Official Title:	**A Phase 1/2, Open-Label, Dose-Escalation, Safety, Tolerability, and Efficacy Study of Epacadostat and Nivolumab in Combination With Immune Therapies in Subjects With Advanced or Metastatic Malignancies (ECHO-208)**
NCT Number:	NCT03347123
Document Date:	Clinical Study Protocol version 2: 05 December 2018

Clinical Study Protocol

INCB 24360-208

A Phase 1/2, Open-Label, Dose-Escalation, Safety, Tolerability, and Efficacy Study of Epacadostat and Nivolumab in Combination With Immune Therapies in Subjects With Advanced or Metastatic Malignancies (ECHO-208)

Product:	**Epacadostat (INCB024360)**
IND Number:	**135,201**
EudraCT Number:	**2017-001743-12**
Phase of Study:	**1/2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Original Protocol (Version 0):	**12 JUL 2017**
Amendment (Version) 1:	**31 JUL 2017**
Amendment (Version) 2:	**05 DEC 2018**

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and conducted in adherence to the study Protocol, Good Clinical Practices as defined in Title 21 of the US Code of Federal Regulations Parts 11, 50, 54, 56, and 312, as well as ICH GCP consolidated guidelines (E6) and applicable regulatory requirements.

INVESTIGATOR'S AGREEMENT

I have read the INCB 24360-208 Protocol Amendment 2 (dated 05 DEC 2018) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

(Printed Name of Investigator)

(Signature of Investigator) (Date)

SYNOPSIS

Name of Investigational Product: Epacadostat, Nivolumab, Ipilimumab, Lirilumab

Title of Study: A Phase 1/2, Open-Label, Dose-Escalation, Safety, Tolerability, and Efficacy Study of Epacadostat and Nivolumab in Combination With Immune Therapies in Subjects With Advanced or Metastatic Malignancies (ECHO-208)

Protocol Number: INCB 24360-208	**Study Phase:** 1/2

Indication:

Phase 1 (Dose Escalation): Advanced or metastatic solid tumors.

Phase 2 (Dose Expansion): Advanced or metastatic non–small cell lung cancer (NSCLC), unresectable or metastatic melanoma (MEL) and recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN).

Primary Objectives	**Primary Endpoints**
Phase 1:	
To evaluate the safety, tolerability, and dose-limiting toxicities (DLTs) and to define a maximum tolerated dose (MTD) and/or pharmacologically active dose (PAD) of epacadostat in combination with nivolumab and ipilimumab, and in combination with nivolumab and lirilumab, in subjects with advanced or metastatic solid tumors.	Safety and tolerability will be assessed by monitoring frequency, duration, and severity of adverse events (AEs) through physical examinations, by evaluating changes in vital signs and electrocardiograms (ECGs), and through clinical laboratory blood and urine sample evaluations.
Phase 2:	
Treatment Group A: To evaluate the efficacy of epacadostat in combination with nivolumab and ipilimumab in subjects with advanced or metastatic NSCLC and unresectable or metastatic MEL by assessing objective response rate (ORR) per RECIST v1.1.	ORR, defined as the percentage of subjects having complete response (CR) or partial response (PR), will be determined by investigator evaluation of radiographic disease assessment per RECIST v1.1.
Treatment Group B: To evaluate the efficacy of epacadostat in combination with nivolumab and lirilumab in subjects with recurrent or metastatic SCCHN by assessing ORR per RECIST v1.1.	
Secondary Objectives	**Secondary Endpoints**
Phase 1:	
To evaluate the efficacy of epacadostat in combination with nivolumab and ipilimumab, and in combination with nivolumab and lirilumab, in subjects with advanced or metastatic solid tumors by assessing ORR per RECIST v1.1.	ORR, defined as the percentage of subjects having CR or PR, will be determined by investigator evaluation of radiographic disease assessment per RECIST v1.1.

Secondary Objectives (Continued)	Secondary Endpoints (Continued)
Phase 1 and Phase 2:	
To evaluate the efficacy of epacadostat in combination with nivolumab and ipilimumab, and in combination with nivolumab and lirilumab, in subjects with advanced or metastatic solid tumors in Phase 1 and in subjects with selected advanced or metastatic solid tumors in Phase 2 by assessing duration of response (DOR) and progression-free survival (PFS) per RECIST v1.1.	DOR is defined as the time from the earliest date of CR or PR until the earliest date at which progression criteria are met as determined by investigator evaluation of radiographic disease assessment per RECIST v1.1, or date of death due to any cause.
	PFS is defined as the time from the start of combination therapy until the earliest date at which progression criteria are met as determined by investigator evaluation of radiographic disease assessment per RECIST v1.1, or date of death due to any cause.
Phase 2:	
To further evaluate the safety and tolerability of epacadostat at the MTD and/or PAD in combination with nivolumab and ipilimumab, and in combination with nivolumab and lirilumab, in subjects with selected advanced or metastatic solid tumors.	Safety and tolerability will be assessed by monitoring frequency, duration, and severity of AEs through physical examinations, by evaluating changes in vital signs and ECGs, and through clinical laboratory blood and urine sample evaluations.
[redacted]	

[redacted]

Overall Study Design:

Note: Amendment 2 will serve to close the study to further enrollment; the primary purpose of the amendment is to provide an updated assessment schedule for subjects enrolled to date (Treatment Group A only). No subjects were enrolled into Treatment Group B.

This is an open-label, nonrandomized, Phase 1/2 study to determine the safety, tolerability, and efficacy of epacadostat when given in combination with nivolumab and ipilimumab, and in combination with nivolumab and lirilumab. The study will be conducted in 2 independent treatment groups: Treatment Group A will evaluate the combination of epacadostat, nivolumab, and ipilimumab; Treatment Group B will evaluate the combination of epacadostat, nivolumab, and lirilumab. Each treatment group will be investigated in 2 phases:

- Phase 1 will consist of a standard 3 + 3 + 3 dose-escalation design to define the MTD or PAD of epacadostat with nivolumab and ipilimumab (Treatment Group A) and with nivolumab and lirilumab (Treatment Group B) in subjects with advanced or metastatic solid tumors; [redacted] and preliminary efficacy will also be explored during this portion.
- Phase 2 will evaluate the efficacy of the MTD or PAD of epacadostat when given in combination with nivolumab and ipilimumab, and in combination with nivolumab and lirilumab, as determined in each of the Phase 1 treatment groups in select solid tumors, and will further evaluate the safety, [redacted] of the combinations.

Treatment Group A will enroll 2 tumor-specific expansion cohorts (Cohorts A1 and A2): Cohort A1 will include subjects with unresectable or metastatic MEL who have not received prior systemic therapy for advanced or metastatic disease; Cohort A2 will include subjects with advanced or metastatic NSCLC who have received no more than 1 prior line of platinum-based chemotherapy therapy for advanced or metastatic disease.

Treatment Group B will enroll 1 expansion cohort (Cohort B1); Cohort B1 will include subjects with recurrent or metastatic SCCHN who have received no more than 1 prior line of platinum-based chemotherapy for recurrent or metastatic disease.

Phase 1 - Dose Escalation

Dose escalation in Treatment Groups A and B will be conducted using a standard 3 + 3 + 3 design as per the dose-escalation schedule outlined in Table S1. A minimum of 3 evaluable subjects will be enrolled in each treatment group beginning with Dose Level 1 (starting dose of epacadostat 50 mg twice daily [BID] in Treatment Groups A and B).

In Treatment Group A, the first 3 evaluable subjects at each dose level will be observed for a minimum of 42 days before the next dose level begins enrollment. To be evaluable for tolerability, subjects must receive at least 75% of planned epacadostat doses (63/84) at the specified dose level, 3 doses of nivolumab, and 1 dose of ipilimumab, or subjects must experience a DLT during the DLT observation period.

In Treatment Group B, the first 3 evaluable subjects at each dose level will be observed for a minimum of 42 days before the next dose level begins enrollment. To be evaluable for tolerability, subjects must receive at least 75% of planned epacadostat doses (63/84) at the specified dose level, 3 doses of nivolumab, and 2 doses of lirilumab, or subjects must experience a DLT during the DLT observation period.

Subjects who discontinue for reasons other than a DLT (eg, events clearly associated with the underlying disease, disease progression, concomitant medication, comorbidity, or an AE clearly unrelated to study treatment) during the DLT observation period will be considered nonevaluable for DLT evaluation and will be replaced.

Alternate doses or dose administration schedules, including sequenced (rather than concurrent) administration of treatment components, [redacted] and safety results.

For both treatment groups, the following dose-escalation rules apply:

- If 0 of the first 3 evaluable subjects at a dose level have a DLT, 3 subjects will be enrolled and treated at the next higher dose level (if applicable).
- If 1 of the first 3 evaluable subjects at a dose level has a DLT, that dose level will be expanded to 6 subjects. If ≤ 1 of 6 subjects in a dose level has a DLT, 3 subjects will be enrolled and treated at the next higher dose level (if applicable).
- If 2 of 6 subjects at a dose level have a DLT, that dose level will be expanded to include 9 subjects.
- If ≥ 2 of 3, ≥ 3 of 6, or ≥ 3 of 9 subjects have DLTs at a specific dose level, that dose level will be determined to have exceeded the MTD, and the previous dose level will be considered the MTD.

If Dose Level 1 in either treatment group (as specified in Table S1) exceeds the MTD, 3 additional subjects may be enrolled and treated at a lower dose (Dose Level -1).

If only 3 evaluable subjects were treated at the dose level selected for Phase 2, then a minimum of 3 additional evaluable subjects will be enrolled before the selected dose is deemed as recommended Phase 2 dose (RP2D).

Dose interruptions and/or modifications may be implemented based on toxicity. Dose modifications should not be made during a DLT observation period without consulting the study medical monitor. Intrasubject dose escalation is not permitted.

Table S1: Epacadostat Phase 1 Dose Levels

Treatment Group A			
Dose Level	**Epacadostat**	**Nivolumab**	**Ipilimumab**
-1	25 mg BID	240 mg Q2W	1 mg/kg IV Q6W
1 (starting dose)	**50 mg BID**[a]		
2	100 mg BID		
Treatment Group B			
Dose Level	**Epacadostat**	**Nivolumab**	**Lirilumab**
-1	25 mg BID	240 mg Q2W	240 mg IV Q4W
1 (starting dose)	**50 mg BID**[a]		
2	100 mg BID		

Q2W = once every 2 weeks; Q4W = once every 4 weeks; Q6W = once every 6 weeks.

