboratory abnormalities should be repeated within 24-72 hours if clinically indicated and monitored as necessary to determine if event meets toxicity criteria.
6) Clinical hematology: CBC with differential ANC, ALC, AEC, and platelet count; serum chemistry: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
7) T3/FT4 to be checked reflexively if clinically indicated because TSH is abnormal.
8) T(cTnt) or I (cTnI) to be obtained at baseline during Pre-Study screening visit for all patients prior to randomization. For patient randomized to Arm B, T(cTnt) or I (cTnI) and CPK/CK-MB will be obtained weekly (±4 day window) starting with C1D1 through surgical evaluation (week 8). T(cTnt) or I (cTnI) and CPK/CK-MB will be obtained during adjuvant Cycles 3 & 4 for Arm B patients. Troponin elevations will require the participant to undergo a cardiac evaluation per **Section 7.2**. Following this evaluation, determination of further treatment will be based on the discussion with the IND Sponsor.
9) Serum or urine bHCG for women of childbearing potential only. Women with modestly elevated bHCG must obtain a negative transvaginal ultrasound in order to enroll on this protocol.
10) AE assessment will be made weekly (via in-person visit, telemedicine, or telephone) through Cycle 4 for patients who received relatlimab
11) Pre-study research blood will be collected after eligibility is confirmed, but prior to first dose of therapy. During adjuvant immunotherapy, research blood will be collected every 3 cycles beginning with Cycle 3, and at the EOT visit at participating sites. Research samples will be collected at the discretion of the PI based on availability of supplies and safety of patient and staff

12) Radiographic evaluation will be performed with a CT chest/abdomen/pelvis, or MRI liver plus CT chest (preferred) starting 3 months after the day of surgery. Patients will preferably have the same imaging modality used at baseline and prior to surgical evaluation. During adjuvant immunotherapy, patients should receive a CT chest/abdomen/pelvis, or MRI liver plus CT of the chest every 3 months (± 1 month) to evaluate for disease recurrence. The EOT scans do not need to be repeated if one has been done within the past 6 weeks.
13) Archival tumor tissue may be collected if it was determined to be unsafe by the study PI to obtain a biopsy.
14) Adjuvant therapy should begin within 90 days after surgical resection. Patients can receive adjuvant therapy every month for 10 months or cycles (whichever comes first). These study requirements also apply to patients who do not undergo surgical resection due to complete or near complete response to neoadjuvant therapy and who continue to receive 10 additional cycles of immunotherapy. Cycle length is 28 days.
15) Additional visits on Days 8, 15, and 22 are for Cycles 1-4 only for patients that received relatlimab
16) EOT visit will occur 30 (±7) days after the final dose (or within 7 days prior to initiation of a new anti-cancer treatment, whichever comes first). NOTE: CT scan assessment at EOT will occur 30 days (± 4 weeks) after the final dose. If the patient is unable to return for an EOT visit (e.g. disease/clinical progression, poor health, intercurrent illness, or initiation of a new anti-cancer therapy, or if the EOT visit occurs early, an assessment for AEs should be made by telephone, telemedicine visit, or email on day 30 (±1 week) after last study dose in place of the PE/PS/vitals. Clinical laboratory values should still be collected. Follow **Section 6.10** for additional details regarding follow-up schedule for subjects who discontinue from treatment.
17) Subjects who discontinue from treatment should be contacted by telephone or email at 100 days (±14 day reporting window) from their last dose of study drug or within 7 days before initiation of a new antineoplastic treatment (whichever comes first) to assess for treatment related toxicities. In addition, all SAEs occurring during this time should be reported as well.
18) Subjects who continue without local recurrence or disease progression will enter the clinical follow-up portion of the trial. Clinical follow-up will occur per standard of care for 5 years or study closure (whichever comes first) to monitor overall survival and disease free survival. Information of other cancer therapies after discontinuation from the study treatment will also be collected. After disease progression, subjects will enter the survival follow-up portion of the trial.
19) Subjects who discontinue treatment and have disease progression will enter the survival follow-up portion of the trial. Subjects will be contacted per standard of care to monitor overall survival. Information of other cancer therapies after discontinuation from the study treatment will be collected as well.
20) Prior to first adjuvant dose for patients who undergo surgical resection.
21) Prior to first adjuvant dose and every 3rd cycle thereafter
22) Lipase, PT/INR and PTT test collected only on C3D1

12. STUDY ENDPOINTS

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with study drug.

Evaluable for response. All subjects who have received at least one dose of study drug as part of this study and undergo a surgical evaluation are evaluable for response. Methods for evaluation of response are described below.

12.1 Primary Endpoint

The primary endpoint focuses on feasibility, which will be measured by the proportion of patients that experience a treatment-related AE that precludes continuing on to surgery within 60 days of the last dose of neo-adjuvant immunotherapy. This outcome specifically focuses on whether or not the treatment is a barrier to surgery. Individuals who do not go on to receive surgery due to other causes (e.g. progressive disease, patient refusal) will not be counted as feasibility failures since none of the patients would be expected to proceed to surgery under the standard of care. The proportion of failures will be calculated.

12.2 Secondary Endpoints

12.2.1 Safety

Safety will be assessed by the frequency of adverse events occurring up to 100 days after the last dose of study drug using CTCAE v5.0.

Safety assessed by the following measures:

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

12.2.2 R0 Resection Rate

R0 resection is defined by a microscopically margin-negative resection, in which no tumor (gross or microscopic) remains in the primary tumor bed.

12.2.3 Tumor Response Rate

The tumor response rate is defined as the proportion of patients who have either radiologic or pathologic complete response. A pathologic complete response is defined as a definitive surgical resection with no residual cancer in the primary hepatic tissue or nodes (ypT0ypN0). Complete radiologic response is defined as an absence of visible disease on CT imaging by RECIST 1.1 evaluation.

12.2.4 Disease Free Survival (DFS)

DFS is defined as the duration of time since achieving freedom of disease to identification of recurrent disease on imaging or death, whichever occurs first. The pattern of recurrence (local vs. metastatic, or both) will also be inquired. Individuals will be censored at the date of the last scan if no event occurs. Patients who do not achieve disease-free status, including those who do not undergo surgical resection, will be excluded from disease-free survival analyses.

12.2.5 Overall Survival (OS)

OS is defined as the duration of time from randomization to time of death. Individuals will be censored at the date of the last contact if no event occurs.

12.2.6 Overall Response Rate (ORR)

ORR is defined as the proportion of patients achieving a complete response (CR) or partial response (PR) based on the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). Please refer to **Appendix D** for additional information. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST 1.1 criteria.

