CLINICAL STUDY PROTOCOL

Protocol Title: An Open-label, Multi-center, Rollover Study in Subjects with Advanced Solid Tumor Malignancies After Participation in a Vopratelimab (JTX-2011) Clinical Study

Product: Vopratelimab (JTX-2011)

Protocol Number: JTX-2011-R01

Protocol Version: 2.0 (Amendment 1), 03 August 2021

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The experimental protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the Institutional Review Board and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in such declaration, the ICH E6 guidelines of Good Clinical Practice, 21 Code of Federal Regulations (CFR) 21.50 Protection of Human Patients and 21 CFR 21.56 Institutional Review Boards, and all other applicable regulatory authority requirements.

SPONSOR PROTOCOL APPROVAL PAGE

An Open-label, Multi-center, Rollover Study in Subjects with Advanced Solid Tumor Malignancies After Participation in a Vopratelimab (JTX-2011) Clinical Study

Protocol Number: JTX-2011-R01

Protocol Version 2.0 (Amendment 1), 03 August 2021

Approved by:

Sponsor's Responsible Medical Officer:

Signature DocuSigned by: Johan Baeck F507126FABA9453... _____ Date 8/11/2021

Johan Baeck, MD
Senior Vice President, Clinical Development & Medical Affairs, on behalf of

Elizabeth Trehu, MD, FACP
Chief Medical Officer

INVESTIGATOR SIGNATURE OF AGREEMENT PAGE

Protocol Title: **An Open-label, Multi-center, Rollover Study in Subjects with Advanced Solid Tumor Malignancies After Participation in a Vopratelimab (JTX-2011) Clinical Study**

Protocol Number: **JTX-2011-R01**

AGREEMENT

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PROTOCOL COMPLIANCE: The signature of the Principal Investigator below constitutes his/her agreement to comply with the contents of this Protocol and to conduct this study according to Good Clinical Practices (GCP) and applicable requirements.

Principal Investigator's Name	Principal Investigator's Title
Principal Investigator's Address	
Principal Investigator's Signature	Date

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LIST OF TERMS, ACRONYMS, AND ABBREVIATIONS

Abbreviation	Definition
ADL	Activities of daily living
AE	Adverse event
ALT	Alanine Transaminase (SGPT)
AST	Aspartate Transaminase (SGOT)
CFR	Code of Federal Regulations
CRO	Contract Research Organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte antigen 4
DSUR	Drug Safety Update Report
EC	Ethics Committee
eCRF	Electronic case report form
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICOS	Inducible CO-Stimulator of T cells
IgG1	Immunoglobulin G1
IND	Investigational New Drug (Application)
irAE	Immune-related adverse event(s)
IRB	Institutional Review Board
kg	Kilogram
mg	Milligram
NCI	National Cancer Institute
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PFS	Progression-free survival
PD-1	Programmed cell death protein 1
PI	Principal Investigator
PK	Pharmacokinetic(s)
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAF	Safety Population
US	United States

PROTOCOL SYNOPSIS

Study Title:	An Open-label, Multi-center, Rollover Study in Subjects with Advanced Solid Tumor Malignancies After Participation in a Vopratelimab (JTX-2011) Clinical Study
Protocol Number:	JTX-2011-R01
Sponsor:	Jounce Therapeutics, Inc.
Study type:	Interventional
Study Purpose and Rationale	JTX-2011-R01 is a rollover study that is designed to provide continued access to vopratelimab for eligible subjects with advanced solid tumor malignancies who have previously participated in a vopratelimab study (the parent study). In addition to providing continued access to study treatment for subjects who have received clinical benefit in the parent study, this study will enable evaluation of the long-term safety and efficacy of vopratelimab when administered as either a single agent or in combination with other anticancer agents in accordance with the dosing regimens administered under the parent study protocols or those approved by the medical monitor as based on other dosing regimens that have been shown to be safe and well tolerated. Assessments in this rollover study will be more limited than those in the parent study and will allow for incorporation of institutional standard of care guidelines.
Primary Objective	Evaluate the long-term safety of continued treatment with vopratelimab monotherapy or combination treatment
Secondary Objectives	Evaluate the progression-free survival (PFS) in subjects treated with vopratelimab monotherapy or combination therapy
Exploratory Objectives	Examine changes from baseline in parent protocol in pharmacodynamic biomarkers including but not limited to phenotypes of immune cell subsets after treatment with vopratelimab monotherapy or vopratelimab in combination with nivolumab or in sequence with ipilimumab Examine the correlation between pharmacodynamic biomarkers and duration of response and PFS

Study Design	This rollover study is designed to provide continued access to vopratelimab for eligible subjects with advanced solid tumor malignancies who have previously participated in a vopratelimab clinical study after closure of the parent study. Eligible subjects must have tolerated vopratelimab in the parent study without significant toxicities that otherwise would preclude further dosing in the opinion of the Investigator and/or Sponsor. Subjects must also be expected to receive continued benefit from treatment with vopratelimab in the opinion of the Investigator and/or Sponsor. Subjects will continue to receive vopratelimab at the same dose and schedule received in the parent study. Any changes to the dose and schedule of vopratelimab must be in accordance with a dose and schedule previously shown to be safe and well tolerated and must be discussed with the medical monitor. Subjects who received combination treatment on the parent study will also continue to receive the partner drug (e.g., nivolumab or ipilimumab) at the same dose and schedule as in the parent study. Any changes to the dose and schedule of nivolumab or ipilimumab must be discussed with the medical monitor. Safety will be evaluated continuously for the duration of a subject's participation. Imaging for disease status will be performed in accordance with institutional standard of care guidelines and must be performed at least every 6 months (± 3 weeks). All subjects must sign a new informed consent form to be enrolled in the rollover study. Subjects may continue to receive study treatment until loss of clinical benefit or unacceptable toxicity as defined by the Investigator and/or Sponsor, withdrawal of consent, loss to follow-up, or death.
Study Drugs	Vopratelimab is a humanized IgG1K monoclonal antibody that is an agonist of Inducible CO-Stimulator of T cells (ICOS). Nivolumab, marketed as Opdivo®, is a human IgG4K anti-PD-1 monoclonal antibody manufactured by Bristol-Myers Squibb. Ipilimumab, marketed as Yervoy®, is a human IgG1K cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody manufactured by Bristol-Myers Squibb.
Inclusion Criteria	Subject is currently receiving and tolerating vopratelimab therapy and receiving clinical benefit from study treatment in the opinion of the Investigator and/or Sponsor. Subject has demonstrated compliance with the parent study requirements, as assessed by the Investigator and/or Sponsor, and is able and willing to comply with the necessary visits and assessments as part of the rollover study. Written informed consent must be obtained prior to enrolling in the rollover study and receiving study treatment. If consent cannot be expressed in writing, it must be formally documented and witnessed, ideally via an independent trusted witness. Women of childbearing potential and males with partners of child-bearing potential must agree to use adequate birth control throughout their participation and for 5 months following the last study treatment.

Exclusion Criteria	Subject was permanently discontinued from the parent study due to unacceptable toxicity, non-compliance with study procedures, withdrawal of consent, or any other reason. Subject is receiving concurrent anticancer treatment (excluding combination drugs such as nivolumab or ipilimumab as a component of the combination dosing regimen used in the parent study). Women who are pregnant or breastfeeding. Subject has any medical or social condition that, in the opinion of the Investigator, might place a subject at increased risk, affect compliance, or confound safety or other clinical study data interpretation.
Efficacy Assessments	The antitumor activity of study treatment will be assessed using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as assessed by the local Investigator and based on imaging performed according to institutional standard of care guidelines, but at least every 6 months (± 3 weeks).
Safety Assessments	Safety will be monitored through adverse event (AE) documentation, clinical laboratory evaluations, physical examinations, and vital signs performed at every visit. Safety and tolerability will be assessed by the incidence and severity of AEs and serious adverse events (SAEs) as determined by the current version of the Common Terminology Criteria for Adverse Events (CTCAE). Immune-related AEs will also be assessed.
Biomarker Assessments	Pharmacodynamic biomarkers in peripheral blood, including peripheral blood mononuclear cell (PBMC)-based assays of immune cell phenotype, will be assessed approximately every 3 months (± 4 weeks) and at the end of treatment and correlated with efficacy outcomes, if sufficient samples are available. Sample collection may be discontinued at any time per the Sponsor's discretion.
Sample Size Determination and Statistical Analyses	Patients on study treatment in a Jounce-sponsored clinical study and eligible for rollover may be enrolled. For the study objectives, no prospective sample size determination is required. Data will be summarized descriptively as appropriate.

1 BACKGROUND AND RATIONALE FOR CLINICAL DEVELOPMENT

Please refer to the current vopratelimab Investigator's Brochure for background information and clinical experience with vopratelimab administered as a single agent and in combination with nivolumab or in sequence with ipilimumab.

2 RATIONALE

JTX-2011-R01 is a rollover study that is designed to provide continued access to vopratelimab for eligible subjects with advanced solid tumor malignancies who have previously participated in a vopratelimab study (the parent study). In addition to providing continued access to study treatment for subjects who have received clinical benefit in the parent study, this study will enable evaluation of the long-term safety and efficacy of vopratelimab when administered as either a single agent or in combination with other anticancer agents in accordance with the dosing regimens administered under the parent study protocols. Any changes to the dose and schedule of the study drugs must be discussed with the medical monitor. Assessments in this rollover study will be more limited than those in the parent study and will allow for incorporation of institutional standard of care guidelines.