[redacted]

[a] If epacadostat 50 mg BID exceeds the MTD, 25 mg BID may be evaluated.

Phase 2 - Dose Expansion

The Phase 2 dose expansion cohorts will begin when the MTD or PAD of epacadostat has been determined in Phase 1 for the respective treatment group. This portion of the study will evaluate the efficacy of the MTD or PAD of epacadostat and will further evaluate the safety, [redacted] of the combinations.

Treatment Group A will enroll 2 expansion cohorts in parallel:

- **Cohort A1:** Approximately 35 subjects with unresectable or metastatic MEL who have not received prior systemic treatment for advanced or metastatic disease. Serial pretreatment and on-treatment biopsies are required for all subjects enrolled, if clinically feasible.
- **Cohort A2:** Approximately 35 subjects with advanced or metastatic NSCLC without known driver mutations (including EGFR, BRAF, ALK, and ROS1) who have received no more than 1 prior line of therapy for advanced or metastatic disease. Serial pre-treatment and on-treatment biopsies are required for all subjects enrolled, if clinically feasible.

Treatment Group B will enroll 1 expansion cohort:

- **Cohort B1:** Approximately 35 subjects with recurrent or metastatic SCCHN who have received no more than 1 prior line of platinum-based chemotherapy for recurrent or metastatic disease. Serial pretreatment and on-treatment biopsies are required for all subjects enrolled, if clinically feasible.

Enrollment into the Phase 2 expansion cohorts will begin when the MTD or PAD of epacadostat for the corresponding treatment group in Phase 1 has been determined; however, priority will be given to any open dose-escalation cohorts in Phase 1.

In Phase 2 of the study, toxicities will continue to be monitored. If the cumulative incidence of ≥ Grade 3 immune-related AEs is > 40% after a cumulative minimum of 10 subjects have been enrolled into the expansion cohorts within each treatment group, further enrollment in those expansions will be interrupted until the sponsor, investigators, and regulatory authorities (if applicable) determine the appropriate course of action. If an expansion cohort in a particular treatment group is discontinued because of toxicity, a new expansion may be initiated at a previously tested lower dose level of epacadostat.

The sponsor may elect to prioritize enrollment to specific treatment groups or expansion cohorts based on emerging safety or efficacy data in collaboration with investigational sites.

Study Population:

Inclusion Criteria:

Phase 1 only:

- Subjects with histologically or cytologically confirmed locally advanced or metastatic solid tumors who have disease progression on or after treatment with available therapies that are known to confer clinical benefit, or who are intolerant to treatment, or who refuse standard treatment.

  Note: Locally advanced disease must not be amenable to resection with curative intent.
- Has received no more than 2 prior treatment regimens (including chemotherapy and/or targeted therapy; not including neoadjuvant and/or adjuvant therapy) for advanced or metastatic disease.
- Has baseline core or excisional tumor archival biopsy specimen available or willingness to undergo a pretreatment biopsy to obtain the specimen. Archival specimen must be a tumor block or 25 unstained slides (minimum of 20). A formalin-fixed paraffin-embedded (FFPE) tumor tissue block is preferred. If a block is not available, a minimum of 20 to 25 unstained freshly cut slides may be submitted to the testing laboratory as specified Laboratory Manual.

  Note: Unstained slides must have been prepared from an FFPE block obtained within 6 months before screening.

Phase 2:

Cohort A1 (MEL):

- Subjects with histologically confirmed unresectable Stage III or Stage IV MEL not amenable to local therapy who have received no prior systemic treatment (excluding adjuvant or neoadjuvant chemotherapy) for advanced or metastatic disease. Mucosal or cutaneous MEL is acceptable; however, subjects with ocular MEL are excluded.
  - Must have documentation of BRAF mutation status.
  - [redacted]

Cohort A2 (NSCLC):

- Subjects with histologically or cytologically confirmed Stage IIIB, Stage IV, or recurrent squamous or nonsquamous NSCLC and who have received no more than 1 prior line of platinum-based chemotherapy for advanced or metastatic disease.
  - Subjects with known driver mutations (including EGFR or BRAF mutations, or ALK or ROS1 rearrangements) are excluded.
  - Prior adjuvant or neoadjuvant chemotherapy completed less than 6 months before study entry will be counted as 1 prior line of therapy.

Cohort B1 (SCCHN):

- Subjects with histologically confirmed squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx that is not amenable to local therapy with curative intent (surgery or radiation with or without chemotherapy) and who have received no more than 1 prior line of platinum-based chemotherapy for recurrent or metastatic disease.
  - Must have documentation of human papillomavirus status (eg, p16 status) of tumor (oropharyngeal only).
  - Histologically confirmed recurrent or metastatic carcinoma of the nasopharynx and salivary gland or nonsquamous histologies are excluded.

Phase 2 (all cohorts):

- Willingness to undergo serial pretreatment and on-treatment core or excisional tumor biopsies. Biopsy requirement may be omitted with medical monitor approval if it is not clinically feasible due to location of known disease or concomitant condition. Biopsies will be confirmed to contain adequate tumor tissue by a local pathology review.

All subjects (Phase 1 and Phase 2):

- Ability to comprehend and willingness to sign an informed consent form.
- Men or women aged 18 years or older.
- Presence of measurable disease per RECIST v1.1. Tumor lesions located in a previously irradiated area, or in an area subjected to other locoregional therapy, are considered measurable if progression has been demonstrated in the lesion following such therapy.
- ECOG performance status of 0 or 1.
- Expected survival of $\geq$ 12 weeks.
- Willingness and ability to comply with the scheduled visits, treatment plan, and laboratory tests.

Key Exclusion Criteria:

- Laboratory and medical history parameters not within the Protocol-defined range; all screening laboratory tests should be performed within 7 days of Cycle 1 Day 1. If the screening laboratory tests outlined below were performed more than 7 days before Cycle 1 Day 1, the hematology, serum chemistry, and liver chemistry test results must be confirmed on Cycle 1 Day 1 before initiation of study treatment.
  - Absolute neutrophil count $< 1.5 \times 10^9$/L.
  - Platelets $< 100 \times 10^9$/L.
  - Hemoglobin < 9 g/dL or < 5.6 mmol/L (transfusion is acceptable to meet this criterion).
  - Serum creatinine ≥ 1.5 × institutional upper limit of normal (ULN), or measured or calculated creatinine clearance (CrCl) < 50 mL/min for subjects with creatinine levels > 1.5 × institutional ULN (glomerular filtration rate can also be used in place of CrCl).
  - **Phase 1 only:** Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 1.5 × institutional ULN.
  - **Phase 2 only:** AST or ALT ≥ 2.5 × institutional ULN.
  - Total bilirubin ≥ 1.5 × institutional ULN or conjugated (direct) bilirubin ≥ institutional ULN. If an institutional ULN for conjugated bilirubin is not available, then conjugated bilirubin should be < 40% of total bilirubin to be considered eligible.
  - International normalized ratio or prothrombin time > 1.5 × institutional ULN.
  - Activated partial thromboplastin time > 1.5 × institutional ULN unless subject is receiving anticoagulant therapy, as long as PTT is within therapeutic range of intended use of anticoagulants.
  - **Phase 1 only:** Albumin ≤ 3.0 g/dL or with medical monitor approval.
- Receipt of anticancer medications or investigational drugs within the following interval before the first administration of study drug:
  - ≤ 21 days for chemotherapy or targeted small-molecule therapy
    Note: Use of bisphosphonates is permitted.
  - ≤ 28 days for previous monoclonal antibody used for anticancer therapy.
    Note: Use of denosumab is permitted.
  - ≤ 28 days or 5 half-lives (whichever is longer) before Cycle 1 Day 1 for all other investigational agents or devices. For investigational agents with long half-lives (eg, > 5 days), enrollment before the fifth half-life requires medical monitor approval.
- Previous radiotherapy within 7 days of Cycle 1 Day 1 (except for radiation to central nervous system (CNS), which requires a ≥ 28-day washout as described below). Subjects must also not require chronic use of corticosteroids and must not have had radiation pneumonitis as a result of treatment.
- Known active CNS metastases and/or carcinomatous meningitis.
  Note: Subjects with previously treated brain metastases may participate provided that they are stable (without evidence of progression by imaging for at least 28 days before Cycle 1 Day 1 and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases or cerebral edema, and have not required steroids for at least 14 days before Cycle 1 Day 1.
- Prior treatment with any immune checkpoint inhibitor (eg, anti–cytotoxic T-lymphocyte–associated protein 4 [CTLA-4], anti–programmed cell death protein 1/programmed cell death ligand 1 [anti–PD-1/PD-L1], anti–PD-2/PD-L2, anti–killer cell immunoglobulin-like receptor, and any other antibody or drug specifically targeting T-cell costimulation) and/or an IDO inhibitor. Subjects who have received experimental vaccines or other immune therapies should be discussed with the medical monitor to confirm eligibility.
  Note: Subjects in Cohort A1 who received adjuvant anti–CTLA-4 therapy and had disease progression ≥ 6 months after completion of planned treatment may enroll.

- Any unresolved toxicity > Grade 1 from previous anticancer therapy, except for stable chronic toxicities not expected to resolve, such as peripheral neurotoxicity, alopecia, and fatigue.
- Subjects who are receiving an immunologically based treatment for any reason, including chronic use of systemic steroid or at doses ≥ 10 mg/day prednisone equivalent within 7 days before the first dose of study drug. Use of inhaled or topical steroids or systemic corticosteroids < 10 mg prednisone equivalent is permitted.
- Receipt of a live vaccine within 30 days of planned start of study therapy.

  Note: Examples of live vaccines include but are not limited to the following: measles, mumps, rubella, chicken pox/zoster, yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines are live attenuated vaccines and are not allowed.
- Active infection requiring systemic therapy.
- Subjects with any active or inactive autoimmune disease or syndrome (eg, rheumatoid arthritis, moderate or severe psoriasis, multiple sclerosis, inflammatory bowel disease) that has required systemic treatment in the past 2 years or who are receiving systemic therapy for an autoimmune or inflammatory disease (ie, with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs).