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the time of study enrollment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at the time of study enrollment and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality,

lesion conspicuity, and measurement. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at study enrollment and the lesions should be measured/assessed on the same pulse sequence.

12.3 Exploratory Endpoints

Intratumoral changes in pre- and post-treatment core biopsy specimens and at resection will be studied primarily using multiplex immunohistochemistry (IHC), but may be confirmed with other laboratory techniques. Our proposed data integration of imaging mass cytometry/CODEX, RNAseq, TCRseq, and BCRseq will enable us to develop a rich molecular, cellular, and spatially-preserved atlas of the anti-tumor immune response in HCC. By correlating these data with pathologic responses to therapy, we hope to identify early immune determinants of HCC response and resistance.

13. DATA REPORTING / REGULATORY REQUIREMENTS

AE guidelines and instructions for AE reporting can be found in **Section 8 (Adverse Events: List and Reporting Requirements)**.

Each Principal Investigator will comply with all regulated local reporting requirements and regulations, including ICH E6 guidelines for Good Clinical Practices.

13.1 Data Collection and Processing

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

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

<u>Protocol Chair</u>
The Protocol Chair and/or designee is responsible for performing the following tasks:

- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments.
- Assuring that all participating institutions are using the correct version of the protocol.
- Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study.
- Reviewing and ensuring reporting of SAE
- Reviewing data from all sites.

Coordinating Center (Johns Hopkins University)

The Coordinating Center (or its representative) is responsible for performing the following tasks:

- Ensuring that IRB approval has been obtained at each participating site prior to the first subject registration at that site, and maintaining copies of IRB approvals from each site.
- Monitoring subject registration.
- Collecting and compiling data from each site.
- Establishing procedures for documentation, reporting, and submitting of AE's and SAE's to the Protocol Chair, and all applicable parties.
- Facilitating audits by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.

Participating Sites

Participating sites are responsible for performing the following tasks:

- Following the protocol as written, and the guidelines of Good Clinical Practice (GCP).
- Submitting data to the Coordinating Center.
- Consent subjects promptly and randomize eligible subjects in EDC.
- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol.
- Maintaining regulatory binders on site and providing copies of all required documents to the Coordinating Center.
- Collecting and submitting data according to the schedule specified by the protocol.

13.2 Safety Meetings

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

Monthly teleconferences will be scheduled to include the Coordinating Center and the clinical trial sites. During these meetings, the Coordinating Center and clinical trial sites shall discuss the following: study protocol updates, safety data, enrollment status, and progress of data for objectives.

13.3 Monitoring

The SKCCC Compliance Monitoring Program will provide external monitoring in accordance with SKCCC DSMP (Version 6.0, 02/21/2019). The SMC Subcommittee will determine the level of patient safety risk and level/frequency of monitoring. Data monitoring of this protocol will occur on a regular basis with the frequency dependent on the rate of subject accrual and the progress of the study. Eligibility for all sites will be monitored by the Protocol Chair or authorized representatives of the Coordinating Center. The protocol will be internally monitored by the Principal Investigator at each site. The PI shall internally monitor the progress of the trial,

including review and confirmation of all safety/treatment-related outcomes, response assessments, safety reports and/or any related source documentation. IND sponsor is ultimately responsible for external monitoring of the trial. External monitoring will occur according to the following guidelines:

Johns Hopkins SKCCC: The protocol will be monitored externally by the SKCCC CRO in accordance with SKCCC guidelines. Trial monitoring and reporting will be done through the Safety Monitoring Committee (SMC) at SKCCC.

Participating Site(s): The protocol will be monitored by authorized representatives of the Coordinating Center.

Authorized representatives of the Coordinating Center may visit the satellite sites to perform audits or inspections, including source data verification. The purpose of these audits or inspections is to systematically and independently examine all trial-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), and any applicable regulatory requirements.

Additional data and safety monitoring oversight will also be performed by the SKCCC Safety Monitoring Committee (SMC - as defined in the DSMP) and the SKCCC DSMB as detailed below.

Interim analysis of toxicity, outcome and ongoing scientific investigations will be performed at least annually by the Sidney Kimmel Comprehensive Cancer Center Data Safety Monitoring Board (SKCCC DSMB). The SKCCC DSMB will review aspects of this trial that are outlined in the responsibilities section of the Data and Safety Monitoring Board (DSMB) Guidance. If the committee decides that amendments should be made to this trial, recommendations will be made in writing to the Study Principal Investigator. The study team will submit modifications to the IRB within 60 days of receipt from the DSMB. The Associate Director of Clinical Research, will arbitrate any disagreements between the DSMB and the study Principal Investigator. These changes may include early termination of accrual if deemed appropriate.

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

13.4 Study Documentation

13.4.1. Informed Consent and Authorization for use and Disclosure of Protected Health Information

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

13.4.2. Investigator Study Files

Documentation about the investigator and study staff, the IRB and the institution, is required before study site initiation. A list of required documents will be provided by the IND Sponsor or designee to each participating investigator. Copies of these documents as well as supplemental information, such as the investigator's obligations, IB, clinical study protocol and amendments, safety information, investigational agent information, biological samples and laboratory procedures, SRM, study logs and IND Sponsor/investigator/study monitor correspondence will be kept on-site in study site-specific files.

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

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

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

13.4.3. Case Report Forms and Source Documentation

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

13.4.4. Retention of Study Documents

According to ICH E6, Section 4.9, all CRFs, as well as supporting paper and electronic documentation and administrative records, must be retained for at least 2 years after the

last approval of a marketing application and until there are no pending or contemplated marketing applications, or at least 2 years have elapsed since the formal discontinuation of clinical development of an individual product. Longer retention periods may apply. The IND Sponsor will notify investigators as to when documents no longer need to be retained. No study documents will be destroyed or moved to a new location without prior written approval from the IND Sponsor. If the investigator relocates, retires or withdraws from the clinical study for any reason, all records required to be maintained for the study should be transferred to an agreed-upon designee, such as another investigator at the institution where the study was conducted.

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

13.4.5. Data Confidentiality and Subject Anonymity

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

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

14. STATISTICAL CONSIDERATIONS

This is a two arm randomized trial to evaluate the feasibility of perioperative nivolumab or nivolumab with relatlimab for treating patients with potentially resectable HCC.