3 STUDY DESIGN

JTX-2011-R01 is a rollover study that is designed to provide continued access to vopratelimab for eligible subjects with advanced solid tumor malignancies who have previously participated in a vopratelimab study (the parent study) after closure of the parent study.

Eligible subjects must have tolerated vopratelimab in the parent study without significant toxicities that otherwise would preclude further dosing in the opinion of the Investigator and/or Sponsor. Subjects must also be expected to receive continued benefit from treatment with vopratelimab in the opinion of the Investigator and/or Sponsor.

Subjects will continue to receive vopratelimab at the same dose and schedule received in the parent study, and ideally will experience no treatment interruption between the end of participation in the parent study and entry into the rollover study. Any changes to the dose and schedule of vopratelimab must be in accordance with a dose and schedule previously shown to be safe and well tolerated and must be discussed with the medical monitor. Subjects who received combination treatment on the parent study will also continue to receive the partner drug (e.g., nivolumab or ipilimumab) at the same dose and schedule as in the parent study. Any changes to the dose and schedule of nivolumab or ipilimumab must be discussed with the medical monitor.

Safety will be evaluated continuously for the duration of a subject's participation. Imaging for disease status will be performed in accordance with institutional standard of care guidelines and must be performed at least every 6 months (± 3 weeks).

All subjects must sign a new informed consent form to be enrolled in the rollover study. Subjects may continue to receive study treatment until loss of clinical benefit or unacceptable toxicity as defined by the Investigator and/or Sponsor, withdrawal of consent, loss to follow-up, or death.

4 STUDY OBJECTIVES

4.1 Primary Objective

Evaluate the long-term safety of continued treatment with vopratelimab monotherapy or combination treatment

4.2 Secondary Objectives

Evaluate the progression free survival (PFS) in subjects treated with vopratelimab monotherapy or combination therapy

4.3 Exploratory Objectives

Examine changes from baseline in parent protocol in pharmacodynamic biomarkers including but not limited to phenotypes of immune cell subsets after treatment with vopratelimab monotherapy or vopratelimab in combination with nivolumab or in sequence with ipilimumab.

Examine the correlation between pharmacodynamic biomarkers and duration of response and PFS.

5 POPULATION SELECTION CRITERIA

5.1 Patient Population

This rollover study will enroll subjects who have been treated as part of a vopratelimab clinical study that has closed. At the time of rollover study entry, subjects must be continuing to receive study drug(s) as part of the active parent study. Subjects must not have any ongoing, significant toxicities at the time of rollover study entry that would preclude further dosing in the opinion of the Investigator and/or Sponsor.

5.2 Inclusion Criteria

- Subject is currently receiving and tolerating vopratelimab therapy and receiving clinical benefit from study treatment in the opinion of the Investigator and/or Sponsor.
- Subject has demonstrated compliance with the parent study requirements, as assessed by the Investigator and/or Sponsor, and is able and willing to comply with the necessary visits and assessments as part of the rollover study.
- Written informed consent must be obtained prior to enrolling in the rollover study and receiving study treatment. If consent cannot be expressed in writing, it must be formally documented and witnessed, ideally via an independent trusted witness.
- Women of childbearing potential and males with partners of child-bearing potential must agree to use adequate birth control throughout their participation and for 5 months following the last study treatment.

5.3 Exclusion Criteria

- Subject was permanently discontinued from the parent study due to unacceptable toxicity, non-compliance with study procedures, withdrawal of consent, or any other reason.
- Subject is receiving concurrent anti-cancer treatment (excluding combination drugs such as nivolumab or ipilimumab as a component of the combination dosing regimen used in parent study).
- Women who are pregnant or breastfeeding.
- Subject has any medical or social condition that, in the opinion of the Investigator, might place a subject at increased risk, affect compliance, or confound safety or other clinical study data interpretation.

5.4 Reproductive Restrictions

There are no data regarding the effect of vopratelimab on the unborn fetus. Vopratelimab should not be administered to pregnant women. Embryo-fetal toxicity is a labeled warning for nivolumab and ipilimumab (Opdivo® Full Prescribing Information {Bristol-Myers Squibb Company 2021}, Yervoy® Full Prescribing Information {Bristol-Myers Squibb Company 2021}). Women of childbearing potential must have a negative serum or urine pregnancy test prior to administration of each dose of vopratelimab throughout the study. Women of childbearing potential and males with partners of childbearing potential must agree to use adequate birth control throughout their participation and for 5 months following the last study treatment.

6 STUDY TREATMENTS AND ADMINISTRATION

6.1 Study Drug Dosage and Administration

For this study, the investigational drug refers to vopratelimab, which will be supplied by the Sponsor, Jounce Therapeutics. Study drug(s) refer to vopratelimab and any partner drugs administered in the parent study (e.g., nivolumab, ipilimumab).

All dosages prescribed and dispensed to subjects and all dose changes during the study must be recorded on the Dosage Administration Record electronic case report form (eCRF).

For all study medication administration, a physician must be present at the site or immediately available to respond to emergencies during all administrations of all study medications. Note that the infusion time is not inclusive of the flush post study drug administration.

Vopratelimab is administered as a single agent or in combination with nivolumab or in sequence with ipilimumab at a subject's prior identified tolerable dose regimen and schedule. Any changes to the dose and schedule of the study agents must be discussed with the medical monitor as stated in Section 3.

When vopratelimab is administered on the same day as nivolumab, vopratelimab should be dosed first with a 30-minute (-5/+10 minutes) evaluation period prior to administration of combination therapy. In instances where an infusion reaction occurs during dosing of vopratelimab, administration of combination therapy may be delayed beyond the 30-minute (-5/+10 minutes) evaluation period.

If treating in sequence with ipilimumab, continue to follow dosing guidelines from the parent study for up to 4 doses. Administer ipilimumab as a 90-minute IV infusion or per the approved label infusion time (-5/+10 minutes) at a dose of 3 mg/kg q6w for up to 4 doses. Note that the approved schedule for ipilimumab administration is q3w; this protocol administers ipilimumab at a less frequent schedule. Additional doses of ipilimumab beyond 4 doses total may be considered on a patient by patient basis in consultation with the medical monitor.

Further instructions for the preparation and dispensation of vopratelimab, nivolumab, and ipilimumab are described in the Study Pharmacy Manual.

6.1.1 Contraindications

Based on the immune-stimulatory mechanism of action of vopratelimab, it should not be administered to subjects with any of the following:

Active disease requiring systemic immunosuppressive therapy. Exceptions allowed on a patient by patient basis upon discussion with the medical monitor;
Any known primary or acquired diagnosis of immunodeficiency, or treatment with systemic steroids or any other form of immunosuppressive therapy. Exception: inhaled or topical steroids and adrenal replacement doses are permitted in the absence of active autoimmune disease.
Please refer to the respective prescribing information for contraindications to nivolumab and ipilimumab.

6.1.2 Concomitant Medications

Concomitant medication use will be assessed at each visit.

6.1.2.1 Prohibited Concomitant Medications/Therapies

- Concurrent anticancer treatment (exceptions below)
- Systemic steroids or any other form of immunosuppressive therapy

6.1.2.2 Allowed Concomitant Medications

Subjects may continue to receive any medications/therapies that were administered during the parent study.

- Inhaled, topical or oral steroids and adrenal replacement doses are permitted.
- Palliative radiation to non-target lesions only is allowed during study treatment in consultation with the medical monitor.
- One-time dose of immunosuppressive agents used prophylactically for contrast allergies
- Steroids administered prophylactically for infusion related reactions in subjects who have demonstrated infusion related reactions to study drug on a prior dose
- Vaccines

6.2 Nivolumab Dosage and Administration

Nivolumab, marketed as Opdivo®, is a human immunoglobulin IgG4K anti-PD-1 monoclonal antibody manufactured by Bristol-Myers Squibb for the treatment of cancer. Nivolumab acts as an immunomodulator by blocking ligand activation of the PD-1 receptor on activated T cells. Please refer to the Pharmacy Manual for vopratelimab and most recent package insert for Opdivo® Full Prescribing Information for more information {Bristol-Myers Squibb Company 2021}.

6.3 Ipilimumab Dosage and Administration

Ipilimumab, marketed as Yervoy®, is a human IgG1K CTLA-4-blocking antibody manufactured by Bristol-Myers Squibb for the treatment of melanoma. Ipilimumab binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Ipilimumab will be administered using the dose and schedule from the parent study. Please refer to the Pharmacy Manual and most recent package insert for Yervoy® Full Prescribing Information for more information {Bristol-Myers Squibb Company 2021}.

6.4 Study Drug Procurement

6.4.1 Drug Ordering

The initial shipment of study drug(s) to a clinical site will occur after all essential regulatory documents are collected for that site. Please refer to the Pharmacy Manual for information on re-supply shipments.

6.4.2 Drug Accountability

Each Investigator/designee is responsible for taking an inventory of each shipment of study drug supplied by the Sponsor received and comparing it with the accompanying accountability form.