  Note: Exceptions include subjects with vitiligo or resolved childhood asthma/atopy, hypothyroidism stable on hormone replacement, controlled asthma, or Type I diabetes, Graves' disease, or Hashimoto's disease that are treated and controlled, or with medical monitor approval.
- Evidence of interstitial lung disease or active, noninfectious pneumonitis, including symptomatic and/or pneumonitis requiring treatment.
- History of organ transplant that requires use of immunosuppressive therapy.
- Has known history of or is positive for hepatitis B (hepatitis B surface antigen [HbsAg] reactive) or hepatitis C.
  - Hepatitis B virus DNA must be undetectable and HBsAg negative at the screening visit.
  - Hepatitis C antibody testing is allowed for screening purposes in countries where hepatitis C virus (HCV) RNA is not part of standard of care. In these cases, HCV antibody–positive subjects will be excluded.
  - Subjects who have had definitive treatment for HCV are permitted if HCV RNA is undetectable at the screening visit.

  Note: Testing must be performed to determine eligibility.
- Known history of human immunodeficiency virus (HIV; HIV 1/2 antibodies).
- History or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful. Screening QTc interval > 480 milliseconds is excluded (corrected by Fridericia or Bazett formula). In the event that a single QTc is > 480 milliseconds, the subject may be enrolled if the average QTc for 3 consecutive ECGs is < 480 milliseconds. For subjects with an intraventricular conduction delay (QRS interval > 120 milliseconds), the JTc interval may be used in place of the QTc with medical monitor approval. The JTc must be < 340 milliseconds if JTc is used in place of the QTc. Subjects with left bundle branch block are excluded.
- Clinically significant cardiac disease, including unstable angina, acute myocardial infarction within 6 months of Cycle 1 Day 1, New York Heart Association Class III or IV congestive heart failure. Medically controlled arrhythmia stable on medication is permitted.
- Bleeding associated with tumors that invade or are adjacent to major blood vessels, as shown unequivocally by imaging studies, or history of bleeding related to disease under study within 3 months of enrollment.

- 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.
- Women who are pregnant or breastfeeding.

Epacadostat, Dosage, and Mode of Administration:

In Phase 1, the dose of epacadostat will be dependent on treatment group and dose level assignment. In Phase 2, the dose of epacadostat will be dependent upon the MTD or PAD determined in Phase 1.

Epacadostat is an investigational agent and will be self-administered BID orally beginning on Cycle 1 Day 1 and continuously thereafter for both treatment groups. All BID doses will be taken in the morning and evening, approximately 12 hours apart without regard to food. If a dose is missed by more than 4 hours, then that dose should be skipped and the next scheduled dose should be taken at the usual time.

Note: Subjects who are ongoing on study treatment as of the date of Amendment 2 may discontinue epacadostat at the discretion of the treating investigator.

Combination Therapy, Dosage, and Mode of Administration:

Treatment Group A:

Nivolumab will be administered as a 240 mg IV infusion over 30 minutes (± 5 minutes) on Day 1 of each cycle, until loss of clinical benefit. Nivolumab will be administered after epacadostat and will be administered starting with Cycle 1 for all subjects. Intrasubject dose escalation of nivolumab is not allowed.

Ipilimumab will be administered as a 1 mg/kg IV infusion over 30 minutes (± 5 minutes) on Day 1 of Cycle 1 and then Day 1 of every third cycle thereafter (ie, Cycle 4, Cycle 7, etc). Ipilimumab will be administered after nivolumab on visit days when both agents are given. Intrasubject dose escalation of ipilimumab is not allowed.

Treatment Group B:

Nivolumab will be administered as a 240 mg IV infusion over 30 minutes (± 5 minutes) on Day 1 of each cycle until loss of clinical benefit. Nivolumab will be administered after epacadostat and will be administered starting with Cycle 1 for all subjects. Intrasubject dose escalation of nivolumab is not allowed.

Lirilumab will be administered as a 240 mg IV infusion over 60 minutes (± 5 minutes) on Day 1 of Cycle 1 and then Day 1 of every other cycle thereafter (ie, Cycle 3, Cycle 5, etc). Lirilumab will be administered after nivolumab on visit days when both agents are given. Intrasubject dose escalation of lirilumab is not allowed.

Treatment Cycles and Duration of Treatment:

Study treatment will be administered in continuous 14-day cycles. Subjects will continue to receive study treatment for up to 2 years as long as the subject is deriving benefit and has not met any of the Protocol-defined conditions for treatment discontinuation. Intrasubject dose-escalation is not permitted.

Study Schedule/Procedures:

The study comprises the following parts:

- **Screening:** Up to 28 days before enrollment. Screening will begin at the time that the subject signs the informed consent and will continue until the date the subject is enrolled in the study (Cycle 1 Day 1).
- **Treatment:** Treatment cycles will be 14 days in length. Subjects will have regularly scheduled study visits on Day 1 (± 3 days) of each cycle. Clinic visits will also occur on Day 8 (± 1 day) during the first 3 cycles.
- **End of treatment:** + 7 days after withdrawal from study treatment.
- **Safety follow-up:** 30 days (+ 7 days), 100 days (± 7 days), and 150 days (± 7 days; Treatment Group B only) after the last dose of study treatment.

Safety Assessments:

Subjects will have regularly scheduled study visits at the clinical site on Day 1 of every cycle where targeted physical examinations, vital sign collection, collection of concomitant medications, and AE assessments will be performed. Twelve-lead ECGs will be performed at screening, Cycle 1 Day 1, Cycle 2 Day 1, and at the end-of-treatment visit. Laboratory assessments will be collected during each treatment cycle. Toxicities will be monitored continuously and will be graded using the National Cancer Institute's CTCAE v4.03 criteria.

Regular telephone conferences with study investigators will be scheduled by the sponsor in order to review cohort-specific data and overall safety data, agree on dose escalation, adjudicate individual high-grade AEs as potentially dose-limiting, and guide other major study decisions.

Efficacy Assessments:

Disease assessments will be performed based on RECIST v1.1 [redacted] Assessment of tumor size (by computed tomography scan or magnetic resonance imaging) will be performed at screening (before beginning therapy), at 8 and 16 weeks (± 7 days) after the start of treatment, and then every 12 weeks (± 7 days) thereafter until disease progression, death, study treatment discontinuation, or withdrawal of consent, whichever occurs first.

[redacted] If a follow-up scan was not performed after unconfirmed progressive disease (eg, due to patient refusal, investigator discretion, or patient death), the initial date of unconfirmed progression will be considered the date of progressive disease. Continuation of treatment while awaiting radiographic confirmation of progression is allowed, where feasible and with the consent of the subject, provided that the subject meets the definition of clinical stability defined as follows:

- Absence of clinically significant signs and symptoms (including worsening of laboratory values) indicating disease progression.
- No decline in ECOG performance status.
- No requirement for intensified management of disease-related symptoms.
- Absence of rapid progression of disease.
- Absence of progressive tumors at critical anatomical sites (eg, spinal cord compression) requiring urgent alternative medical intervention.

Subjects who discontinue study drug are no longer required to undergo study-related imaging, and RECIST v1.1 disease progression does not need to be confirmed.

[redacted]

Estimated Duration of Participation:

Up to 28 days for screening; continuous treatment in consecutive 14-day cycles for up to 2 years; and 30, 100, and 150 days for safety follow-up (150 day follow-up for Treatment Group B only). Study participation, including post-treatment safety follow-up, is expected to average approximately 12 to 18 months for an individual subject.

Estimated Number of Subjects:

Approximately 141 subjects will be enrolled in the study.

Treatment Group A:

Phase 1: Approximately 18 subjects.

Phase 2: Cohort A1 – approximately 35 subjects
Cohort A2 – approximately 35 subjects

Treatment Group B:

Phase 1: Approximately 18 subjects.

Phase 2: Cohort B1 – approximately 35 subjects

Principal Coordinating Investigator: TBD

Statistical Methods:

Phase 1 of the study will use a 3 + 3 + 3 design to evaluate the safety of epacadostat in combination with nivolumab and ipilimumab (Treatment Group A) and in combination with nivolumab and lirilumab (Treatment Group B) in subjects with advanced or metastatic solid tumors. During the Phase 1 portion of the study, the sample size at each dose level depends on the number of observed toxicities. Between 3 and 9 subjects are expected to be treated at each dose level. Phase 2 expansion cohorts will evaluate the efficacy and further evaluate the safety, tolerability, [redacted] of the MTD or PAD of epacadostat determined in each of the Phase 1 treatment groups in select solid tumors. A sample size of 35 subjects is expected to be enrolled in each of the Phase 2 expansion cohorts (A1, A2, and B1). This sample size for Cohort A1 (MEL) yields a power of 80% to detect a target ORR of about 20% increase (Ha: 79%) from historical response rate (H0: 59%). For Cohort A2 (NSCLC), this yields a power of 80% to detect a target ORR of about 22% increase (Ha: 52%) from historical response rate (H0: 30%). For Cohort B1 (SCCHN), this yields a power of 80% to detect a target ORR of about 22% increase (Ha: 46%) from historical response rate (H0: 24%). This assumes a 1-sided alpha of 5%. Subjects who undergo serial prestudy and on-treatment tumor biopsies in expansion Cohorts A1, A2, and B1 may be at risk of being nonevaluable for response; therefore, additional subjects may be enrolled in a specific efficacy expansion cohort to achieve a minimum 35 response-evaluable subjects.

The clinical safety data (eg, vital signs, ECGs, laboratory tests, AEs) will be descriptively summarized. The ORR will be summarized with 95% exact binomial confidence interval (CI), if appropriate. Kaplan-Meier estimates of median DOR, PFS, and OS will be provided with 95% CIs.

Safety Monitoring Committee: A Safety Monitoring Committee (SMC) will review safety data at regular intervals throughout Phase 2. Details regarding SMC membership and roles and responsibilities of the committee will be specified in the SMC charter.