14.1 Primary Endpoint

The primary endpoint focuses on feasibility, which will be measured by the proportion of patients that experience a treatment-related AE that precludes continuing on to surgery within 60 days of the last dose of immunotherapy. This outcome specifically focuses on whether or not the treatment is a barrier to surgery. Individuals who do not go on to receive surgery due to other causes (e.g. progressive disease, patient refusal) will not be counted as feasibility failures since none of the patients would be expected to proceed to surgery under the standard of care. The proportion of failures will be calculated.

14.2 Safety Endpoints

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

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

14.3 Sample Size/Accrual Rate

Up to 33 patients may be enrolled to obtained a total of 30 evaluable patients (15 per arm). Patients are considered evaluable if they receive at least one dose of study drug. The primary goal is to establish feasibility based upon the number of patients who do no experience a treatment-related AE that precludes continuing on to surgery. Patients will be randomized in a 1:1 ratio to receive nivolumab or nivolumab + relatlimab neoadjuvant therapy.
Patients who were randomized but didn't receive study treatment will be replaced.

For each arm, a failure rate of more than 33% would be considered unacceptable. If 6 of 10 meet the criteria for failure, the lower bound of 90% confidence interval of failure rate is 0.35 (which is above the 33% threshold) we would conclude that the treatment was not feasible.

14.4 Stratification Factors

The study has two treatment arms and patients will be randomly assigned to one of them. There is no stratification factor for randomization

14.5 Analysis of Secondary Endpoints

For each arm, R0 resection rate will be estimated among the patients who receive at least one dose of neoadjuvant immunotherapy, as well as among those who continue to receive surgery. CR and MPR will each be estimated among patients who receive at least one dose of neoadjuvant immunotherapy and receive surgery. Fisher's exact test will be used to compare between arms.

Objective response rate (ORR) will be determined as the proportion of patients that achieve complete response and partial response at approximately 8 weeks after neoadjuvant immunotherapy.

Disease-free survival and overall survival will summarized using Kaplan-Meier method for each arm, and log-rank test will be used for comparisons between arms for exploratory purpose. The rates at 12 month, 18 month, 3 year, and 5 year will be estimated using Kaplan-Meier method, respectively.

13.6 Analysis of Exploratory Endpoints

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

14.6 Reporting and Exclusions

14.6.1 Evaluation of Toxicity

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

14.6.2 Evaluation of Response

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

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

All conclusions should be based on all eligible patients. Sub-analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

REFERENCES

1 Park, J. W. *et al.* Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. *Liver Int* **35**, 2155-2166, doi:10.1111/liv.12818 (2015).

2 Zhou, X. D. *et al.* Experience of 1000 patients who underwent hepatectomy for small hepatocellular carcinoma. *Cancer* **91**, 1479-1486, doi:10.1002/1097-0142(20010415)91:8<1479::aid-cncr1155>3.0.co;2-0 (2001).

3 Ascierto, P. A. *et al.* Initial efficacy of anti-lymphocyte activation gene-3 (anti-LAG-3; BMS-986016) in combination with nivolumab (nivo) in pts with melanoma (MEL) previously treated with anti-PD-1/PD-L1 therapy. *Abstract at 2017 ASCO Annual Meeting.*

4 Belghiti, J., Panis, Y., Farges, O., Benhamou, J. P. & Fekete, F. Intrahepatic recurrence after resection of hepatocellular carcinoma complicating cirrhosis. *Ann Surg* **214**, 114-117, doi:10.1097/00000658-199108000-00004 (1991).

5 Chen, M. F. *et al.* Postoperative recurrence of hepatocellular carcinoma. Two hundred five consecutive patients who underwent hepatic resection in 15 years. *Arch Surg* **129**, 738-742, doi:10.1001/archsurg.1994.01420310070012 (1994).

6 Lise, M. *et al.* Prognostic factors affecting long term outcome after liver resection for hepatocellular carcinoma: results in a series of 100 Italian patients. *Cancer* **82**, 1028-1036, doi:10.1002/(sici)1097-0142(19980315)82:6<1028::aid-cncr4>3.0.co;2-a (1998).

7 Portolani, N. *et al.* Early and late recurrence after liver resection for hepatocellular carcinoma: prognostic and therapeutic implications. *Ann Surg* **243**, 229-235, doi:10.1097/01.sla.0000197706.21803.a1 (2006).

8 Tabrizian, P., Jibara, G., Shrager, B., Schwartz, M. & Roayaie, S. Recurrence of hepatocellular cancer after resection: patterns, treatments, and prognosis. *Ann Surg* **261**, 947-955, doi:10.1097/SLA.0000000000000710 (2015).

9 Bouattour, M. *et al.* BIOSHARE multicenter neoadjuvant phase 2 study: Results of pre-operative sorafenib in patients with resectable hepatocellular carcinoma (HCC)—From GERCOR IRC. *Journal of Clinical Oncology* **34**, 252-252, doi:10.1200/jco.2016.34.4_suppl.252 (2016).