Study drug(s) must be used only as directed in this protocol. The Investigator/designee must keep accurate written records of all study drug received from Jounce/Sponsor Representative. Additionally, the Investigator/designee must keep accurate records of study drug(s) dispensed to subjects in this protocol including the number of vials used to prepare subject doses, lot number, date dispensed, subject identification number, dose administered, balance forward, and the initials of the person dispensing the medication. Based on the entries in the site drug accountability forms, it must be possible to reconcile drug product delivered with that used. All study drug must be accounted for and all discrepancies investigated and documented appropriately.

Study drug stock may not be removed from the investigative site where originally shipped without prior knowledge and consent of Jounce or their delegated Contract Research Organization (CRO).

At the end of the study, all unused vials of study drug will be destroyed by the investigative site according to that site's drug destruction procedures or processed through a "buy-back" procedure through the depot, as applicable. Jounce will indicate which steps should be taken by each site at the end of the study. All certificates of delivery/drug receipts must be signed prior to shipment.

6.5 Subject Numbering and Treatment Assignment

Each subject is identified in the study by a number that is assigned when the subject is first enrolled in the rollover protocol. The subject number is retained as the primary identifier for the subject throughout participation in the rollover study. The subject number consists of the center number assigned by the Sponsor, cohort identifier, and a sequential subject number suffix so that each subject is numbered uniquely across the entire database. Subject numbers will be assigned by the Sponsor at the time of rollover entry.

The subject identifier, along with the dose and date of last study treatment(s), from the parent study will be captured in the relevant eCRF for the rollover study.

7 DOSE MODIFICATION AND PATIENT WITHDRAWAL

7.1 Criteria for Dose Modification

7.1.1 Delayed Cycles

A change in the start of a cycle of +3 days for social reasons (e.g., holidays) is permitted if unavoidable. Subjects who require frequent treatment delays should be discussed with the Medical Monitor.

If a cycle delay of >14 days not due to treatment-related toxicity occurs, the circumstances surrounding the delay will be discussed with the Medical Monitor prior to dosing the subject for the next cycle.

7.1.2 Dose Interruptions

Same day dose interruptions may occur; however, the study drug should be infused within 4 hours of the interruption. If the interruption is due to toxicity, please refer to Section 7.1.4 for dose modifications.

7.1.3 Dose Hold

Dose holds will be documented.

7.1.4 Dose Modifications

Any changes to the dose and schedule of the study agents must be discussed with the medical monitor as stated in Section 3.

7.1.4.1 Dose Modifications for Vopratelimab

Dose modifications and management of toxicity for vopratelimab are provided in Table 1.

Table 1: Dose Modifications and Toxicity Management for Vopratelimab, Nivolumab, and Ipilimumab

Adverse Event	Toxicity Grade	Dose Modification	Recommended Management[a]
Diarrhea or Colitis	Grade 2	• Withhold study drug(s) until resolution to Grade 0-1. • When symptoms resolve to Grade 0-1, resume vopratelimab only. If symptoms do not recur after 1 cycle of vopratelimab, resume combination therapy.[b] • If symptoms persist 2' 6 weeks, or subject is unable to reduce the corticosteroid dose to less than 7.5 mg prednisone or equivalent per day, discuss subject continuation with the Medical Monitor.[b]	If symptoms persist > 5 days or recur: 0.5 to 1 mg/kg/day prednisone equivalents followed by steroid taper[a]
	Grade 3	• Permanently discontinue ipilimumab/nivolumab. • Withhold vopratelimab until resolution to Grade 0-1. When symptoms resolve to Grade 0-1, resume vopratelimab.[b] • If symptoms persist 2' 6 weeks, or subject is unable to reduce the corticosteroid dose to less than 7.5 mg prednisone or equivalent per day, discuss subject continuation with the Medical Monitor.[b]	1-2 mg/kg/day prednisone equivalents followed by steroid taper[a] If symptoms persist 2' 3-5 days or recur after improvement, consider administering IV corticosteroid or noncorticosteroid[a]
	Grade 4	• Permanently discontinue study drug(s).	1-2 mg/kg/day prednisone equivalents followed by steroid taper[a] Administer IV corticosteroid until symptoms improve to grade 1[a] Consider early infliximab 5-10 mg/kg if symptoms refractory to corticosteroid within 2-3 days[a]

Adverse Event	Toxicity Grade	Dose Modification	Recommended Management[a]
Pneumonitis	Grade 2	• Withhold study drug(s) until resolution to Grade 0-1. • When symptoms resolve to Grade 0-1, resume vopratelimab only. If symptoms do not recur after 1 cycle of vopratelimab, resume combination therapy.[b] • Permanently discontinue ipilimumab/nivolumab if symptoms last 6 weeks or longer.	1-2 mg/kg/day prednisone equivalents followed by steroid taper[a]
	Grade 3 or 4	• Permanently discontinue study drug(s).	1-2 mg/kg/day prednisone equivalents followed by steroid taper If no improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g twice a day or IVIG for 5 days or cyclophosphamide[a] Empirical antibiotics
Hepatitis	Grade 2 AST/ALT (>3 to 5 × ULN) or bilirubin (1.5 to 3 × ULN)[b]	• Withhold study drug(s) until resolution to Grade 0-1. • When symptoms resolve to Grade 0-1, resume vopratelimab only. If symptoms do not recur after 1 cycle of vopratelimab, resume combination therapy.[b] • Permanently discontinue ipilimumab/nivolumab if symptoms last 6 weeks or longer.	0.5 to 1 mg/kg/day prednisone equivalents or investigator discretion[a]
	Grade 3 or 4 AST/ALT (>5 × ULN) or bilirubin (>3 x ULN)[b]	• Permanently discontinue study drug(s).	1-2 mg/kg/day prednisone equivalents or investigator discretion[a] If corticosteroid refractory or no improvement after 3 days, may offer mycophenolate mofetil or azathioprine
Hypophysitis	Grade 2 or 3	• Withhold study drug(s) until patient is stabilized on replacement hormone and discuss resuming combination therapy with medical monitor.	Hormonal supplementation as needed (e.g., hydrocortisone 10-20 mg orally in the morning, 5-10 mg orally in early afternoon; levothyroxine by weight). Continue hormonal replacement as medically indicated
	Grade 4	• Withhold study drug(s) until patient is stabilized on replacement hormone and discuss resuming combination therapy with medical monitor.	Hormonal supplementation as above. Consider initial pulse dose therapy with prednisone 1-2 mg/kg oral daily (or equivalent) tapered over at least 1-2 weeks. Continue hormonal replacement as medically indicated

Adverse Event	Toxicity Grade	Dose Modification	Recommended Management[a]
Adrenal insufficiency	Grade 2	• Withhold study drug(s) until patient is stabilized on replacement hormone and discuss resuming combination therapy with medical monitor.	Initiate outpatient treatment at 2 to 3 times maintenance (if prednisone, 20 mg daily; if hydrocortisone, 20-30 mg in the morning, and 10-20 mg in the afternoon) to manage acute symptoms. Taper maintenance doses over 5-10 days. May require fludrocortisone (0.1 mg/day) for mineralocorticoid replacement in primary adrenal insufficiency. Continue hormonal replacement as medically indicated.
	Grade 3 or 4	• Withhold study drug(s) until patient is stabilized on replacement hormone and discuss resuming combination therapy with medical monitor.	See in clinic or, for after hours, make an emergency department referral for normal saline (at least 2L) and IV stress-dose corticosteroids on presentation (hydrocortisone 10 mg or dexamethasone 4 mg (if the diagnosis is not clear and stimulation testing will be needed). Taper stress-dose corticosteroids down to maintenance doses over 7-14 days after discharge. Maintenance therapy as in Grade 2 above
Thyroid disorders	Hypothyroidism	• Withhold study drug(s) until symptoms return to baseline and discuss resuming combination therapy with medical monitor.	Hormone replacement therapy. Continue hormonal replacement as medically indicated.
	Hyperthyroidism	• Withhold study drug(s) until symptoms return to baseline and discuss resuming combination therapy with medical monitor.	Beta-blocker (e.g. – atenolol, propranolol) for symptomatic relief. For severe symptoms or concern for thyroid storm, hospitalize subject and initiate prednisone 1-2 mg/kg/day or equivalent tapered over 1-2 weeks. Consider also use of potassium iodide oral solution or thionamide (methimazole or propylthiouracil)