TABLE OF CONTENTS

SYNOPSIS 3
LIST OF ABBREVIATIONS 22
1. INTRODUCTION 25
1.1. Background 25
1.1.1. The Role of the Immune System in Cancer and Overall Study Rationale 25
1.1.2. Inhibition of Indoleamine 2,3-Dioxygenase 1 as a Target for Cancer 25
1.1.3. Inhibition of Killer Cell Immunoglobulin-Like Receptors as a Target for Cancer 26
1.2. Overview of Epacadostat 27
1.2.1. Risks From Epacadostat 27
1.3. Overview of Lirilumab 28
1.3.1. Risks From Lirilumab 29
1.4. Overview of Nivolumab 29
1.4.1. Risks From Nivolumab 29
1.4.2. Risks From Nivolumab in Combination With Ipilimumab 30
1.4.3. Risks From Nivolumab in Combination With Lirilumab 30
1.4.4. Risks From Nivolumab in Combination With Epacadostat 30
1.5. Overview of Ipilimumab 31
1.5.1. Risks From Ipilimumab 31
1.5.2. Risks From Ipilimumab in Combination With Epacadostat 31
1.6. Overall Risk/Benefit Assessment of the Combination Regimens 32
1.7. Rationale for Dose and Schedule of the Combination Therapies 33
1.8. Rationale for Shorter Infusion Times for Nivolumab and Ipilimumab 34
1.9. Rationale for Efficacy Endpoints 35
2. STUDY OBJECTIVES AND ENDPOINTS 37
3. SUBJECT ELIGIBILITY 39
3.1. Subject Inclusion Criteria 39
3.2. Subject Exclusion Criteria 41
4. INVESTIGATIONAL PLAN 45
4.1. Overall Study Design 45
4.1.1. Phase 1 – Dose Escalation 46
4.1.2. Phase 2 – Dose Expansion 48

4.2. Measures Taken to Avoid Bias 48
4.3. Number of Subjects 49
4.3.1. Planned Number of Subjects 49
4.3.2. Replacement of Subjects 49
4.4. Duration of Treatment and Subject Participation 49
4.5. Overall Study Duration 49
4.6. Study Termination 50
5. TREATMENT 50
5.1. Treatment Assignment 50
5.1.1. Subject Numbering and Treatment Assignment 50
5.1.2. Randomization and Blinding 50
5.2. Study Drugs 51
5.2.1. Epacadostat 51
5.2.1.1. Supply, Packaging, and Labeling 51
5.2.1.2. Storage 51
5.2.2. Nivolumab 51
5.2.2.1. Description and Administration 51
5.2.2.2. Supply, Packaging, and Labeling 51
5.2.3. Ipilimumab 52
5.2.3.1. Description and Administration 52
5.2.3.2. Supply, Packaging, and Labeling 52
5.2.4. Lirilumab 53
5.2.4.1. Description and Administration 53
5.2.4.2. Supply, Packaging, and Labeling 53
5.3. Treatment Compliance 53
5.4. Treatment Interruptions and Adjustments 53
5.4.1. Dose Modifications 53
5.4.2. Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose 54
5.4.2.1. Management of Dose-Limiting Toxicities or Other Urgent Situations 55
5.4.2.2. Follow-Up of Dose-Limiting Toxicities 56
5.4.3. Procedures for Cohort Review and Dose Escalation 56
5.4.4. Criteria and Procedures for Dose Interruptions and Adjustments of Study Treatment 56

5.4.4.1. Epacadostat Dose Modifications 56
5.4.4.2. Nivolumab, Ipilimumab, and Lirilumab Dose Modifications 57
5.4.5. Management of Immune-Related Adverse Events 58
5.4.5.1. Procedures and Guidelines for Pneumonitis 60
5.4.5.2. Procedures and Guidelines for Enterocolitis 60
5.4.5.3. Procedures and Guidance for Hepatitis 62
5.4.5.4. Procedures for Immune-Mediated Dermatitis 63
5.4.5.5. Procedures for Immune-Mediated Neuropathies 63
5.4.5.6. Procedures for Immune-Mediated Endocrinopathies 64
5.4.5.7. Procedures for Other Immune-Mediated Adverse Reactions, Including Ocular Manifestations 65
5.4.6. Procedure for Subjects Exhibiting Serotonin Syndrome 66
5.4.7. Management of Infusion Reactions 67
5.4.8. Criteria for Permanent Discontinuation of Study Treatment 69
5.5. Withdrawal of Subjects From Study Treatment 69
5.5.1. Withdrawal Criteria 69
5.5.1.1. Treatment After Initial Evidence of Radiologic Evidence of Disease Progression 70
5.5.2. Withdrawal Procedures 72
5.6. Concomitant Medications 72
5.6.1. Permitted Medications 72
5.6.2. Restricted Medications 73
5.6.3. Prohibited Medications 73
6. STUDY ASSESSMENTS 74
6.1. Screening 83
6.2. Treatment 83
6.3. End of Treatment 83
6.4. Follow-Up 83
6.4.1. Safety Follow-Up 83
6.5. End of Study 84
6.6. Unscheduled Visits 84
7. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES 85
7.1. Administration of Informed Consent Form 85

7.2. Interactive Response Technology Procedure....85
7.3. Demography and Medical History....85
7.3.1. Demographics and General Medical History....85
7.3.2. Disease Characteristics and Treatment History....85
7.4. Prior and Concomitant Medications and Procedures....85
7.5. Safety Assessments....86
7.5.1. Adverse Events....86
7.5.2. Physical Examinations....86
7.5.2.1. Comprehensive Physical Examination....86
7.5.2.2. Targeted Physical Examination....86
7.5.3. Vital Signs and Weight....87
7.5.4. 12-Lead Electrocardiograms....87
7.5.5. Laboratory Assessments....87
7.5.5.1. Serum Chemistry....88
7.5.5.2. Liver Chemistry....88
7.5.5.3. Hematology....88
7.5.5.4. Coagulation Panel....88
7.5.5.5. Endocrine Function....88
7.5.5.6. Urinalysis....88
7.5.5.7. Hepatitis Screening Tests....88
7.5.5.8. Pregnancy Testing....89
7.6. Efficacy Assessments....89
7.6.1. Assessment of Disease....89
7.6.2. Initial Tumor Imaging....89
7.6.3. Tumor Imaging During the Study....90
[redacted]....90
[redacted]....90
[redacted]....90
[redacted]....91
7.8. Other Study Procedures....92
7.8.1. Distribution of Subject Reminder Cards and Subject Diaries....92
8. SAFETY MONITORING AND REPORTING....92
8.1. Adverse Events....92

8.1.1. Definitions 92
8.1.2. Reporting 92
8.2. Laboratory Test Abnormalities 94
8.3. Serious Adverse Events 94
8.3.1. Definitions 94
8.3.2. Reporting 95
8.4. Emergency Unblinding of Treatment Assignment 96
8.5. Pregnancy 96
8.6. Warnings and Precautions 96
8.7. Safety Monitoring Committee 96
8.8. Product Complaints 97
9. STATISTICS 97
9.1. Study Populations 97
9.2. Selection of Sample Size 98
9.2.1. Sample Size in Phase 1 98
9.2.2. Sample Size in Phase 2 98
9.3. Level of Significance 98
9.4. Statistical Analyses 98
9.4.1. Efficacy Analyses 99
9.4.2. Safety Analyses 99
9.4.2.1. Adverse Events 99
9.4.2.2. Clinical Laboratory Tests 100
9.4.2.3. Vital Signs 100
9.4.2.4. Electrocardiograms 100
9.4.2.5. Adverse Events of Special Interest 101
[redacted] [redacted] 101
[redacted] [redacted] 101
9.5. Analyses for the Safety Monitoring Committee 101
9.6. Interim Analysis 101
10. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES 102
10.1. Investigator Responsibilities 102
10.2. Accountability, Handling, and Disposal of Study Drug 103

10.3. Data Management 104
10.4. Data Privacy and Confidentiality of Study Records 104
10.5. Financial Disclosure 105
10.6. Publication Policy 105
11. REFERENCES 106
APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS 110
APPENDIX B. MANAGEMENT GUIDELINES FOR IMMUNE-RELATED ADVERSE EVENTS 111
APPENDIX C. PHARMACOKINETIC ANALYTICAL PARAMETERS 119
APPENDIX D. MONOAMINE OXIDASE INHIBITORS AND DRUGS ASSOCIATED WITH SIGNIFICANT MONOAMINE OXIDASE INHIBITORY ACTIVITY 120
APPENDIX E. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS V1.1 121
APPENDIX F. PROTOCOL AMENDMENT SUMMARY OF CHANGES 122

LIST OF TABLES

Table 1: Summary Statistics of Predicted Lirilumab Exposure 34
Table 2: Study Objectives and Endpoints 37
Table 3: Epacadostat Phase 1 Dose Levels 47
Table 4: Nivolumab Product Description 52
Table 5: Ipilimumab Product Description 52
Table 6: Lirilumab Product Description 53
Table 7: Definition of Dose-Limiting Toxicity 55
Table 8: Dose Reductions of Epacadostat (Treatment Groups A and B) 57
Table 9: General Guidelines for Interruption and Restarting of Study Treatment 57
Table 10: General Guidelines for Immune-Related Adverse Events 59
Table 11: Guidelines for Management of Noninfectious Pneumonitis 60
Table 12: Guidelines for Management of Enterocolitis 61
Table 13: Recommended Approach for Handling Hepatitis 62
Table 14: Recommended Approach for Handling Dermatitis 63
Table 15: Recommended Approach for Handling Neuropathies 64
Table 16: Recommended Approach for Handling Endocrinopathies 65
Table 17: Sign and Symptoms of Serotonin Syndrome 67
Table 18: Infusion Reaction Treatment Guidelines 68
Table 19: Imaging and Treatment After First Radiologic Evidence of Progressive Disease 71
Table 20: Recommendations for Warfarin Dose Modifications 73
Table 21: Schedule of Clinical Assessments – Treatment Group A (Epacadostat + Nivolumab + Ipilimumab) 75
Table 22: Schedule of Laboratory Assessments – Treatment Group A (Epacadostat + Nivolumab + Ipilimumab) 77
Table 23: Schedule of Clinical Assessments – Treatment Group B (Epacadostat + Nivolumab + Lirilumab) 78
Table 24: Schedule of Laboratory Assessments – Treatment Group B (Epacadostat + Nivolumab + Lirilumab) 80
Table 25: Local Laboratory Tests: Required Analytes 82
Table 26: Schedule of ECG Assessments 87
[redacted] [redacted] 90

[redacted] 91

[redacted] 91

Table 30: Sample Size Calculation for Each Phase 2 Cohort: Comparing to a Known Proportion 98

Table 31: Criteria for Clinically Notable Vital Sign Abnormalities....100

Table 32: Criteria for Clinically Notable Electrocardiogram Abnormalities 101

LIST OF FIGURES

Figure 1: Study Design....46

LIST OF ABBREVIATIONS

The following abbreviations and special terms are used in this clinical study Protocol.