APPENDIX A PERFORMANCE STATUS CRITERIA

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

APPENDIX B RECOMMENDED MANAGEMENT ALGORITHMS

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

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

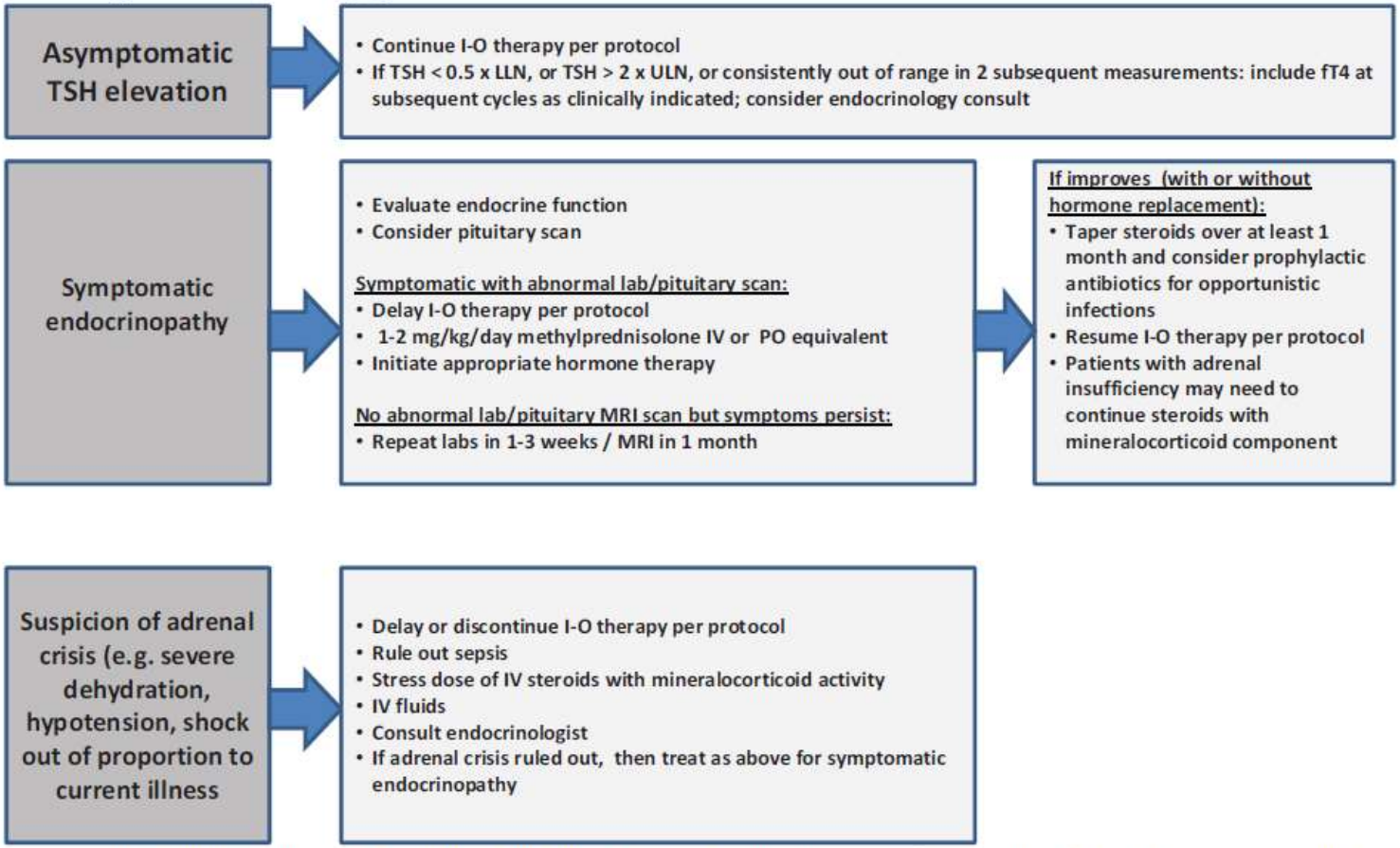
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

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

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

Endocrinopathy Management Algorithm

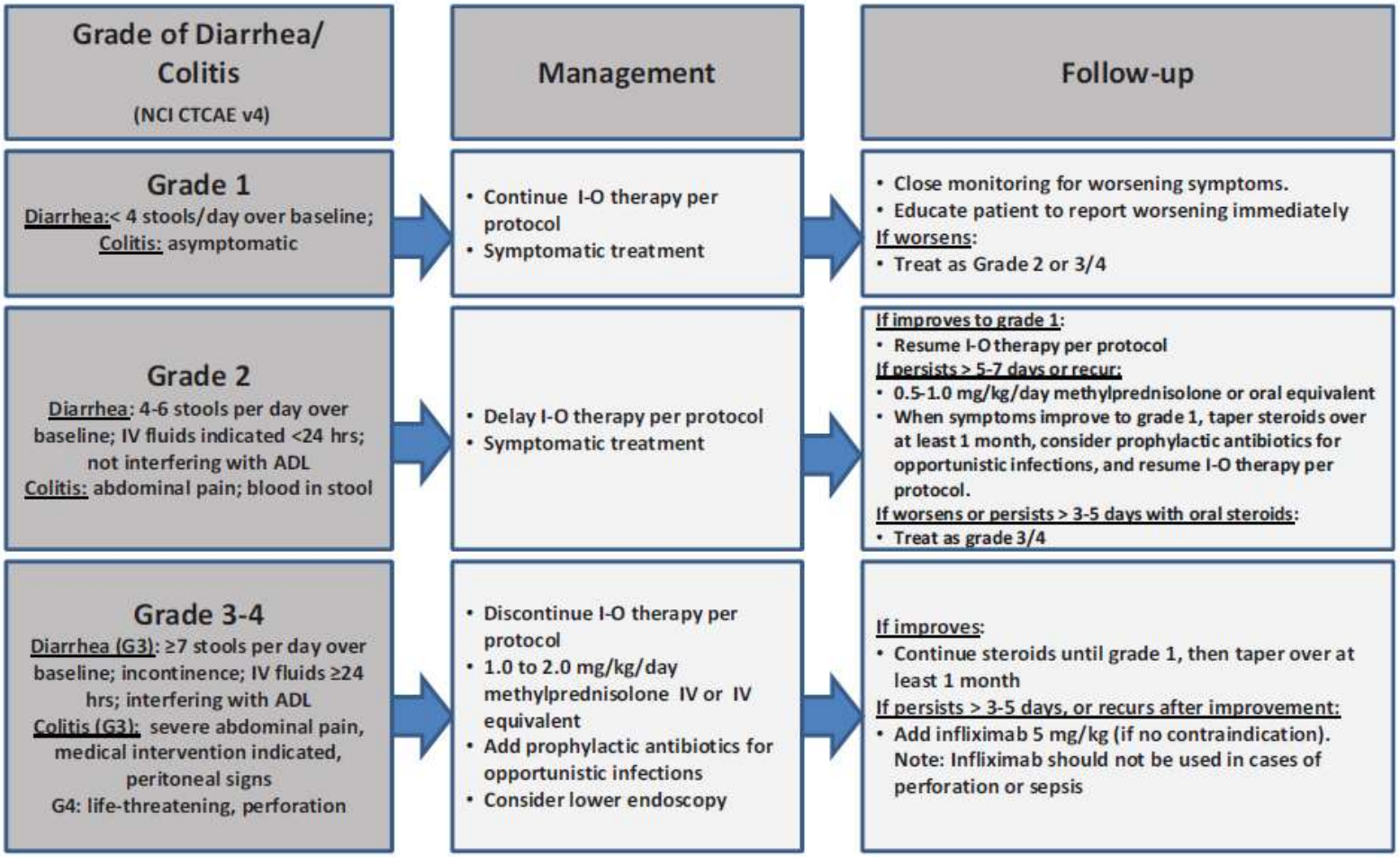
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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