Adverse Event	Toxicity Grade	Dose Modification	Recommended Management[a]
Type 1 Diabetes Mellitus	Grade 1 hyperglycemia Grade 1: Asymptomatic or mild symptoms; fasting glucose value >ULN (160 mg/dL); fasting glucose value > ULN (8.9 mmol/L); no evidence of ketosis or laboratory evidence of T1DM	• May continue study drug(s) with close clinical follow-up and laboratory evaluation.	Grade 1: May initiate oral therapy for those with new onset T2DM Screen for T1DM if appropriate, for example, acute onset with prior normal values or clinical concern for ketosis
	Grade 2 hyperglycemia Grade 2: Moderate symptoms, able to perform ADL, fasting glucose value > 160-250 mg/dL; fasting glucose value > 8.9-13.9 mmol/L, ketosis or evidence of T1DM at any glucose level	• Hold study drug(s) until glucose control obtained; resume study drug(s) when hyperglycemia resolves to Grade 0 or 1	Grade 2: Moderate symptoms, able to perform ADL, fasting glucose value . 160-250 mg/dL; fasting glucose value 8.9-13.9 mmol/L, with ketosis or evidence of T1DM at any glucose level Titrate oral therapy or add insulin for worsening control in T2DM Should administer insulin for T1DM (or as default therapy if there is confusion about type) Urgent endocrine consultation for any subject with T1DM; in the absence of endocrinology, internal medicine may suffice Consider admission for T1DM if early outpatient evaluation is not available or signs of ketoacidosis are present
	Grade 3 or 4 hyperglycemia	• Withhold study drug(s) until metabolic control is achieved with insulin. Resume vopratelimab upon resolution of hyperglycemia to Grade 0-1. If symptoms do not recur after 1 cycle of vopratelimab, resume ipilimumab/nivolumab therapy.	Administer insulin until metabolic control is achieved. Continue insulin as medically indicated Admit for inpatient management: concerns for developing diabetic ketoacidosis, symptomatic subjects regardless of diabetes type, new onset T1DM unable to see endocrinology

Adverse Event	Toxicity Grade	Dose Modification	Recommended Management[a]
Nephritis and Renal Dysfunction	Grade 2: serum creatinine (>1.5 to 3 × ULN)	• Withhold study drug(s) until resolution to Grade 0-1. • When resolved to Grade 0-1, resume vopratelimab. If increase in serum creatinine does not recur after 1 cycle of vopratelimab, resume ipilimumab/nivolumab therapy.[b]	0.5 to 1 mg/kg/day prednisone equivalents followed by steroid taper. If worsening or no improvement occurs iQ ” days, increase dose of corticosteroids to 1-2 mg/kg/day prednisone equivalents and permanently discontinue study drug(s).[a] Evaluate for other causes (recent IV contrast, medications, fluid status, etc)
	Grade 3: serum creatinine (> 3 to 6 × ULN)	• Permanently discontinue study drug(s).	1-2 mg/kg/day prednisone equivalents[a] Consult nephrology Evaluate for other causes (recent IV contrast, medications, fluid status, etc) If improved to Grade 1, taper corticosteroids over at least 4 weeks If elevation persists >3-5 days or worsen, consider additional immunosuppression (e.g. – mycophenolate)
	Grade 4: serum creatinine (> 6 × ULN)	• Permanently discontinue study drug(s).	1-2 mg/kg/day prednisone equivalents[a] Consult nephrology Evaluate for other causes (recent IV contrast, medications, fluid status, etc) If improved to Grade 1, taper corticosteroids over at least 4 weeks If elevations persist >2-3 days or worsen, consider additional immunosuppression (e.g. – mycophenolate)
Rash	Grade 2	• Withhold study drug(s). When symptoms resolve to Grade 0-1, resume vopratelimab. If symptoms do not recur after 1 cycle of vopratelimab, resume ipilimumab/nivolumab.[b]	Should treat skin with topical emollients, oral antihistamines, and medium- to high-potency topical corticosteroids. 0.5 to 1 mg/kg/day prednisone equivalents[a]
	Grade 3	• Withhold study drug(s) until resolution to Grade 0-1. • When symptoms resolve to Grade 0-1, resume vopratelimab only; permanently discontinue ipilimumab/nivolumab.	Should treat skin with topical emollients, oral antihistamines, and high-potency topical corticosteroids. 1-2 mg/kg/day prednisone equivalents[a]
	Grade 4	• Permanently discontinue study drug(s).	1-2 mg/kg/day prednisone equivalents[a] Admit for inpatient management

Adverse Event	Toxicity Grade	Dose Modification	Recommended Management[a]
Neuropathy	Grade 2	• Withhold study drug(s) until resolution to Grade 0-1; if symptoms persist 2' 6 weeks, discuss subject continuation with the Medical Monitor. • When symptoms resolve to Grade 0-1, resume vopratelimab. If symptoms do not recur after 1 cycle of vopratelimab, resume ipilimumab/nivolumab therapy.[b] • Permanently discontinue study drug(s) for related reactions lasting 6 weeks or longer or if the subject is unable to reduce the corticosteroid dose to less than 7.5 mg prednisone or equivalent per day.	(peripheral neuropathy) Initial observation OR initiate prednisone 0.5-1 mg/kg (if progressing from mild). Neurontin, pregabalin, or duloxetine for pain (Autonomic neuropathy) Initial observation OR initiate prednisone 0.5-1 mg/kg (if progressing from mild). Neurologic consultation
	Grade 3 or 4	• Permanently discontinue study drug(s).	(Peripheral neuropathy) Neurologic consultation Initiate IV methylprednisolone 2-4 mg/kg Monitor pulmonary function, concurrent autonomic dysfunction, neuropathic pain, constipation/ileus. Offer frequent neurochecks (Autonomic neuropathy) Initiate methylprednisolone 1g IV daily for 3 days followed by oral corticosteroid taper Neurologic consultation
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	• Permanently discontinue study drug(s).	If etiologies other than immune-mediated adverse events are ruled out, permanently discontinue study drug(s) and administer 1-2 mg/kg/day prednisone equivalents[a] Administer concurrent IV acyclovir until PCR results obtained and negative
	Immune-mediated encephalitis	• Permanently discontinue study drug(s).	1-2 mg/kg/day prednisone equivalents[a] If limited or no improvement, may offer rituximab or plasmapheresis

Adverse Event	Toxicity Grade	Dose Modification	Recommended Management[a]
Uveitis, iritis	Grade 2	• Withhold study drug(s). • When symptoms resolve to Grade 0-1, resume study drug(s) only if local immunosuppressive therapy was used. Permanently discontinue ipilimumab/nivolumab if systemic therapy was required.	Urgent ophthalmology referral. Topical corticosteroids, cycloplegic agents, systemic corticosteroids. May resume vopratelimab once off systemic corticosteroids, which are purely indicated for ocular adverse effects or once corticosteroids for other concurrent systemic irAEs are reduced to :S 10 mg; continued topical/ocular corticosteroids are permitted when resuming vopratelimab to manage and minimize local toxicity
	Grade 3 or 4	• Permanently discontinue study drug(s).	Emergent ophthalmology referral. Systemic corticosteroids (IV prednisone 1-2 mg/kg or methylprednisolone 0.8-1.6 mg/kg) and intravitreal/periocular/topical corticosteroids per ophthalmologist opinion
Episcleritis	Grade 2	• Temporarily withhold study drug(s) until after ophthalmology consult.	Urgent ophthalmology referral Topical corticosteroids, cycloplegic agents, systemic corticosteroids
	Grade 3 or 4	• Permanently discontinue study drug(s).	Emergent ophthalmology referral. Systemic corticosteroids and topical corticosteroids with cycloplegic agents
Other	Grade 2 adverse reactions	• Withhold study drug(s) until resolved to Grade 0-1. • When symptoms resolve to Grade 0-1, resume vopratelimab only. If symptoms do not recur after 1 cycle of vopratelimab, resume ipilimumab/nivolumab. • If symptoms persist 2' 6 weeks or unable to reduce the corticosteroid dose to less than 7.5 mg prednisone or equivalent per day, subject continuation must be discussed between the Investigator and Medical Monitor	If symptoms persist > 5 days or recur, consider 0.5-1 mg/kg/day prednisone equivalent followed by corticosteroid taper If symptoms persist 2' 6 weeks obtain organ class consultation

Adverse Event	Toxicity Grade	Dose Modification	Recommended Management[a]
	Other Grade 3 adverse reaction	• Permanently discontinue ipilimumab/nivolumab. • Withhold vopratelimab until resolution to Grade 0-1. • When symptoms resolve to Grade 0-1, resume vopratelimab only.	Consider 1-2 mg/kg/day prednisone equivalents[a]
	Recurrence of same Grade 3 adverse reaction	• Discuss subject continuation with the Medical Monitor.	1-2 mg/kg/day prednisone equivalents[a]
	Persistent Grade 3 adverse reaction lasting 2' 1 weeks	• Permanently discontinue study drug(s).	1-2 mg/kg/day prednisone equivalents[a] Urgent organ class consultation Consider additional immunosuppressive agents (e.g. – mycophenolate)
	Life-threatening or Grade 4 adverse reaction	• Permanently discontinue study drug(s).	1-2 mg/kg/day prednisone equivalents[a] Emergent organ class consultation Consider additional immunosuppressive agents (e.g. – mycophenolate)
	Requirement for 10 mg prednisone per day or greater prednisone or equivalent for > 3 months	• Permanently discontinue study drug(s).	Urgent organ class consultation Consider additional immunosuppressive agents (e.g. – mycophenolate)

Abbreviations: ADL = activities of daily living; ALT = alanine aminotransferase; AST = aspartate aminotransferase; IV = intravenous; T1DM = Type 1 diabetes mellitus; T2DM = Type 2 diabetes mellitus; ULN = upper limit of normal.
Toxicity graded per the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE v5.0)
[a] If steroids have been administered, taper steroids over the course of at least 4 to 6 weeks or per institution guidelines.
[b] Subjects must have partial resolution of symptoms (Grade 0-1) and must be receiving < 7.5 mg of prednisone or equivalent per day in order to resume study treatment.