Abbreviation	Definition
[redacted]	[redacted]
AE	adverse event
ALK	anaplastic lymphoma kinase gene
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BCG	Bacillus Calmette-Guérin
BID	twice daily
BRAF	BRAF gene
BMS	Bristol-Myers Squibb
CA	cancer antigen
CFR	Code of Federal Regulations
CI	confidence interval
CL	clearance
CNS	central nervous system
CR	complete response
CrCl	creatinine clearance
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CTLA-4	cytotoxic T-lymphocyte–associated protein 4
DC	dendritic cell
DLT	dose-limiting toxicity
DOR	duration of response
eDMC	external Data Monitoring Committee
EOT	end of treatment
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor gene
EU	European Union
FDA	Food and Drug Administration

Abbreviation	Definition
FFPE	formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	gastrointestinal
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HPV	human papillomavirus
ICF	informed consent form
ICH	International Conference on Harmonisation
[redacted]	[redacted]
[redacted]	[redacted]
IDO1	indoleamine 2,3-dioxygenase 1
IEC	independent ethics committee
IgG	immunoglobulin G
IN	Investigator Notification
INR	international normalized ratio
[redacted]	[redacted]
irAE	immune-related adverse event
IRB	institutional review board
[redacted]	[redacted]
IRT	Interactive Response Technology
[redacted]	[redacted]
IV	intravenous
JTc	corrected JT interval
KIR	killer cell immunoglobulin-like receptor
MAOI	monamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
MEL	melanoma
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NK	natural killer
nM	nanomolar

Abbreviation	Definition
NSCLC	non–small cell lung cancer
ORR	objective response rate
[redacted]	[redacted]
PAD	pharmacologically active dose
PD	progressive disease
PD-1	programmed cell death protein 1
PDAC	pancreatic ductal adenocarcinoma
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PET	positron emission tomography
PET/CT	positron emission tomography - computed tomography
PFS	progression-free survival
[redacted]	[redacted]
PR	partial response
PT	prothrombin time
Q2W	once every 2 weeks
Q3W	once every 3 weeks
Q4W	once every 4 weeks
Q6W	once every 6 weeks
QTc	corrected QT interval
RCC	renal cell carcinoma
RECIST v1.1	Response Evaluation Criteria In Solid Tumors version 1.1
ROS1	ROS1 gene
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SMC	Safety Monitoring Committee
SmPC	summary of product characteristics
SNRI	serotonin norepinephrine reuptake inhibitor
SS	serotonin syndrome
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
Treg	T regulatory cell
ULN	upper limit of normal
US	United States of America

1. INTRODUCTION

1.1. Background

1.1.1. The Role of the Immune System in Cancer and Overall Study Rationale

The immune response is controlled by a series of checks and balances to allow for robust immune responses to pathogens while preventing either an excessive inflammatory event or an autoimmune response. Through immune surveillance, the immune system has also been shown to recognize, attack, and destroy tumor cells (Wolchok and Saenger 2008). Targeting the immune system as an anticancer strategy is a proven and effective approach for the treatment of many types of cancer, and immunotherapy is now an accepted standard of care in several tumor types. Approved checkpoint inhibitors, including the PD-1–blocking antibody nivolumab and the CTLA-4 blocking antibody ipilimumab, allow for the immune response to continue to proliferate in spite of inhibitory signals. Both of these agents have demonstrated antitumor activity when administered as monotherapy, and emerging data suggest that combined blockade of both targets results in an enhanced antitumor response (Larkin et al 2015, Hellmann et al 2016, Goldman et al 2017); however, despite the encouraging activity observed with dual PD-1 and CTLA-4 blockade, multiple other immune inhibitory mechanisms are present concurrently within the tumor microenvironment, suggesting that combination approaches targeting additional mechanisms of immune tolerance may be required for optimal therapeutic effect (Quezada and Peggs 2013). Two promising approaches to overcoming these mechanisms include inhibition of IDO1 and blockade of KIR inhibitory receptors.

1.1.2. Inhibition of Indoleamine 2,3-Dioxygenase 1 as a Target for Cancer

IDO1 is a heme-containing, monomeric oxidoreductase that catalyzes the degradation of the essential amino acid tryptophan to N-formyl-kynurenine. Kynurenine can be subsequently metabolized through a series of enzymatic steps to nicotinamide adenine dinucleotide. IDO1 is the first rate-limiting enzyme in one of the catabolic pathways of tryptophan.

The expression and activity profiles of IDO1 are distinct from those of tryptophan dioxygenase, an enzyme predominantly expressed in liver that catalyzes the same enzymatic reaction as IDO1 and maintains proper tryptophan balance in response to dietary uptake. In contrast to tryptophan dioxygenase, IDO1 is expressed in a variety of tissues, with particularly high levels found in areas of contact with potential sources of immune challenge (eg, gut, respiratory tract, placenta, spleen), consistent with a role for regulating tryptophan metabolism in a local microenvironment (Mellor and Munn 2004). Within the immune system, IDO1 activity is specifically induced in cells such as DCs and macrophages at localized sites of inflammation (Munn and Mellor 2007).

IDO1-driven oxidation of tryptophan results in a strong inhibitory effect on the development of T-cell–mediated responses by blocking T-cell activation and inducing T-cell apoptosis (Mellor et al 2003). Both the reduction in local tryptophan levels and the production of tryptophan catabolites that are inhibitory to cell proliferation contribute to the immunosuppressive effects (Frumento et al 2002) such as DC maturation and T-cell growth arrest and cell death (Mellor and Munn 1999). IDO1 activity also promotes the differentiation of naive T cells to cells with a regulatory phenotype (Treg; Fallarino et al 2006). Because increased

Treg activity has been shown to promote tumor growth, and Treg depletion has been shown to allow an otherwise ineffectual antitumor immune response to occur (Zou 2006), IDO1-driven expansion of Tregs may provide an additional mechanism whereby IDO1 could promote an immunosuppressive environment.

A critical role for IDO1 in immunomodulation has been confirmed in numerous animal models, including models of allograft tolerance, inflammation, and cancer (Mellor and Munn 2004). While IDO1 inhibition can exacerbate disease in models of autoimmune disorders (Mellor and Munn 2004), IDO1 null mice show no evidence of susceptibility to developing spontaneous autoimmunity or alterations in immune system development (Mellor et al 2003), suggesting that IDO1 inhibition, in a therapeutic setting, may produce minimal side effects in subjects without pre-existing autoimmune conditions.

Within the context of cancer, there are several lines of evidence to suggest that IDO1 is a key regulator of the immunosuppressive mechanisms responsible for tumor escape from immune surveillance. Several groups have demonstrated that blockade of IDO1 activity can directly influence the ability of tumor-bearing animals to reject tumors (Uyttenhove et al 2003, Muller et al 2005). In addition, studies with 1-methyl-tryptophan demonstrate that IDO1 inhibition dramatically increases the efficacy of various chemotherapeutic agents (eg, platinum compounds, taxane derivatives, cyclophosphamide) without increased toxicity (Muller et al 2005). Although the specific mechanisms responsible for this potentiation remain to be fully elucidated, the effects were not observed in T-cell–deficient animals, suggesting that the results may be the consequence of the disablement of immunosuppressive mechanisms that exist within the tumor microenvironment.

Based on studies examining serum levels of tryptophan and kynurenine, IDO1 appears to be chronically activated in subjects with cancer, and IDO1 activation correlates with more extensive disease (Huang et al 2010, Weinlich et al 2007). IDO1 has subsequently been found to be overexpressed by a wide variety of human tumor cell types, as well as by the DCs that localize to the tumor-draining lymph nodes (Uyttenhove et al 2003, Munn et al 2004). Increased expression of IDO1 in tumor cells has been shown to be an independent prognostic variable for reduced OS in subjects with MEL, head and neck, ovarian, colorectal, and pancreatic cancers (Okamoto et al 2005, Laimer et al 2011, Brandacher et al 2006, Ino et al 2006, Nakamura et al 2007, Witkiewicz et al 2008, Hamid et al 2009).

Together, these results suggest that the IDO1 pathway is a key regulatory element responsible for the induction and maintenance of tumor immune tolerance. Small molecule inhibitors of IDO1 may provide an innovative and tractable method to treat malignancies.

1.1.3. Inhibition of Killer Cell Immunoglobulin-Like Receptors as a Target for Cancer

Natural killer cells constitute 15% of peripheral blood lymphocytes and play a vital role in the innate immune system's ability to combat viral infections and cancers by secreting immunoregulatory cytokines and by killing infected or transformed cells (Purdy et al 2009). Activation of NK cells, which is regulated by the balance of positive and negative receptor signaling, results in release of granules containing perforin and granzymes into target cells to induce apoptosis, as well as release of cytokines and chemokines into the micro-environment to recruit other immune cells (Purdy et al 2009, Kohrt et al 2014). The concurrent release of cytokines and chemokines results in a microenvironmental milieu that recruits other immune cells.

Natural killer cells have the capability of binding every cell in the body (Ljunggren et al 1990). Binding of normal cells does not result in cytotoxic activity because of the ability of NK cells to simultaneously use a different set of receptors to bind major histocompatibility complex Class I molecules. Binding to HLA is used as a mechanism to distinguish self from nonself, and this recognition controls the activational state of NK cells. Thus, KIR/HLA interaction directly affects NK cell responsiveness. There are both inhibitory and activating KIRs, which is a factor that results in diversity of KIR inheritance and expression. KIR is also expressed on NK cells and a small subset of T cells (Uhrberg et al 2001). Thus, mechanistically, blockade of inhibitory KIR could induce antitumor effects by allowing for NK cell (and possibly some T cell) activation.

1.2. Overview of Epacadostat

Epacadostat is a novel, potent, and selective inhibitor of the IDO1 enzyme in both human tumor cells and human DCs. With the recent emergence of immune checkpoint inhibitors targeting PD-1, PD-L1, and CTLA-4, epacadostat is being investigated in combination with several of these agents across multiple tumor types in several ongoing Phase 1, 2, and 3 studies. Refer to the current Investigator's Brochure for additional details regarding epacadostat (epacadostat IB) for preclinical and clinical study data.

1.2.1. Risks From Epacadostat

In the first-in-human study in subjects with refractory solid tumors (INCB 24360-101), epacadostat monotherapy was well-tolerated at doses ranging from 50 mg QD to 700 mg BID (Beatty et al 2013). Twenty-five of the 52 subjects (48.1%) administered epacadostat had a single SAE. The most frequently reported SAEs were disease progression (7.7%), followed by abdominal pain, nausea, and hypoxia (5.8% each). Treatment-emergent AEs were reported in all subjects. The most commonly reported treatment-related AEs were fatigue and nausea (48.1%). The incidence and severity of fatigue were not dose-related. Two DLTs occurred: 1 DLT of radiation pneumonitis at the 300 mg dose level and 1 DLT of fatigue at the 400 mg BID dose level.