GI Adverse Event Management Algorithm

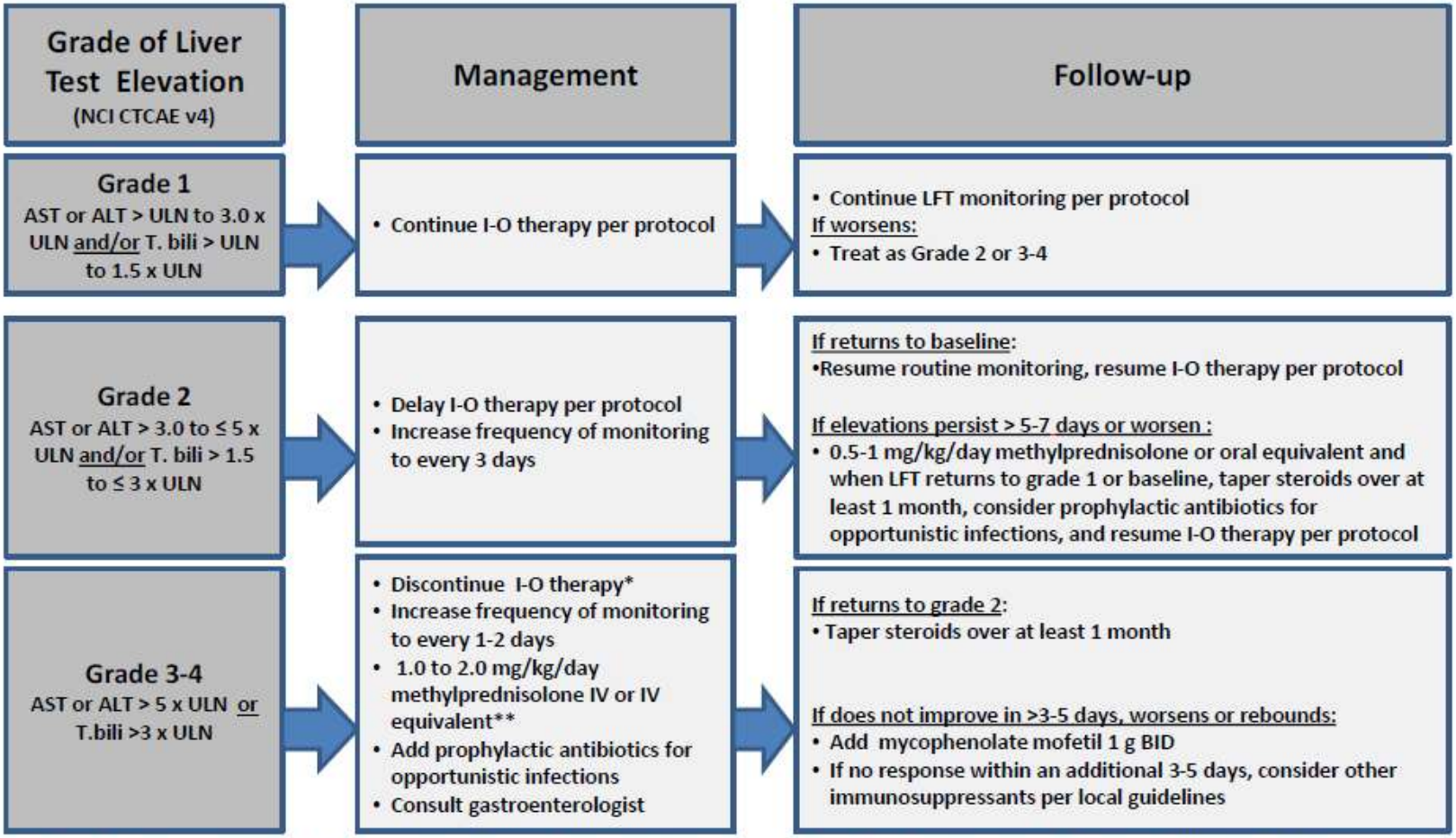
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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.

Hepatic Adverse Event Management Algorithm

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



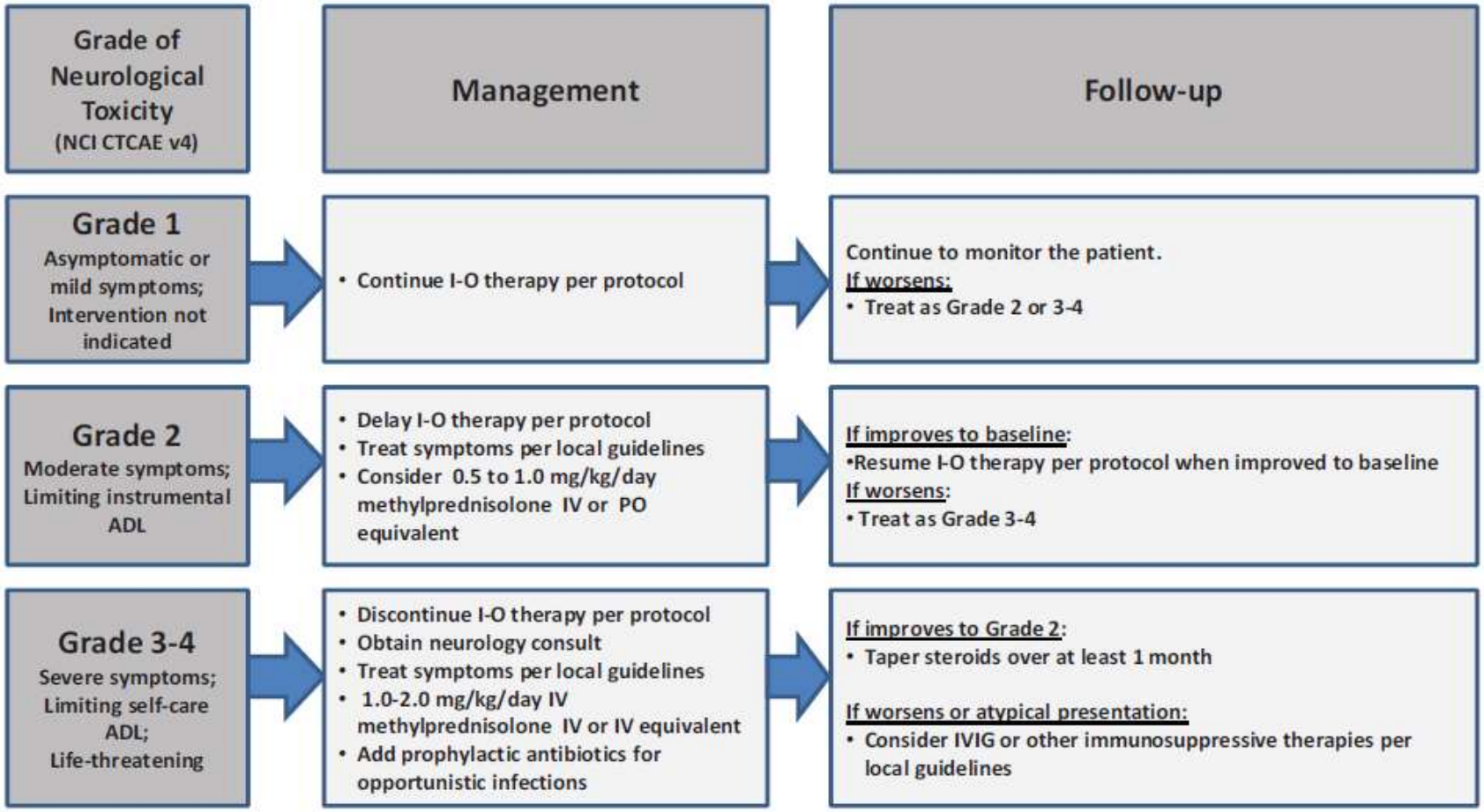
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