7.1.4.2 Dose Modifications and Toxicity Management for Vopratelimab in Combination with Nivolumab

For dose modifications for nivolumab please follow the prescribing information (Opdivo® Full Prescribing Information {Bristol-Myers Squibb Company 2021}). In the event of a toxicity that requires that study treatment be withheld until resolution to Grade 0 or 1, the first administration of study drug after resolution of toxicity should be vopratelimab alone. Nivolumab may be added at the next dose, at the discretion of the investigator and the medical monitor, if the toxicity does not recur with vopratelimab monotherapy.

7.1.4.3 Dose Modifications and Toxicity Management for Vopratelimab in Combination with Ipilimumab

For dose modifications for ipilimumab please follow the prescribing information (Yervoy® Full Prescribing Information {Bristol-Myers Squibb Company 2021). In the event of a toxicity that requires that study treatment be withheld until resolution to Grade 0 or 1, the first administration of study drug after resolution of toxicity should be vopratelimab alone. Ipilimumab may then be added in sequence at the next dose, at the investigator's discretion, if the toxicity does not recur with vopratelimab monotherapy.

7.2 Infusion-Related Reactions

Post-infusion observation is per institutional guidelines. Signs and symptoms of an infusion reaction may include the following: headache, fever, facial flushing, pruritus, myalgia, nausea, chest tightness, dyspnea, vomiting, erythema, abdominal discomfort, diaphoresis, shivers, hypertension, hypotension, lightheadedness, palpitations, urticaria and somnolence. Although unlikely, serious allergic reactions (e.g., anaphylaxis) may occur at any time during the infusion.

7.2.1 Grade 2 Infusion-Related Reactions

In the case of Grade 2 occurrence of signs and symptoms consistent with infusion related reaction, follow institutional protocol and reduce the rate of infusion of vopratelimab to half the initial rate; consider interrupting infusion of vopratelimab if symptoms do not respond to medical intervention. If signs and symptoms resolve with intervention including interruption of, vopratelimab infusion may be restarted at half the initial rate.

7.2.2 Grade 3 Infusion-Related Reactions

In the case of Grade 3 or greater occurrence of signs and symptoms consistent with infusion related reaction, discontinue infusion of vopratelimab.

7.2.3 Infusion-Related Reaction Prophylaxis

For subjects who experience a Grade 2 or 3 infusion-related reaction and remain on treatment, institutional practice for prevention of infusion reactions may be followed for all subsequent cycles.

8 WITHDRAWAL OF SUBJECTS

A subject is free to withdraw from treatment at any time for any reason without prejudice to their future medical care by the physician or at the institution. However, subjects who withdraw from treatment should be encouraged to return for the End-of-study visit and complete all safety assessments. If a subject refuses to undergo the End-of-study procedures, the reason for refusal should be fully documented in the subject's eCRF.

The Investigator or Jounce may also withdraw the subject from treatment at any time in the interest of his or her safety. The primary reason for withdrawal must be recorded in the subject's medical record and on the withdrawal form in the eCRF. If a subject is withdrawn for more than one reason, each reason should be documented in the source document and the most medically significant reason should be entered on the eCRF.

The withdrawal of a subject from treatment should be discussed where possible with the Medical Monitor before the subject stops taking study drug. If study treatment is discontinued, the final evaluations will be performed as completely as possible.

The reason for termination, date of stopping study treatment and the total treatment period must be recorded in the eCRF and source documents.

8.1 Criteria for Withdrawal

The Medical Monitor may be contacted on a case-by-case basis if clarification is required. Reasons for withdrawal include:

- Withdrawal of consent by the subject or refusal by the subject to continue treatment and/or procedures/observations;
- In the case of radiographic progression accompanied by clinical progression. However, in the case of radiographic progression where the subject is clinically stable, it is recommended to continue treatment as long as, in the investigator's opinion, the subject is clinically stable;
- Occurrence of unmanageable adverse events (AEs) in the judgment of the Investigator or subject, justifies withdrawal due to its severity, nature, or requirement for treatment, regardless of the causal relationship to study drug;

- Pregnancy;
- If the Investigator feels it is in the subject's best interest to withdraw;
- Other reasons (e.g., significant protocol violation, non-compliance, loss to follow-up);
- Termination of the study by Sponsor.

9 OVERALL STUDY ASSESSMENTS

Duration of participation on this study will be dependent on the amount of time a subject derives clinical benefit. An End-of-study visit will be performed 28 days (± 7 days) after the last dose of study treatment.

9.1 Rollover Entry/Cycle 1 Day 1

Enrollment into the rollover study should occur upon exit from the parent study to avoid any interruptions in study treatment administration.

All assessments should be performed prior to vopratelimab dosing, unless otherwise noted.

- Signing of informed consent form.
- Review eligibility criteria to determine whether a subject may enter the rollover study.
- Physical examination.
- Vital signs pre-and post-infusion.
- Weight.
- Serum or urine pregnancy test for women of childbearing potential. The pregnancy test will not be required for women who are surgically sterile or who are greater than 1 year post-menopausal.
- Laboratory assessments including hematology and chemistry; additional laboratory measurements may be performed in accordance with institutional guidelines.
- Pharmacodynamic biomarkers; Collection of samples may be discontinued at any time per the Sponsor's discretion.
- Record ongoing concomitant medications and AEs.
- Study treatment (vopratelimab ± partner drug) administration on the same dose and schedule as a subject was receiving at the time of discontinuation from the parent study. Study drug administration between the parent and rollover study should be maintained per the dose and schedule on the parent study. Any changes to the dose and schedule of vopratelimab must be in accordance with a dose and schedule previously shown to be safe and well tolerated and must be discussed with the medical monitor. Any changes to the dose and schedule of nivolumab or ipilimumab must be discussed with the medical monitor.

9.2 Day 1 (± 3 Days) of Subsequent Cycles

The following evaluations and procedures will be performed on Day 1 of subsequent cycles. All assessments should be performed prior to vopratelimab dosing, unless otherwise noted.

- Physical examination.
- Vital signs pre-and post-infusion.
- Weight.
- Pregnancy test for women of childbearing potential.
- Laboratory assessments including hematology and chemistry; additional laboratory measurements may be performed in accordance with institutional guidelines.
- Concomitant medication review.
- AE assessment.
- Study treatment (vopratelimab ± partner drug) administration on the same dose and schedule as a subject was receiving at the time of discontinuation from the parent study. Any changes to the dose and schedule of vopratelimab must be in accordance with a dose and schedule previously shown to be safe and well tolerated and must be discussed with the medical monitor. Any changes to the dose and schedule of nivolumab or ipilimumab must be discussed with the medical monitor.
- Disease imaging (e.g., CT scan) for response assessment in accordance with Section 9.2.3.

9.2.1 Subsequent Dosing Days

Subjects should continue to receive study drug administration dosing within every cycle per the dose and schedule administered in the parent study. Any changes to the dose and schedule of vopratelimab must be in accordance with a dose and schedule previously shown to be safe and well tolerated and must be discussed with the medical monitor. Any changes to the dose and schedule of nivolumab or ipilimumab must be discussed with the medical monitor.

9.2.2 Approximately Every 3 Months (± 4 Weeks)

A visit should be performed approximately every 3 months (± 4 weeks) to align with a scheduled study drug administration or other clinic visit. At this time, peripheral blood sampling should be performed for pharmacodynamic biomarkers. Collection of samples may be discontinued at any time per the Sponsor's discretion.

9.2.3 Every 6 Months (± 3 Weeks)

Disease imaging (e.g., computed tomography [CT] scan) should be performed for response assessment in accordance with institutional standard of care guidelines, but at least every 6 months (± 3 weeks).

9.3 End of Study

At the end of study (within 28 days ± 7 days after last dose of study drug):

- Physical examination.
- Vital signs.
- Weight.
- Laboratory assessments including hematology and chemistry; additional laboratory measurements may be performed in accordance with institutional guidelines
- Peripheral blood sampling for pharmacodynamic biomarkers; Collection of samples may be discontinued at any time prior to end of study per the Sponsor's discretion.
- In the case of progressive disease, disease imaging (e.g., CT scan) for response assessment in accordance with institutional standard of care guidelines, but at least every 6 months (± 3 weeks).
- Concomitant medication review.
- AE assessment.

10 DESCRIPTION OF STUDY ASSESSMENTS

Demographic and medical history information for individual subjects will be transferred from the parent study.

10.1 Physical Examination

At all visits, a targeted physical examination will be performed per institutional guidelines. Clinically significant physical examination data will be recorded on the eCRF as AEs, as appropriate.

10.2 Vital Signs

Measurements of vital signs include blood pressure, temperature, heart rate, respiratory rate, and oxygen saturation. Vital signs should be taken prior to and at the end of each vopratelimab infusion. Clinically significant vital sign data will be recorded on the eCRF as AEs, as appropriate.

10.3 Weight

The determination of vopratelimab dose will be based on the subject's weight. Weight will be recorded on the eCRF at each visit.

10.4 Response Assessment

The anti-tumor activity of study treatment will be assessed using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as assessed by study investigators. Imaging for efficacy assessments will be performed in accordance with institutional standard of care guidelines, but at least every 6 months (± 3 weeks) and will be recorded on the eCRF.