An uncommon risk of IDO1 inhibition is an increase in serotonin levels that could precipitate a cluster of AEs termed SS when administered alone or in combination with other serotonergic agents. This rare syndrome has been associated with some MAOIs and combinations of serotonergic drugs (Boyer and Shannon 2005). The clinical manifestations of SS range from barely perceptible to lethal; onset is rapid (within 12 hours of drug[s] administration). Based on preliminary studies in the rat, concentrations of epacadostat in the cerebrospinal fluid were below the quantifiable limit of detection (2 nM) after IV dosing, and total brain homogenate concentrations were approximately 15% of corresponding plasma concentrations. In another preclinical study in rats, the effect of epacadostat on the brain extracellular fluid concentration of serotonin was evaluated either alone or when co-administrated with the mechanism of action inhibitor linezolid with or without the SSRI fluoxetine. Both control conditions resulted in 2- to 6-fold increases in serotonin. In contrast, neither epacadostat alone or in combination with linezolid had an effect on the brain extracellular serotonin levels. These preclinical data suggest that SS is unlikely after treatment with either epacadostat alone or in combination with MAOIs such as linezolid (Zhang et al 2016). Therefore, taken together, epacadostat exhibits apparent limited penetration across the blood-brain barrier and is likely not associated with significant

effects on tryptophan metabolism in the brain that may affect brain serotonin levels. As of 27 FEB 2017, 2 subjects across the epacadostat program (958 subjects treated) have reported SS or symptoms of SS and both were mild in their severity and resolved. One subject from Study INCB 24360-202 reported chills, increased blood pressure, and temperature (all Grade 1) on Cycle 1 Day 1 and resolved within 1 week while dosing was stopped. The subject was taking an SSRI, and although he experienced mild symptoms, the full constellation of SS was not observed, nor could it be ruled out. The SSRI was discontinued and subject restarted epacadostat about 1 week later at the same dose level of 100 mg BID without further incident. The other subject from Study INCB 24360-202 reported Grade 1 tremors and Grade 2 agitation on Cycle 4 Day 5 and was assessed for SS on Cycle 5 Day 1. The subject was not on an SSRI but on a medication for anxiety (alprazolam). The events resolved and the dosing with epacadostat was interrupted for 1 week. Re-treatment started with a lower dose of epacadostat at 50 mg BID PO from 75 mg BID on Cycle 5 Day 3. Although the incidence is uncommon, use of MAOIs will be prohibited during the study. A list of prohibited MAOIs is provided in Appendix D. Subjects will be provided with a leaflet describing the signs and symptoms of the syndrome along with instructions to seek immediate medical care if any of these signs or symptoms are observed.

1.3. Overview of Lirilumab

Lirilumab is a fully human monoclonal antibody that is designed to act as a checkpoint inhibitor by blocking the interaction between KIR2DL-1,-2,-3 inhibitory receptors and their ligands facilitating activation of NK cells and potentially some subsets of T cells, ultimately leading to antitumor activity.

Lirilumab is being studied as a potential immunotherapy alone and in combination with other agents in subjects with various hematologic malignancies and solid tumors. As of 15 JUL 2016, a total of 377 subjects have been treated in 1 concluded, 1 terminated, and 3 ongoing clinical trials assessing safety, PK, biomarker modulation, and clinical activity. The first is a monotherapy, dose-escalation, Phase 1 study to determine the MTD. The second is a double-blind, placebo-controlled, Phase 2 study of lirilumab in subjects with acute myeloid leukemia who are in complete remission but ineligible for allogeneic transplant. One-third of subjects in this study will receive placebo. The third, fourth, and fifth are Phase 1/2 studies of lirilumab in combination with the anti–PD-1 antibody nivolumab, the anti–CTLA-4 antibody ipilimumab, and the SLAMF7 antibody elotuzumab, respectively, to determine whether coordinate modulation of the innate and adaptive immune systems results in greater clinical benefit. Preliminary data from an initial cohort of subjects in a study exploring lirilumab with nivolumab suggest a strong signal of potential efficacy (Leidner et al 2016). Specifically, preliminary data in 29 evaluable subjects with SCCHN treated with the combination showed an ORR of 24% (7/29) in the all comer population and an ORR of 41% (7/17) in the PD-L1+ (≥ 1%) population. No responses (0/12) were observed in the PD-L1− population. Put into context, nivolumab monotherapy in a similar population of patients with previously treated SCCHN (recently approved by the US FDA for the treatment of patients with recurrent or metastatic SCCHN with disease progression on or after platinum-based therapy) showed an ORR of 13.1% (32/240) in all SCCHN subjects and an ORR of 17.0% (15/88) in subjects with ≥ 1% PD-L1 expression. Also of note, in 5 out of the 7 lirilumab plus nivolumab responders, the reduction in tumor burden was substantial, exceeding greater than 80%. Responses appeared durable, with the median DOR not reached. These results indicate lirilumab plus nivolumab may

have clinically meaningful greater clinical activity than nivolumab alone, particularly in inflamed (PD-L1+) tumors and with little added toxicity. Refer to the current lirilumab IB for additional details regarding lirilumab for preclinical and clinical study data.

1.3.1. Risks From Lirilumab

As of the data cutoff for the current lirilumab IB (15 JUL 2016), 377 subjects have been treated with lirilumab or placebo in 1 Phase 1/2 study (ongoing), 3 Phase 1 studies (1 concluded, 1 ongoing, and 1 terminated), and 1 ongoing Phase 2 study. Of those subjects, 37 subjects received lirilumab monotherapy, 152 subjects received either lirilumab monotherapy or placebo in a 2:1 ratio, 149 subjects received lirilumab in combination with nivolumab, 22 subjects received lirilumab in combination with ipilimumab, and 17 subjects received elotuzumab in combination with lirilumab. In total, approximately 326 subjects received lirilumab. The majority of AEs in these 5 studies were mild or moderate (Grade 1 or 2), self-limiting, and manageable. The most common related AEs in the monotherapy trials were asthenia, fatigue, pruritus, infusion-related reaction, chills, and neutropenia. The most common related AEs in the combination studies were fatigue, nausea, cough, diarrhea, and pyrexia. Additional details on the safety profile of lirilumab are available in the lirilumab IB.

1.4. Overview of Nivolumab

Nivolumab (OPDIVO®) is a fully human IgG4 monoclonal antibody that binds to PD-1 and blocks interaction with PD-L1 and PD-L2 and restores T-cell antitumor function (Brahmer et al 2010). Nivolumab has been approved as monotherapy in the United States for metastatic NSCLC that has progressed on or after platinum-based chemotherapy, for advanced RCC after previous antiangiogenic therapy, for classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation and post-transplantation brentuximab vedotin, for recurrent or metastatic SCCHN with disease progression on or after platinum-based therapy, and for locally advanced metastatic urothelial carcinoma with disease progression during or after platinum-containing chemotherapy or disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. Nivolumab is also approved in combination with ipilimumab in patients with unresectable or metastatic MEL (Opdivo 2017). Nivolumab is approved in the European Union as monotherapy or in combination with ipilimumab for advanced (unresectable or metastatic) MEL, as monotherapy for locally advanced or metastatic NSCLC after prior chemotherapy, for advanced RCC after prior therapy, for recurrent or metastatic SCCHN, and for Hodgkin lymphoma following autologous stem cell transplant and treatment with brentuximab vedotin (Opdivo SmPC 2015).

1.4.1. Risks From Nivolumab

Overall, the safety profile of nivolumab monotherapy is manageable and generally consistent across completed and ongoing clinical studies, with no MTD reached at any dose tested up to 10 mg/kg. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level. The most common adverse reactions (≥ 20%) reported have been fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, and pyrexia. Most AEs were low grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. Infusion reactions are also possible following administration of nivolumab. The safety profile of

nivolumab combination therapy varies with the agent combined with nivolumab but is generally consistent with the safety profiles observed with either agent alone, and in some cases, both frequency and severity of AEs were greater than those observed with either agent alone.

A pattern of immune-related AEs has been defined, including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin adverse reactions, and encephalitis, for which management algorithms have been developed; these are provided in Appendix B. Most high-grade events were manageable with the use of corticosteroids, or hormone replacement therapy for endocrinopathies, as instructed in these algorithms. Nivolumab should not be used in subjects with active autoimmune disease, given the mechanism of action of the antibody.

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the nivolumab IB.

1.4.2. Risks From Nivolumab in Combination With Ipilimumab

The combination of nivolumab and ipilimumab was initially explored in subjects with advanced or metastatic MEL using doses of 1 mg/kg nivolumab and 3 mg/kg ipilimumab given Q3W for 4 doses followed by 3 mg/kg nivolumab administered Q2W. The toxicity of the combination was significantly higher than either agent alone with 36.4% of subjects discontinuing treatment due to an AE and 68.7% of subjects experiencing Grade 3 or 4 AEs (Larkin et al 2015). More recent published data have demonstrated that lower doses and less frequent administration of ipilimumab improves the toxicity profile of the combination (Antonia et al 2016, Hellmann et al 2016). In a study of 3 mg/kg nivolumab administered Q2W plus 1 mg/kg ipilimumab administered Q6W in first-line NSCLC, only 13% of subjects discontinued due to a treatment-related AE, and only 33% had a Grade 3 or 4 treatment-related AE (Hellmann et al 2016). The most common AEs seen in this treatment group were skin events (36% overall, 5% Grade 3 or 4), endocrine (20% overall, 5% Grade 3 or 4), and GI (23% overall, 5% Grade 3 or 4). Additional details regarding the safety profile of nivolumab and ipilimumab given in combination may be found in the nivolumab IB.

1.4.3. Risks From Nivolumab in Combination With Lirilumab

As of 30 AUG 2016, a total of 159 subjects had been treated with the combination of lirilumab and nivolumab. Adverse events evaluated as related to treatment were reported in 114 subjects (72%); Grade 3 to 4 treatment-related AEs were reported in 24 subjects (15%). The most common related AEs reported in > 10% subjects were fatigue (20.8%), pruritus (18.9%), infusion-related reaction (17.6%), and rash (16.4%). Amylase increased and lipase increased were reported in 4 subjects (2.7%). There were no related Grade 5 events reported. Twelve subjects (7.5%) reported related events leading to study discontinuation. Additional details regarding the safety profile of nivolumab and lirilumab given in combination may be found in the lirilumab IB.