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

Neurological Adverse Event Management Algorithm

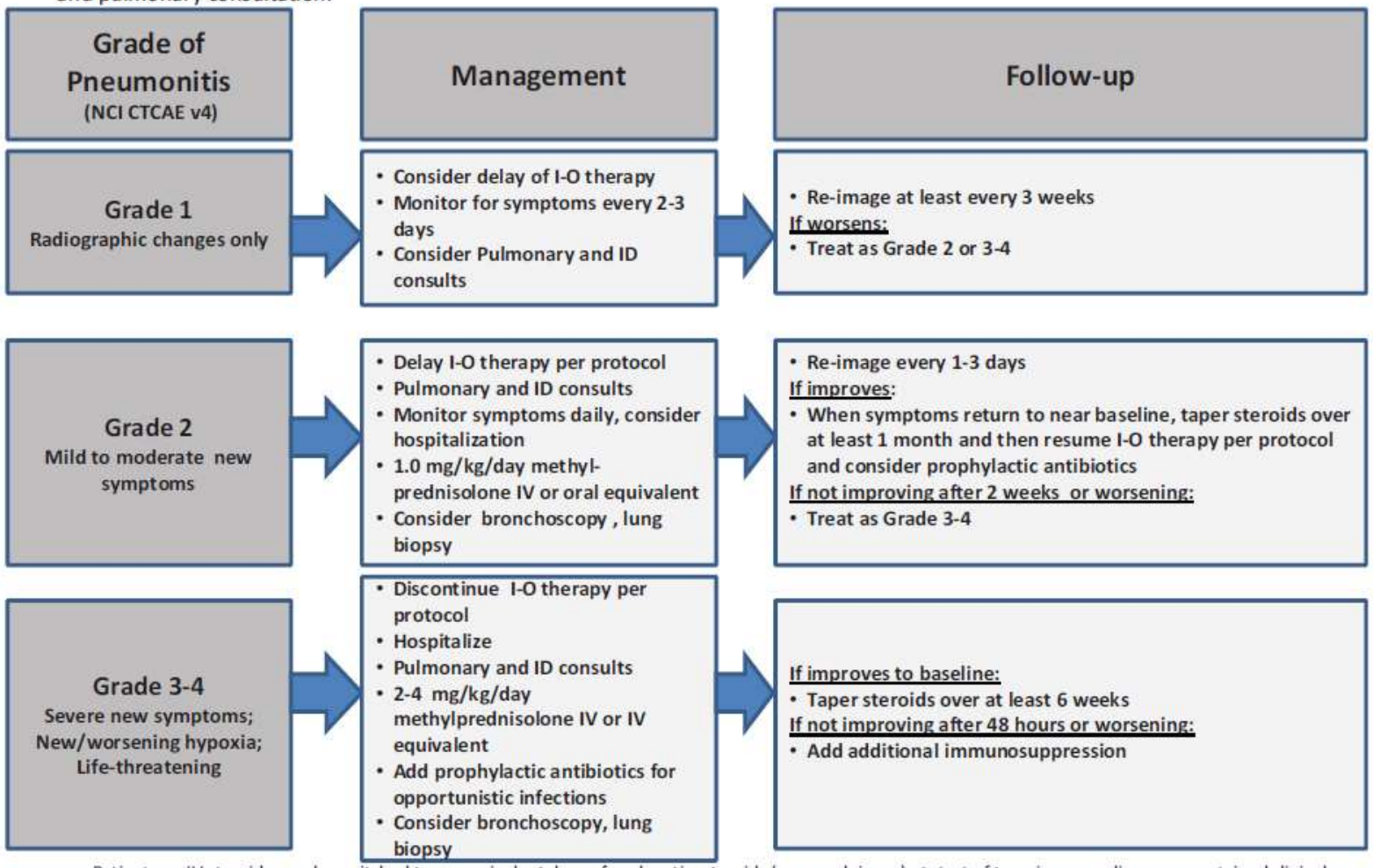
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