10.5 Clinical Laboratory Evaluations

Clinical laboratory assays will include chemistry and hematology, as well as any other measurements according to institutional standard of care guidelines, performed at local laboratories according to the laboratory's normal procedures Abnormal laboratory values that are unexpected and not explained by the subject's clinical condition should be repeated until confirmed, explained, or resolved. In the judgment of the Investigator, any clinically significant changes will be recorded on the eCRF as an AE.

10.6 Biomarkers

Pharmacodynamic biomarkers in peripheral blood, including peripheral blood mononuclear cell (PBMC)-based assays of immune cell phenotype, will be assessed approximately every 3 months (± 4 weeks) and at the end of treatment to determine the effect on peripheral T cells. Biomarker sampling will be recorded on the eCRF. Sample collection may be discontinued at any time per the Sponsor's discretion.

Please refer to the separate Laboratory Manual detailing the biomarker sample collection times, preparation, storage and shipping process.

10.6.1 Retention of Samples

If allowable by local guidelines and/or policies, all blood and PBMC samples will be retained for potential additional testing at a later date or to enable development of a companion diagnostic that would help to identify subjects most likely to benefit from vopratelimab in the future.

Samples will be retained at a secure storage facility (to be selected, qualified, and contracted by Jounce Therapeutics) in case there is need for retesting. At the end of ten (10) years after the final clinical study report is written (or some other period based on local guidelines and/or policies), or if Jounce no longer requires the samples, they will be destroyed. Analyses may be conducted by Jounce Therapeutics, Inc. or by a designated lab at their discretion.

Biospecimens will not be labeled with any personal identifiers (e.g., date of birth, initials). They will be labeled with the subject's study number to allow for future exploratory research analyses to be correlated to the study data and treatment/dose assignments.

10.7 Pregnancy Test

A serum or urine pregnancy test must be performed and reviewed on all women of childbearing potential prior to every dose of study drug. Test results will be recorded on the eCRF.

10.8 Adverse Events and Serious Adverse Events

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or serious adverse event (SAE) as provided in this protocol.

10.8.1 Definition of an Adverse Event (AE)

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including clinically significant abnormal laboratory finding), symptom, disease, or exacerbation of a pre-existing condition temporally associated with the use of study drug, whether or not related to the study drug.

Disease progression should not be recorded as an AE/SAE. New or increasing symptoms related to disease progression should be reported as an AE or AEs. When possible, the primary diagnosis of the event meeting SAE criteria should be recorded as the AE/SAE term. (For instance, if a subject is hospitalized for shortness of breath and it is confirmed that this is a symptom of a malignant pleural effusion, then malignant pleural effusion should be reported as the event term, rather than disease progression).

10.8.2 Observation and Recording of AEs

AEs that occur on the parent study and are ongoing at the time of entry into the rollover study will be recorded as medical history. Any such AE that worsens on the rollover study should be recorded as a new AE at the worsened severity.

Study personnel will assess AEs at every visit. The date of onset and resolution (if applicable) of the AE will be documented in the source documents and on the appropriate eCRF page. The Investigator will monitor all AEs to the final study visit or to a satisfactory resolution if the AE is ongoing.

All AEs will be recorded from the time of signed informed consent until the End-of-study visit (28 days ± 7 days after the last dose of study drug[s]) and are to be recorded on the appropriate AE pages in the eCRF and in source documents. AEs for the End-of-study visit may be collected by a telephone contact if the subject is not able to attend an on-site End-of-study visit. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually.

All study drug related AEs/SAEs (see Section 10.8.4 for definition) will be followed to resolution (the subject's health has returned to his/her baseline status or all variables have returned to normal), or until new therapy initiated. Where appropriate, medical tests and examinations will be performed to document resolution of the event(s).

SAEs will be reported as outlined in Section 10.9 and recorded in the AE eCRF.

10.8.3 Grading and Severity

Grade refers to the severity of the AE/SAE. Severity will be assessed in this study using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (see Appendix 3).

In the event that an AE is not covered by the CTCAE, the assessment of severity will be determined by using the CTCAE general guideline:

Table 2: Grading for Events Not Covered By the CTCAE

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

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The Investigator will evaluate all AEs as to their severity.

- An AE that is assessed as severe should not be confused with an SAE. Severity is a category used for rating the intensity of an event; both AEs and SAEs can be assessed as severe. An event is described as 'serious' when it meets one of the pre-defined outcomes as described in Section 10.9.

Worsening of a pre-treatment event, after initiation of study drug(s) must be recorded as a new AE.

10.8.4 Relationship Categorization

An Investigator qualified in medicine must make the determination of relationship to study drug for each AE/SAE. The Investigator should decide whether, in his or her medical judgment there is a reasonable possibility that the event may have been caused by the study drug. If no valid reason exists for suggesting a relationship, the AE/SAE should be classified as "definitely not". If there is a valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the study drug and the occurrence of the AE/SAE, the AE/SAE should be considered "possibly related". Table 3 should be used for guidance in the determination of relationship:

Table 3: Guidance in Determining the Relationship of an Adverse Event

Relationship	*Definition*
Unrelated	There is no association between study drug and the reported event.
Related	The event follows a reasonable temporal sequence from the time of study drug administration and/or follows a known response pattern to the study drug, but could also have been produced by other factors. A causal relationship also exists between study drug administration and the AE if other conditions (e.g., concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

If the causal relationship between an AE/SAE and study drug(s) is determined to be possibly or probably related, the event will be considered to be related to vopratelimab per investigator assessment for the purposes of expedited regulatory reporting. Note: "Cannot be ruled out" is not a basis for the assessment of possibly or probably related.

10.8.5 Outcome Categorization

Outcome of an AE/SAE may be classified as resolved, resolved with sequelae, unresolved, or fatal. Death is an outcome of an event. The event that resulted in death must be recorded on the appropriate eCRF.

10.8.6 Clinical Laboratory Evaluations

A clinical laboratory AE is any laboratory value that is considered clinically significant by the Investigator and has caused a medical intervention or accompanied by clinical symptoms. Laboratory abnormalities that have not required medical intervention should not be recorded as AEs and will be captured and reported in the laboratory section of the clinical study report. If a

medical intervention occurs, it should be recorded as a treatment with the abnormal laboratory finding as the AE.

The Investigator should decide, based upon the AE criteria and the clinical condition of the subject, whether a change in a laboratory parameter is clinically significant and therefore represents an AE.

10.8.7 Pregnancy

Pregnancy will not be considered an SAE. Any report of pregnancy recorded for any female study participant or a female partner of a male study participant should be reported immediately by completing a Pregnancy Report Form and submitted by e-mail or fax to IQVIA's Drug Safety (see Section 10.9.4).

If the outcome of the pregnancy meets serious criteria (miscarriage or congenital anomaly/birth defect), it should be reported as an SAE.

The pregnant female study participant must be withdrawn from the study. Every effort should be made to gather information regarding the pregnancy outcome until 8 weeks post-partum. It is the responsibility of the Investigator to obtain all pregnancy information.

10.9 Serious Adverse Event Reporting

10.9.1 Definition of a Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence (whether considered to be related to study drug or not, except for those events described in Section 10.9.2) that at any dose:

- Results in death;
- Is life-threatening (the term "life-threatening" in the definition of "serious" refers to an event 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 (at least 24 hours inpatient) or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital abnormality/birth defect;
- Is an Important Medical Event.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition of a serious adverse event above, as these events may be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

10.9.2 SAE Classifications

Elective or previously scheduled hospitalizations for pre-existing conditions which have not worsened after initiation of treatment should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE.

10.9.3 Protocol-Specified Expected Events

Subjects with advanced solid malignancies are at risk for many AEs as a consequence of prior therapy and as a result of their disease.

Subjects receiving immune therapies are at risk for immune-related AEs. Immune-related AEs (irAEs) are typically responsive to interruption or discontinuation of the immunotherapy in combination with immunosuppressive drugs such as steroids or occasionally tumor necrosis factor-blocking antibodies. At present, there is no clear preventive strategy to avoid irAEs {Michot 2016}.

10.9.4 Observation and Recording of SAEs

All SAEs must be reported to IQVIA within 24 hours of first awareness of the event.

SAE Reporting Contact Information
IQVIA Biotech, LLC Safety and Reporting
Fax number: 1-866-761-1274
Phone number: 1-866-758-2798

10.9.5 E-mail: Safety-Inbox.Biotech@IQVIA

Additional follow-up information, if required, or available, should be recorded on a follow-up SAE Report Form and faxed to IQVIA Drug Safety within one business day of discovery by site.

All SAEs, whether related or unrelated to study drug, will be recorded from the time of signed informed consent until resolution or new therapy initiated or for 28 days post final dose if no new therapy is initiated. Any SAEs considered to have at least a possible relationship to the study drug and discovered by the Investigator at any time period after the subject's study treatment has ended should be reported according to the timeframe described above.

Study drug-related SAEs will be followed until resolution, stabilization or subject receives new therapy.

At a minimum, the site number, Investigator's name, subject number, event name, the date of onset, a short description of the event and the Investigator's preliminary assessment of causality must be provided at the time of the initial SAE report.

The onset date of the SAE is defined as the onset date of signs and symptoms or a change in baseline when the SAE met seriousness criteria.

The resolution date of the SAE is defined as the date in which the criteria of seriousness is no longer applicable (e.g., discharge from hospitalization).