1.4.4. Risks From Nivolumab in Combination With Epacadostat

The combination of epacadostat with nivolumab is being explored in Study INCB 24360-204, a Phase 1/2 open-label study of subjects with advanced solid tumors and lymphoma evaluating escalating doses of epacadostat in combination with nivolumab. No DLTs were observed during the dose escalation portion of the study, in which doses of 25 mg BID, 50 mg BID, 100 mg BID

and 300 mg BID were evaluated in a 3 + 3 + 3 design in combination with nivolumab 3 mg/kg Q2W. Epacadostat doses of 100 mg BID and 300 mg BID were selected for Phase 2 evaluation, and nivolumab was converted to a flat dose of 240 mg Q2W. As of the data cutoff dated 13 FEB 2017, the most common (≥ 10%) AEs related to study drug (epacadostat or nivolumab) in subjects treated with 100 mg BID (n = 69) and 300 mg (n = 161) were rash (35% and 32%, respectively), fatigue (23% and 38%, respectively), nausea (19% and 20%, respectively), diarrhea (12% and 16%, respectively), nausea (19% and 10%, respectively) and AST increased (15% and 10%, respectively). Treatment-related Grade 3 or 4 AEs were 25% in subjects treated with 100 mg BID and 27% in subjects treated with 300 mg BID. Rash was the most common ≥ Grade 3 treatment-related AE at the 100 mg BID and 300 mg dose levels (10% and 15%). Adverse events led to discontinuation in 6% and 12% of subjects receiving 100 mg BID and 300 mg BID, respectively. There were no treatment-related deaths (Perez et al 2017).

1.5. Overview of Ipilimumab

Ipilimumab (YERVOY®) is a fully human monoclonal IgG1κ CTLA-4–blocking antibody that binds to the CTLA-4 antigen expressed on a subset of T cells from human and nonhuman primates. Ipilimumab is approved in the US and EU as a monotherapy and in combination with nivolumab for the treatment of patients with advanced MEL. Refer to the Yervoy prescribing information and SmPC for updated information regarding approved indications (Yervoy 2017).

1.5.1. Risks From Ipilimumab

Ipilimumab may cause immune-related adverse reactions, including hepatitis, enterocolitis, dermatitis, neuropathies, endocrinopathies and other immune-mediated adverse reactions. Guidance for the management of these events are provided in Appendix B. The approved dose of ipilimumab is 3 mg/kg Q3W for 4 doses. The most common AEs (≥ 5%) seen at the approved dose are fatigue, diarrhea, pruritus, rash, and colitis. Additional common adverse reactions (≥ 5%), seen in patients receiving a higher dose of 10 mg/kg, include nausea, vomiting, headache, weight loss, pyrexia, decreased appetite, and insomnia (Yervoy 2017).

Additional details on the safety profile of ipilimumab, including results from clinical studies, are available in the ipilimumab IB.

1.5.2. Risks From Ipilimumab in Combination With Epacadostat

The combination of epacadostat with ipilimumab was explored in Study INCB 24360-201, a Phase 1/2 open-label study of subjects with advanced MEL, using 3 mg/kg ipilimumab given Q3W for 4 doses in combination with a starting dose of epacadostat of 300 mg BID. Five of 7 subjects enrolled at the 300 mg BID epacadostat dose developed clinically significant ALT elevations after 30 to 76 days on treatment; none of these subjects had elevated bilirubin, evidence of liver failure, or other evidence of severe liver injury; enrollment was stopped. These subjects were discontinued from therapy and were treated with IV Solu-Medrol® followed by oral prednisone on a tapering schedule and recovered normal liver function; the ALT elevations were reversible with corticosteroids and treatment discontinuation. Enrollment was restarted at 25 mg BID (n = 8), and subsequent cohorts of 50 mg BID continuous (n = 18), 50 mg BID intermittent (2 weeks on epacadostat/1 week off; n = 9), and 75 mg total daily dose (n = 7) were enrolled. Among all doses, the most frequently reported AE was fatigue (66%). Other AEs that

occurred in > 25% of subjects included rash (54.0%), constipation and pruritus (40.0% each), diarrhea and nausea (32.0% each), ALT increased (28.0%), decreased appetite (26.0%), and headache (26.0%). The most frequently reported AE related to study drug (epacadostat or ipilimumab) was fatigue (44.0%). Other treatment-related AEs that occurred in ≥ 20% of subjects included rash (40.0%), pruritus (30.0%), ALT increased (28.0%), and AST increased (24.0%). Immune-related AEs were generally Grade 1/2 and manageable with continued administration or temporary dose interruption; 1 subject each discontinued for immune-related Grade 3 colitis and Grade 3 salivary amylase elevation. There were no treatment-related deaths reported (epacadostat IB).

1.6. Overall Risk/Benefit Assessment of the Combination Regimens

There continues to be a significant unmet need for patients with advanced and metastatic solid tumors who have either not responded to standard treatment or for whom standard treatments provide suboptimal outcomes.

Doublet combinations of nivolumab and ipilimumab, and nivolumab and lirilumab, have demonstrated enhanced clinical activity compared with monotherapy with a manageable safety profile (Larkin et al 2015, Hellmann et al 2016, Goldman et al 2017). Additionally, recent evidence has emerged suggesting that epacadostat may enhance the clinical activity of PD-1–targeting agents in a variety of tumor types, including MEL (Gangadhar et al 2016, Perez et al 2017), NSCLC (Gangadhar et al 2017), and SCCHN (Perez et al 2017, Hamid et al 2017) with minimal additive toxicity. The totality of these data suggest that the proposed combinations to be evaluated in this study (nivolumab/ipilimumab/epacadostat and nivolumab/lirilumab/epacadostat) may provide additional clinical benefit beyond that which has been observed in the aforementioned doublet regimens.

While the addition of epacadostat to each of the doublet combinations of nivolumab and ipilimumab, and nivolumab and lirilumab, has the potential for increased clinical benefit, the combination of 3 immune-targeting therapies also has the potential for increased frequencies of AEs. The principle toxicities of administering agents that modulate the immune system are irAEs including skin manifestations, pneumonitis, hepatitis, enterocolitis, and endocrinopathies. The time of onset of irAEs varies, with skin manifestations and GI toxicity seen early and elevated liver enzymes and endocrinopathies appearing later (Weber et al 2015). As the use of immunotherapies become more prevalent, guidelines for the management of irAEs continue to evolve. Careful monitoring, early diagnosis, and treatment with corticosteroids for more severe events is recommended. Subjects enrolled in this study will be carefully monitored for the onset of irAEs, and guidelines for the management of these toxicities are provided in the Protocol.

The risks of nivolumab and ipilimumab are well-characterized and described in more detail in Section 1.4.2. Additionally, the risks of nivolumab and ipilimumab in combination with epacadostat are detailed in Section 1.4.4 and Section 1.5.2, respectively. Of note, a lower dose and less frequent administration of ipilimumab (1 mg/kg Q6W) was selected for combination with epacadostat in Treatment Group A to minimize AEs based on emerging safety data with the nivolumab and ipilimumab combination (Antonia et al 2016, Hellmann et al 2016) and the prior clinical experience with epacadostat and ipilimumab.

The emerging safety profile of nivolumab and lirilumab, as detailed in Section 1.4.3, is generally consistent with that observed with nivolumab monotherapy. However, addition of epacadostat in

the Treatment Group B combination may result in increased risk of irAEs. Appropriate safety monitoring will be performed during the study to detect any additive toxicity and management guidelines are provided for management of irAEs.

1.7. Rationale for Dose and Schedule of the Combination Therapies

The initial epacadostat dose selected in Treatment Group A, to be administered in combination with nivolumab and ipilimumab, is 50 mg BID. Based on DLTs observed in Phase 1, the dose may be subsequently escalated to 100 mg BID, or the dose may be de-escalated to 25 mg BID. The initial dose selected is based on the safety and tolerability profile of the ipilimumab and epacadostat doublet observed in Study INCB 24360-201 (see Section 1.5.2), where 50 mg BID epacadostat were generally well-tolerated with higher dose intensity ipilimumab (3 mg/kg Q3W × 4 doses) than will be used in this study.

The starting dose of epacadostat in Treatment Group B, to be administered in combination with nivolumab and lirilumab, is 50 mg BID. Based on DLTs observed in Phase 1, the dose may be subsequently escalated to a maximum dose of 100 mg BID, or the dose may be de-escalated to 25 mg BID. The initial dose selected is based on the acceptable safety and tolerability profile of the nivolumab and epacadostat doublet discussed in Section 1.4.4, as well as the emerging safety profile of the nivolumab and lirilumab combination.

In the first-in-human study INCB 24360-101, a detailed interrogation of the effect of dose and exposure on the pharmacodynamics effect of epacadostat on the tryptophan pathway was performed. Using an *ex vivo* assay optimized for determining the inhibition of the metabolism of tryptophan to kynurenine by IDO1, epacadostat treatment produced significant dose-dependent reductions in plasma kynurenine levels and in the plasma kynurenine/tryptophan ratio at all doses and in all patients. Near maximal changes were observed at doses of ≥ 100 mg BID with > 80% to 90% inhibition of IDO1 achieved throughout the treatment period. Complete inhibition of IDO1 is not required for maximally effective activity in preclinical models; however, maximally effective doses in nonclinical models result in exposures that are comparable to monotherapy doses of 50 mg BID to 300 mg BID in humans.

In April 2018, eDMC review of ECHO-301/KEYNOTE-252 study, a Phase 3 study evaluating pembrolizumab 200 mg Q3W in combination with epacadostat 100 mg BID versus pembrolizumab 200 mg Q3W with placebo as first-line treatment in subjects with unresectable or metastatic melanoma, concluded that the coprimary endpoint of improvement in progression-free survival was not met (HR = 1.00; 95% CI 0.83 to 1.21) and that the coprimary endpoint of improvement in overall survival was also not expected to reach statistical significance (HR = 1.13; 95% CI: 0.86 to 1.49). Based on these results, and on the recommendation of the eDMC, the study was stopped. The safety profile observed in the ECHO-301/KEYNOTE-252 study was consistent with that observed in previously reported studies of epacadostat in combination with pembrolizumab (Long et al 2018).

In the context of the ECHO-301/KEYNOTE-252 outcome and the ECHO-208 study design, which limits epacadostat doses to ≤ 100 mg BID, the sponsor will allow for withdrawal of epacadostat for subjects who are continuing on treatment on or after the effective date of Amendment 2 at the discretion of the treating investigator.

The FDA approved dose of nivolumab (240 mg Q2W) has been selected for use in combination with ipilimumab and epacadostat in Treatment Group A and lirilumab and epacadostat in Treatment Group B.