Pulmonary Adverse Event Management Algorithm

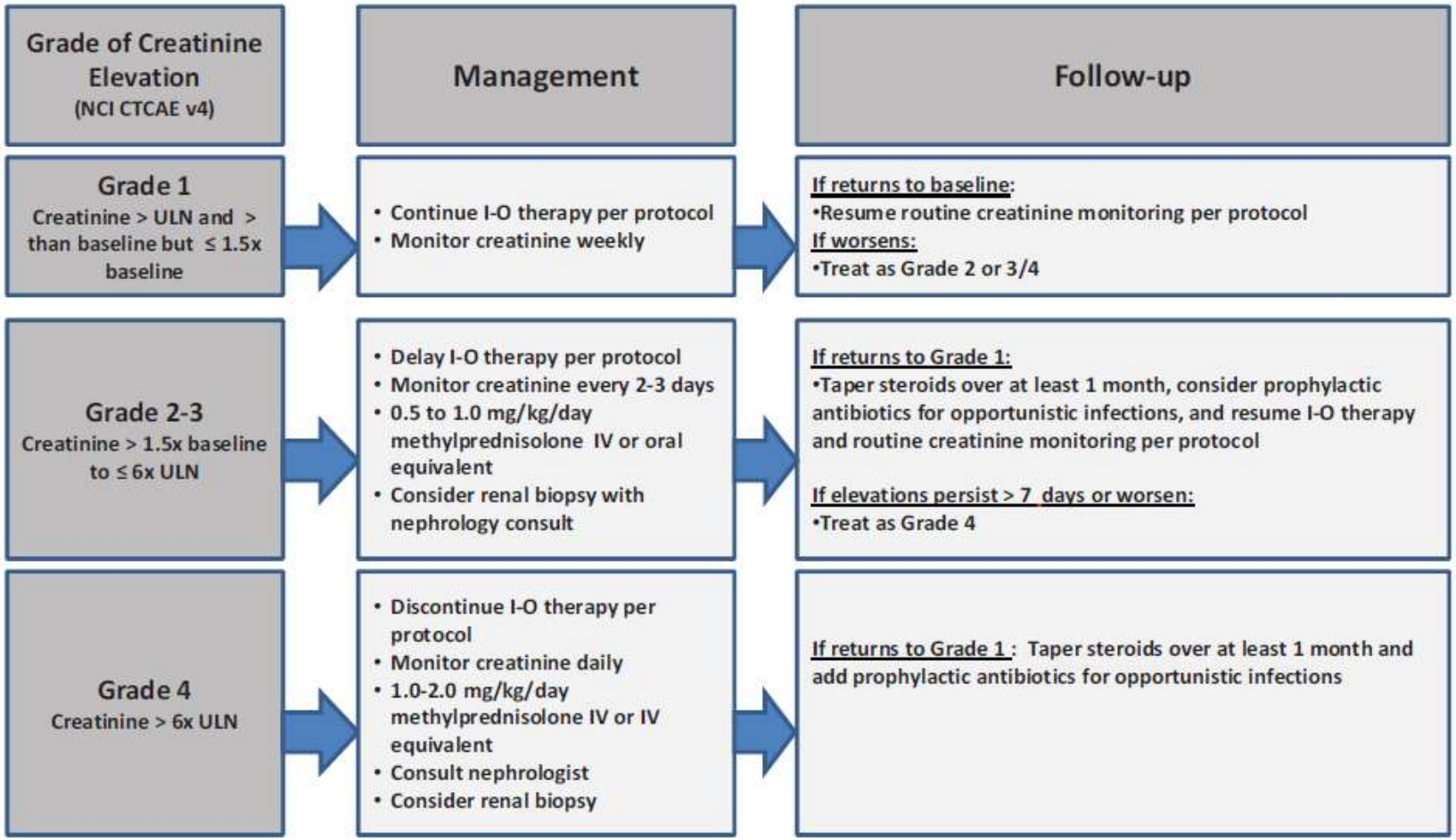
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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

Renal Adverse Event Management Algorithm

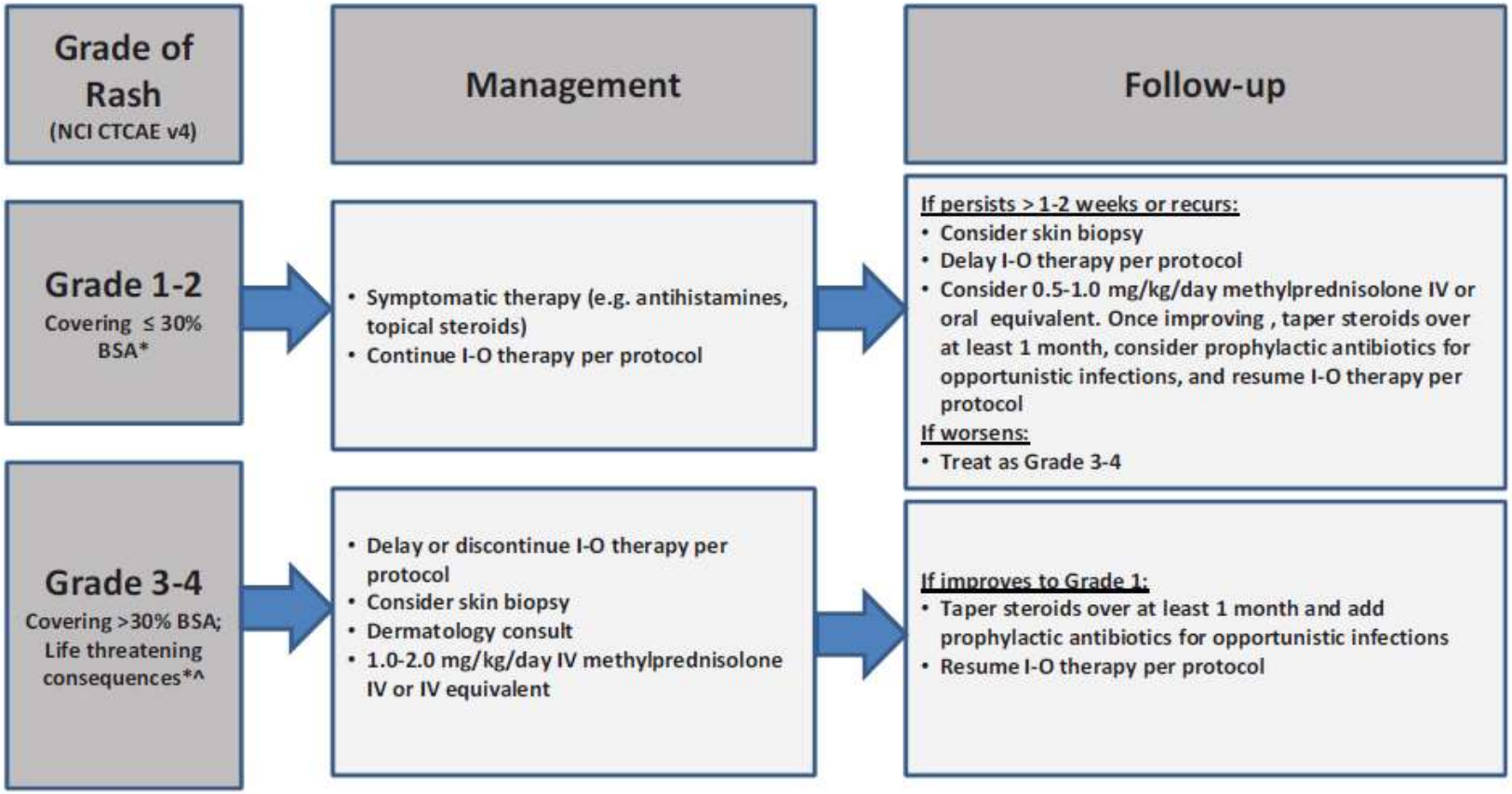
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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.