All SAEs that are ongoing events at the time of death should be considered not resolved at time of death.

The Investigator is encouraged to discuss with the Medical Monitor any SAEs for which the issue of reportability is unclear or in question.

The Investigator must review, sign, and date the SAE Report Form to confirm the accuracy of the information recorded on the SAE Report Form along with the corresponding source documentation.

10.9.6 Regulatory Authorities and Institutional Review Boards

Jounce or its designee is responsible for notifying the investigational sites and all heath authorities (e.g., United States [US] Food and Drug Administration [FDA]) of all expedited SAEs.

The Investigator will notify his or her Institutional Review Board (IRB)/Ethics Committee (EC) of serious, related and unexpected AE(s) or significant risks to subjects. The Investigator must keep copies of all AE information, including correspondence with Jounce or local ECs on file.

It is the responsibility of the Principal Investigator (PI) to notify the IRB/EC of all SAEs that occur at his or her site as per site guidelines. Investigators will be notified of all suspected, unexpected SAEs (7/15 Day Safety Reports) that occur during any clinical studies that are using the investigative compound. Each site is responsible for notifying its IRB/EC of these additional SAEs.

10.9.7 Drug Safety Contact Information

IQVIA Biotech, LLC Safety and Reporting
Fax number: 1-866-761-1274
E-mail: Safety-Inbox.Biotech@IQVIA

Medical Monitor:
Ellen Hooper, MD
Senior Medical Director
Jounce Therapeutics
780 Memorial Drive
Cambridge, MA 02139
(w) 857-320-2548
(m) 914-439-2240
ehooper@jouncetx.com

Back-up Medical Monitor:
Johan Baeck, MD
Senior Vice President, Clinical Development and Medical Affairs
Jounce Therapeutics
780 Memorial Drive
Cambridge, MA 02139
(w) 857-320-2573
(m) 862-926-8158
jbaeck@jouncetx.com

11 STATISTICAL ANALYSES

11.1 Endpoints

Safety and efficacy endpoints, including exposure to the investigational study drug, incidence and severity of treatment-emergent serious and non-serious AEs, investigational study drug discontinuation reason, and death, will be derived.

11.2 Statistical Basis for Sample Size

Patients on study treatment in a Jounce-sponsored clinical study and eligible for rollover may be enrolled. For the study objectives, no prospective sample size determination is required.

11.3 Statistical Analysis

Study data collected will be summarized descriptively as per the requirements of the Investigational New Drug (IND) annual report or Drug Safety Update Report (DSUR). Additional analyses of safety and efficacy data may be performed, if the updates are clinically meaningful, following the pertinent statistical analysis methods specified in the original protocol.

11.3.1 Determination of Sample Size

Not applicable

11.3.2 Analysis Set

The Safety Population (SAF) will include all subjects who have been treated with at least one dose of study drug.

12 DATA QUALITY ASSURANCE

This study will be organized, performed, and reported in compliance with Jounce/CRO's Standard Operating Procedures, protocols and working practice documents, and the requirements of International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)/Good Clinical Practice (GCP) guidelines. Compliance will be achieved through a combination of study specific audits of investigative sites and audits at regular intervals of the Jounce /CRO's systems for data handling, analysis, and reporting.

12.1 Data Collection

Investigators or designees will enter the information required by the protocol onto the eCRFs. Each investigative site will be visited as frequently as documented in the monitoring plan by the CRO on behalf of Jounce to review the eCRFs for completeness and accuracy. The CRO representative will highlight any discrepancies found between source documents and the completed eCRFs and ensure that appropriate site personnel address the discrepancies. When a discrepancy results in corrected eCRF data, the correction will be reviewed again against the correct source documentation. Uniform procedures will be discussed at the Site Initiation Visit.

12.2 Clinical Data Management

Data from eCRFs and other external data will be entered into a clinical database as specified in the CRO's data management plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database.

Data from eCRFs and other external data will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Only authorized personnel will make corrections to the eCRF and all corrections will be documented in an audit trail.

This study will be conducted in compliance with regulations contained within 21Code of Federal Regulations (CFR) Part 11, electronic records/electronic signatures regulations.

13 ADMINISTRATIVE PROCEDURES

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that Jounce and Investigators abide by GCP as described in the ICH Harmonised Tripartite Guideline E6: GCP: Consolidated Guideline, and 21 CFR Parts 50, 54, 56, and 312. Compliance with these regulations also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki. The study will also be carried out in keeping with local legal and regulatory requirements.

13.1 Institutional Review Board (IRB)

It is the responsibility of the Investigator to submit this protocol, the informed consent document (approved by Jounce or its designate), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation. Prior to implementing changes in the study, Jounce and the IRB/EC must also approve any revised informed consent documents and amendments to the protocol.

On the approval letter, the study reference, the date of review and actions taken should be clearly stated. Investigational Product will not be released and the subject recruitment will not begin until this written approval has been received by Jounce or its designee.

The Investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol. The Investigator must also keep the IRB/EC informed of any serious and significant AEs.

13.2 Informed Consent

It is the responsibility of the Investigator to obtain written Informed Consent from subjects. All consent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally authorized representative is requested to sign the Informed Consent Form (ICF) after the subject has received and read the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences and the subject's rights and responsibilities. A copy of the informed consent documentation (consent form or subject information sheet and the consent form, as applicable) must be given to the subject or the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the subject's local language. Signed consent forms must remain in each subject's study file and must be available for verification by study monitors at any time.

Each PI will provide Jounce with a copy of the IRB/EC approved consent forms, and a copy of the IRB/EC written approval, prior to the start of the study. Additionally, if the IRB/EC required modification of the sample subject information and consent document provided by Jounce, the documentation supporting this requirement must be provided to Jounce.

Jounce reserves the right to delay initiation of the study at a site where the informed consent forms do not meet the standards of applicable regulations and ICH GCP.

13.3 Subject Privacy

Jounce and the Investigator affirm and uphold the principle for the subject's right to protection against invasion of privacy. Throughout this study, all data collected and analyzed by Jounce (or designee) will be identified by an identification number.

To verify compliance with this protocol, Jounce will require that the Investigator permit its monitor to review those portions of the subject's primary medical records that directly concern this study (including but not limited to laboratory test results, electrocardiogram reports, and hospital and outpatient records). Should access to such medical records require a waiver or authorization separate from the statement of informed consent, the Investigator will obtain such permission in writing from the subject before the subject is entered into the study.

13.4 Study Monitoring

Monitoring of the study will be performed by a representative of Jounce's CRO. At the monitoring visits, the progress of the study will be discussed with the Investigator, or his/her representative. The ICFs will be reviewed for signatures and the eCRFs checked for completeness and accuracy. Subject source data must be available for review. The Investigator and his/her staff are expected to cooperate with the study monitor and be available during at least a portion of the monitoring visit to review the eCRFs and any queries/resolutions, answer questions, and provide any missing information.

The study monitor will record the date of each visit together with a summary of the status and progress of the study. Proposed actions will be confirmed with the Investigator in writing.

Telephone contact will be made with the Investigator as necessary during the data collection period and during the data and report writing periods.

13.5 Modification of Protocol

All amendments to the protocol must be documented in writing, reviewed, and approved by the Investigator and Jounce, and submitted to the IRB/EC for approval prior to initiation, except in cases where required for subject safety. If the protocol amendment substantially alters the study design or potential risk to the subject, new written informed consent for continued participation in the study must be obtained from each subject.

13.6 Suspension or Termination of Study

Should conditions requiring further clarification arise before the decision to proceed with or terminate the study can be reached, the study will be suspended until the situation has been resolved.

Jounce has the right to terminate this study and remove all study material from the site at any time. Examples of where this might occur include but are not limited to:

- It becomes apparent that subject enrollment is unsatisfactory with respect to quality and/or quantity or data recording is inaccurate and/or incomplete on a chronic basis;
- The incidence and/or severity of AEs in this study indicate a potential health hazard caused by treatment with the study medication.

13.7 Departure from Protocol

No deviation may be made from the protocol unless an amendment has been agreed to in writing by both the Investigator and Jounce and approved by the IRB/EC. Investigative sites will contact the medical monitor to request clarifications regarding any aspect of the clinical study or eligibility of subjects. Any study-wide updates may be released via administrative memo from the Sponsor when appropriate.

When an emergency occurs that requires a departure from the protocol for an individual, a departure will be only for that subject. The Investigator or other physician in attendance in such an emergency will, if circumstances and time permit, contact Jounce or their representatives, immediately by telephone. Such contacts will be made as soon as possible to permit a decision as to whether or not the subject (for whom the departure from protocol was affected) is to continue in the study. The source documents will completely describe the departure from the protocol and state the reasons for such departure. In addition, the IRB/EC will be notified in writing of such departure from protocol.

13.8 Recording, Access and Retention of Source Data

The Investigator must permit authorized representatives of Jounce, the regulatory authorities, the IRB/EC, auditors and interested commercial parties to inspect facilities and records relevant to this study. Source data to be reviewed during this study will include, but are not limited to: subject's medical file, original laboratory reports, X-rays/scans, pathology reports, electrocardiograms, etc. All key data must be recorded in the subject's source documents.

The monitor (auditors, IRB/EC or regulatory inspectors) may check the eCRF entries against the source documents. The consent form will include a statement by which the subjects allow the monitor/auditor/inspector from Jounce or its representatives, regulatory authorities or the IRB/EC access to source data which substantiate information recorded in the eCRFs. These personnel, bound by professional secrecy, will not disclose any personal information or personal medication information.

As described in the ICH GCP Guidelines, 'essential documents', including eCRFs, source documents, consent forms, laboratory test results and the investigational product inventory records, should be retained by the Investigator until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with Jounce. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained. The Investigator must obtain written permission from Jounce prior to the destruction of any study document.

These records must be made available at reasonable times for inspection and duplication, if required, by a properly authorized representative of the US FDA in accordance with the US 21 CFR 312.68 or other regulatory authorities in accordance with regulatory requirements.

13.8.1 Case Report Forms

Electronic CRFs will be used for data collection for this study.

The Investigator is responsible for maintaining adequate and accurate source documents from which accurate information will be transcribed into eCRFs which have been designed to capture all observations and other data pertinent to the clinical investigation. eCRFs should be completed by the Investigator or delegate as stated on the Delegation of Authority Log. Overwriting of information or use of liquid correcting fluid is not allowed in the source document.

The eCRFs must be reviewed and electronically signed and dated by the Investigator once all data has been entered and all queries resolved. Once the Study Monitor has verified the contents of the completed eCRF against the source data, queries may be raised if the data are unclear or contradictory. The Investigator must address all queries.

13.9 Good Clinical Practice (GCP) Compliance

The Investigator must undertake to perform the study in accordance with, ICH GCP Guideline E6, local IRB/EC requirements, and 21 CFR.

It is the Investigator's responsibility to ensure that adequate time and appropriate resources are available at the study site prior to commitment to participate in this study. The Investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The Investigator will maintain a list of appropriately qualified persons to whom the Investigator has delegated significant study-related tasks. An up-to-date copy of the curriculum vitae for the Investigator and sub-Investigator(s) will be provided to Jounce (or designee) before starting the study.

If the subject has a primary physician the Investigator should, with the subject's consent, inform them of the subject's participation in the study.

13.9.1 Quality Control and Quality Assurance

A site monitoring plan will be developed to ensure the human subject protection, study procedures, laboratory, study intervention administration, and data collection processes are of high quality and meet Jounce, GCP/ICH, and regulatory guidelines.

The Investigator will permit authorized representatives of Jounce and the respective regulatory authorities to inspect facilities and records relevant to this study if needed.

Initial site training will be provided by Jounce. Training for new staff will be provided by current study nurses and study coordinators under the supervision of the PI. Additional training will be provided by Jounce as needed.

The Data Management Team will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

13.9.2 Publications

All manuscripts, abstracts or other modes of presentation arising from the results of the study must be reviewed and approved in writing by Jounce, in advance of submission. The review is aimed at protecting Jounce's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results or other information, generated or created in relation to the study must be carried out in accordance with the Clinical Study Agreement.

13.9.3 Confidentiality

Data collected during this study may be used to support the development, registration, or marketing of vopratelimab. After subjects have consented to take part in the study their medical records and the data collected during the study will be reviewed by Jounce and/or its representatives. These records and data may, in addition, be reviewed by the following: independent auditors who validate the data on behalf of Jounce; third parties with whom Jounce may develop, register or market vopratelimab; national or local regulatory authorities and the IRB/EC(s) that gave approval for this study to proceed.

Although subjects will be known by a unique number, their date of birth will also be collected and used to assist Jounce to verify the accuracy of the data, for example, that the laboratory results are assigned to the correct subject.

13.9.4 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other national and local regulatory authorities), Jounce or its representatives, interested commercial parties and the IRB/EC for each study site.

14 APPENDICES

Appendix 1: Schedule of Events (Every 6 Week Administration)

	Rollover Entry/Cycle 1 Day 1 [1]	**Day 1 (± 3 days) of Subsequent Cycles** [2]	**Rollover End of Study**
Timing of Visit		Every 6 Weeks	28 ± 7 days after last dose
Informed Consent	X		
Eligibility Criteria	X		
Physical Examination[3]	X	X	X
Weight (kg)	X	X	X
Vital Signs[4]	X	X	X
Pregnancy Test[5]	X	X	
Hematology	X	X	X
Chemistry	X	X	X
Other Laboratory Assessments per Standard of Care	X	X	X
Blood Samples for Pharmacodynamic Biomarkers	X	X[6]	X
Study Treatment Administration[7]	X	X	
Disease Imaging (e.g., CT scan)		X[8]	X[8]
Concomitant Medications	X	X	X
Adverse Events	X	X	X

Abbreviations: CT = computed tomography; ; RECIST = Response Evaluation Criteria in Solid Tumors
Footnotes:
[1] Enrollment into the rollover study should occur upon exit from the parent study to avoid any interruptions in study treatment administration.
[2] All assessments should be performed prior to vopratelimab dosing, unless otherwise noted.
[3] Targeted physical examination is required at each study administration visit and at the End-of-study visit;.
[4] Vital signs to include temperature, heart rate, respiratory rate, blood pressure, and oxygen saturation. Vital signs should be taken prior to and at the end of each vopratelimab infusion.
[5] Negative serum or urine pregnancy test for women of childbearing potential prior to administration of vopratelimab on Day 1 of each treatment cycle.
[6] Blood sampling for exploratory analyses of pharmacodynamic biomarkers should be collected approximately every 3 months (± 4 weeks) at the time of a scheduled clinic visit. Sample collection may be discontinued at any time per the Sponsor's discretion. Please refer to the Study Laboratory Manual for more details.
[7] Study treatment (vopratelimab ± partner drug) should be administered on the same dose and schedule as a subject was receiving at the time of discontinuation from the parent study. Any changes to the dose and schedule of vopratelimab must be in accordance with a dose and schedule previously shown to be safe and well tolerated and must be discussed with the medical monitor. Any changes to the dose and schedule of nivolumab or ipilimumab must be discussed with the medical monitor.
[8] Disease imaging will be performed in accordance with institutional standard of care guidelines, but at least every 6 months (± 3 weeks). Response will be determined by RECIST (Version 1.1).

Appendix 2: Schedule of Events (Every 3 Week Administration)

	Rollover Entry/ Cycle 1 Day 1[1]	Day 1 (± 3 days) of Subsequent Cycles [2]	Rollover End of Study
Timing of Visit		Every 3 Weeks	28 ± 7 days after last dose
Informed Consent	X		
Eligibility Criteria	X		
Physical Examination[3]	X	X	X
Weight (kg)	X	X	X
Vital Signs[4]	X	X	X
Pregnancy Test[5]	X	X	
Hematology	X	X	X
Chemistry	X	X	X
Other Laboratory Assessments per Standard of Care	X	X	X
Blood Samples for Pharmacodynamic Biomarkers	X	X[6]	X
Study Treatment Administration[7]	X	X	
Disease Imaging (e.g., CT scan)		X[8]	X[8]
Concomitant Medications	X	X	X
Adverse Events	X	X	X

Abbreviations: CT = computed tomography; RECIST = Response Evaluation Criteria in Solid Tumors
Footnotes:
[1] Enrollment into the rollover study should occur upon exit from the parent study to avoid any interruptions in study treatment administration.
[2] All assessments should be performed prior to vopratelimab dosing, unless otherwise noted.
[3] Targeted physical examination is required on study administration days and at the End-of-study visit;
[4] Vital signs to include temperature, heart rate, respiratory rate, blood pressure, and oxygen saturation. Vital signs should be taken prior to and at the end of vopratelimab infusion.
[5] Negative serum or urine pregnancy test for women of childbearing potential prior to administration of vopratelimab on Day 1 of each treatment cycle.
[6] Blood sampling for exploratory analyses of pharmacodynamic biomarkers should be collected approximately every 3 months (± 4 weeks) at the time of a scheduled clinic visit. Sample collection may be discontinued at any time per the sponsor's discretion. Please refer to the Study Laboratory Manual for more details.
[7] Study treatment (vopratelimab ± partner drug) should be administered on the same dose and schedule as a subject was receiving at the time of discontinuation from the parent study. Any changes to the dose and schedule of vopratelimab must be in accordance with a dose and schedule previously shown to be safe and well tolerated and must be discussed with the medical monitor. Any changes to the dose and schedule of nivolumab or ipilimumab must be discussed with the medical monitor.
[8] Disease imaging will be performed in accordance with institutional standard of care guidelines, but at least every 6 months (± 3 weeks). Response will be determined by RECIST (Version 1.1).

Appendix 3: Web Links

CTCAE

The link to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 is:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

FDA Guidance for Investigators

The below links are to the Guidance Documents for Investigators Responsibilities and Safety Reporting Requirements for INDs:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf

http://www.fda.gov/downloads/Drugs/.../Guidances/UCM187772.pdf

Appendix 4: RECIST

See Laboratory Manual for more information

http://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf

{Eisenhauer, 2009}

15 REFERENCE LIST

Opdivo® Prescribing Information. September 2021, Bristol-Myers Squibb Company. https://packageinserts.bms.com/pi/pi_opdivo.pdf

Yervoy® Prescribing Information. September 2021, Bristol-Myers Squibb Company. https://packageinserts.bms.com/pi/pi_yervoy.pdf

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