Skin Adverse Event Management Algorithm

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

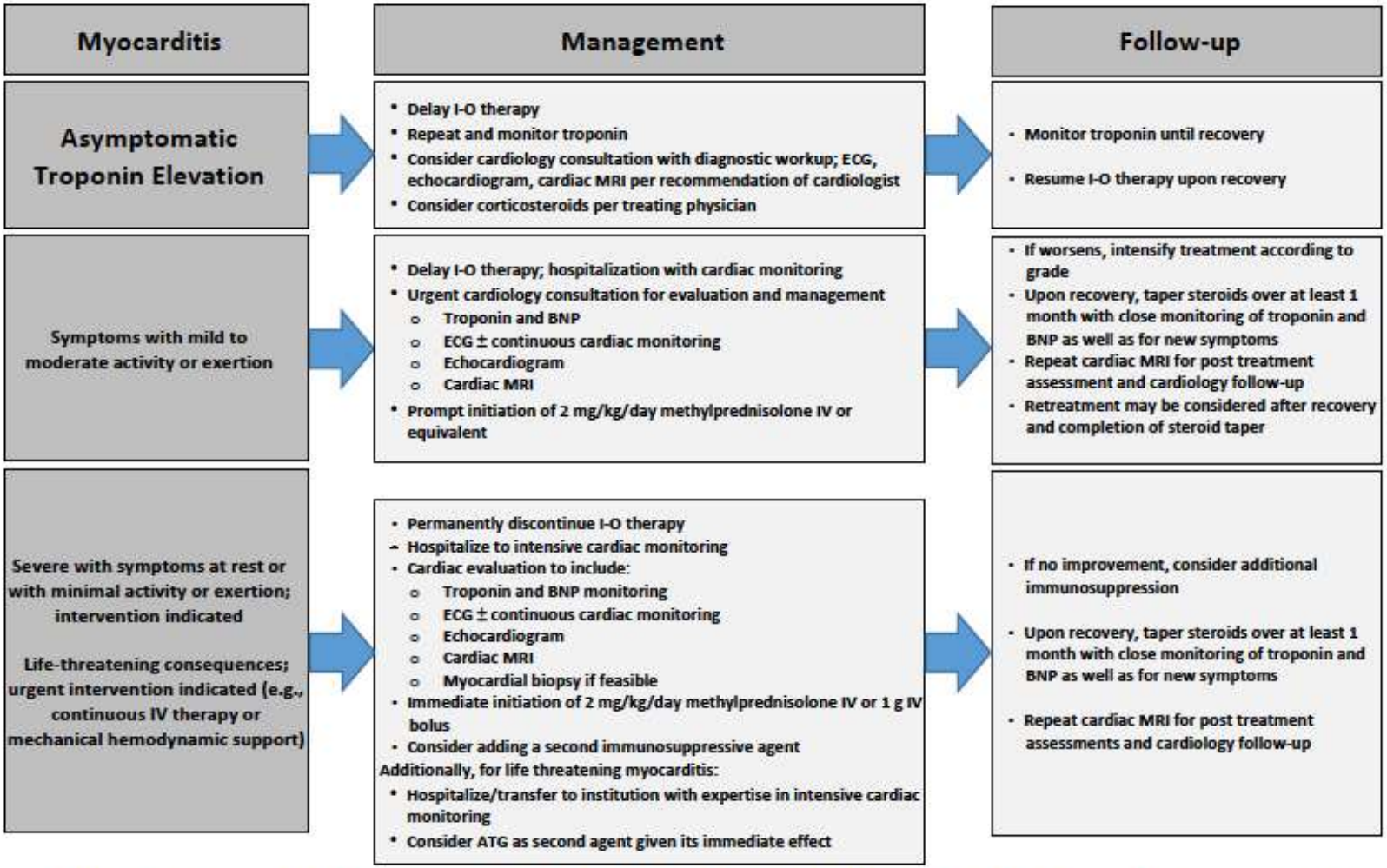


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

APPENDIX 2B RELATLIMAB MYOCARDITIS ADVERSE EVENT MANAGEMENT ALGORITHM



For the protocols under CTCAE version 5.0. 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

APPENDIX C SAE REPORTING FORM

Please notify: Dr. Laheru within 24 hours (email: [redacted]
Regulatory within 24 hours (email: [redacted]
BMS within 24 hours (email: [redacted]

Protocol Title:	**Feasibility and Efficacy of Perioperative Nivolumab and Relatlimab for Patients with Potentially Resectable Hepatocellular Carcinoma (HCC)**		
Protocol Number: CA224-097 J20121	**Signature of PI:**	**Principal Investigator:** Dr. Mark Yarchoan	**Date of Report:**
Report Type: ☐ Initial ☐ Follow-up ☐ Final Follow-up ☐ Death ☐ Addendum to:	**Serious Criteria (check all that apply):** ☐ Death ☐ Life-threatening ☐ Hospitalization or Elongation of Existing Hospitalization ☐ Other Important Medical Event ☐ Cancer ☐ Overdose ☐ Other:_____	**Hospital Admission Date:** **Hospital Discharge Date:**	**Date Event Discovered:** **SAE ID:**

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

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

Section C: Study Drug Information

Investigational Product:
Arm A: Nivolumab (480 mg) IV every 28 days (2 doses neoadjuvant, up to one year of adjuvant)
Arm B: Nivolumab (480 mg) and Relatlimab (480 mg) IV every 28 days (2 doses neoadjuvant, up to one year of adjuvant)

Indication: Resectable Hepatocellular Carcinoma (HCC)

Treatment Arm: ☐ Arm A ☐ Arm B	**Number of Total Cycles:**	**Action taken with the study drug:** ☐ None ☐ Interrupted ☐ Delayed ☐ Discontinued
Date of First Dose:	**Date of Last Dose prior to Event:**	

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

Section D: Brief Description of the Event:

Section E: Relevant Tests/Laboratory Data

Section F: Relevant Medical History

Section G: Concomitant Drug (Not related to SAE)

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

Section H: Comments

Additional Documents: ☐ Please specify

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

RECIST version 1.1 will be used in this study for assessment of tumor response. Either CT or MRI may be used utilized, as per RECIST 1.1.

Disease Parameters

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

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

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

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

Evaluation of Target Lesions

Complete Response (CR):Disappearance of all target lesions. Any pathological lymph nodes

(whether target or non-target) must have reduction in short axis to <10 mm.

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

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

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

Evaluation of Non-Target Lesions

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

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

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

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

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

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

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

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

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

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

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

Reference

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S.

Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.