The ipilimumab dose of 1 mg/kg Q6W will be used in combination with nivolumab and epacadostat in Treatment Group A; although the approved dose of ipilimumab in combination with nivolumab is 3 mg/kg Q3W, recent published data have demonstrated that lower doses and less frequent administration of ipilimumab improves the toxicity profile of the combination with similar efficacy, as discussed in Section 1.4.2.

Lirilumab is being studied as a potential immunotherapy alone and in combination with other agents in subjects with various hematologic malignancies and solid tumors with body weight normalized dosing (mg per kg). A preliminary PK analysis of data collected from 3 studies suggests that lirilumab PK is linear, with dose proportional exposures over a dose range of 0.1 to 10 mg/kg. Lirilumab Cl and volume of distribution was found to increase with increasing body weight, but the increase was less than proportional, indicating that a mg per kg dose represents an overadjustment for the effect of body weight on lirilumab PK. Conversely, given the relationship between lirilumab PK and body weight, a flat dose is expected to lead to lower exposures in heavier subjects, relative to the exposures in lighter subjects.

Table 1 presents summary statistics of the estimated lirilumab peak and trough concentrations after the first dose and steady state (C_{min1}, C_{max1}, $C_{min,ss}$, and $C_{max,ss}$) in subjects receiving 3 mg/kg, together with corresponding statistics of exposures predicted for a flat lirilumab dose of 240 mg. It should be noted that a dose of lirilumab 240 mg is identical to a dose of 3 mg/kg for subjects weighing 80 kg. As evident from the data presented in Table 1, the geometric mean values of C_{min1}, C_{max1}, $C_{min,ss}$, and $C_{max,ss}$ with flat dosing are slightly higher (< 10% difference) than those produced by a 3 mg/kg dose.

Table 1: Summary Statistics of Predicted Lirilumab Exposure

Lirilumab Dose	C_{min1} Geo. Mean [µg/mL] (cv %)	C_{max1} Geo. Mean [µg/mL] (cv %)	$C_{min,ss}$ Geo. Mean [µg/mL] (cv %)	$C_{max,ss}$ Geo. Mean [µg/mL] (cv %)
240 mg	8.897 (61.06)	66.113 (40.06)	14.262 (85.26)	83.209 (41.25)
3 mg/kg	8.261 (58.61)	61.513 (37.54)	13.263 (81.98)	77.678 (38.49)

Refer to the lirilumab IB for additional details.

1.8. Rationale for Shorter Infusion Times for Nivolumab and Ipilimumab

Long infusion times place a burden on patients and treatment centers. Establishing that nivolumab and ipilimumab can be safely administered using shorter infusion times of 30 minutes duration will diminish the burden, provided that there is no change in the safety profile. Previous clinical studies of nivolumab and ipilimumab monotherapies and the combination of nivolumab and ipilimumab have used a 60-minute infusion duration for nivolumab and a 90-minute infusion duration for ipilimumab (1-3 mg/kg dosing for both). However, both nivolumab and ipilimumab have been administered at up to 10 mg/kg with the same infusion duration (ie, 60 minutes).

Establishing that nivolumab can be safely administered using a shorter infusion time (30 minutes) is under investigation. Previous clinical studies of nivolumab monotherapy have used a 60-minute infusion duration, wherein nivolumab has been safely administered up to

10 mg/kg over long treatment periods. Infusion reactions, including high-grade hypersensitivity reactions, have been uncommon across nivolumab clinical program. In Study CA209010 (nivolumab combined with ipilimumab versus sunitinib in previously untreated advanced or metastatic RCC), a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg, and 18.5% at 10 mg/kg). All the events were Grade 1 to 2 and were manageable. An infusion duration of 30 minutes for nivolumab 3 mg/kg (30% of the dose provided at 10 mg/kg) is not expected to present any safety concerns compared with the prior experience at 10 mg/kg of nivolumab dose infused over a 60-minute duration. The safety of nivolumab 3 mg/kg administered as a 30-minute infusion was assessed in CA209153 in subjects (n = 322) with previously treated advanced NSCLC. Overall, there were no clinically meaningful differences in the frequency of hypersensitivity or infusion-related reactions (of any cause or treatment-related) in subjects administered nivolumab over a 30-minute infusion compared with that reported for subjects with the 60-minute infusion. Thus, it was shown that nivolumab can be safely infused over 30 minutes.

Similarly, ipilimumab at 10 mg/kg has been safely administered over 90 minutes. In a study of subjects with advanced Stage II or Stage IV MEL, where ipilimumab was administered up to a dose of 10 mg/kg, on-study drug-related hypersensitivity events (Grade 1/2) were reported in 1 subject (1.4%) in the 0.3 mg/kg group and in 2 subjects (2.8%) in the 10 mg/kg group. There were no drug-related hypersensitivity events reported in the 3 mg/kg group. Across the 3 treatment groups, no Grade 3/4 drug-related hypersensitivity events were reported, and there were no reports of infusion reactions. Administering 1 mg/kg of ipilimumab (the dose in this study) represents approximately one-tenth of the 10 mg/kg dose.

Overall, infusion reactions, including high-grade hypersensitivity reactions, have been uncommon across clinical studies of nivolumab, ipilimumab, and nivolumab/ipilimumab combinations. Furthermore, a 30-minute break after the first infusion will ensure appropriate safety monitoring before the start of the second infusion. Overall, a change in safety profile is not anticipated with 30-minute infusions of nivolumab, ipilimumab, or the combination.

1.9. Rationale for Efficacy Endpoints

RECIST v1.1 (Eisenhauer et al 2009) will be used by the local site to determine eligibility and for the primary analysis of efficacy; however, treatment decisions will be based on [redacted] (Seymour et al 2017), which accounts for the unique tumor kinetics associated with the class of agents being evaluated in this study. [redacted]

[redacted]

In subjects who have initial radiologic evidence of PD, it is at the discretion of the investigator to continue a subject on treatment until repeat imaging is obtained. This decision should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive treatment while waiting for confirmation of PD if they are clinically stable, as defined by the following criteria:

- Absence of clinically significant signs and symptoms (including worsening of laboratory values) indicating disease progression.
- No decline in ECOG performance status.
- No requirement for intensified management of disease-related symptoms.
- Absence of rapid progression of disease.
- Absence of progressive tumor at critical anatomical sites (eg, spinal cord compression) requiring urgent alternative medical intervention.

When feasible, subjects should not be discontinued until progression is confirmed. Subjects who are deemed clinically unstable are not required to have repeat imaging for confirmation of PD and should be withdrawn from all study treatment. See additional details in Section 5.5.1.1.

2. STUDY OBJECTIVES AND ENDPOINTS

Study objectives and endpoints are presented in Table 2.

Table 2: Study Objectives and Endpoints

Primary Objectives	Primary Endpoints
Phase 1:	
To evaluate the safety, tolerability, and DLTs and to define a MTD and/or PAD of epacadostat in combination with nivolumab and ipilimumab, and in combination with nivolumab and lirilumab, in subjects with advanced or metastatic solid tumors.	Safety and tolerability will be assessed by monitoring frequency, duration, and severity of AEs through physical examinations, by evaluating changes in vital signs and ECGs, and through clinical laboratory blood and urine sample evaluations.
Phase 2:	
Treatment Group A: To evaluate the efficacy of epacadostat in combination with nivolumab and ipilimumab in subjects with advanced or metastatic NSCLC and unresectable or metastatic MEL by assessing ORR per RECIST v1.1.	ORR, defined as the percentage of subjects having CR or PR, will be determined by investigator evaluation of radiographic disease assessment per RECIST v1.1.
Treatment Group B: To evaluate the efficacy of epacadostat in combination with nivolumab and lirilumab in subjects with recurrent or metastatic SCCHN by assessing ORR per RECIST v1.1.	
Secondary Objectives	**Secondary Endpoints**
Phase 1:	
To evaluate the efficacy of epacadostat in combination with nivolumab and ipilimumab, and in combination with nivolumab and lirilumab, in subjects with advanced or metastatic solid tumors by assessing ORR per RECIST v1.1.	ORR, defined as the percentage of subjects having CR or PR, will be determined by investigator evaluation of radiographic disease assessment per RECIST v1.1.
Phase 1 and Phase 2:	
To evaluate the efficacy of epacadostat in combination with nivolumab and ipilimumab, and in combination with nivolumab and lirilumab, in subjects with advanced or metastatic solid tumors in Phase 1 and in subjects with selected advanced or metastatic solid tumors in Phase 2 by assessing DOR and PFS per RECIST v1.1.	DOR is defined as the time from the earliest date of CR or PR until the earliest date at which progression criteria are met as determined by investigator evaluation of radiographic disease assessment per RECIST v1.1, or date of death due to any cause.
	PFS is defined as the time from the start of combination therapy until the earliest date at which progression criteria are met as determined by investigator evaluation of radiographic disease assessment per RECIST v1.1, or date of death due to any cause.

Table 2: Study Objectives and Endpoints (Continued)

Secondary Objectives (Continued)	Secondary Endpoints (Continued)
Phase 2:	
To further evaluate the safety and tolerability of epacadostat at the MTD and/or PAD in combination with nivolumab and ipilimumab, and in combination with nivolumab and lirilumab, in subjects with selected advanced or metastatic solid tumors.	Safety and tolerability will be assessed by monitoring frequency, duration, and severity of AEs through physical examinations, by evaluating changes in vital signs and ECGs, and through clinical laboratory blood and urine sample evaluations.
[redacted]	

Table 2: Study Objectives and Endpoints (Continued)

3. SUBJECT ELIGIBILITY

Deviations from eligibility criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or subject safety. Therefore, adherence to the criteria as specified in the Protocol is essential.

3.1. Subject Inclusion Criteria

A subject who meets all of the following criteria may be included in the study:

Phase 1 only:

1. Subjects with histologically or cytologically confirmed locally advanced or metastatic solid tumors who have disease progression on or after treatment with available therapies that are known to confer clinical benefit, or who are intolerant to treatment, or who refuse standard treatment.

   Note: Locally advanced disease must not be amenable to resection with curative intent.

2. Has received no more than 2 prior treatment regimens (including chemotherapy and/or targeted therapy; not including neoadjuvant and/or adjuvant therapy) for advanced or metastatic disease.

3. Has baseline core or excisional tumor archival biopsy specimen available or willingness to undergo a pretreatment biopsy to obtain the specimen. Archival specimen must be a tumor block or 25 unstained slides (minimum of 20). A FFPE tumor tissue block is preferred. If a block is not available, a minimum of 20 to 25 unstained freshly cut slides may be submitted to the testing laboratory as specified Laboratory Manual.

   Note: Unstained slides must have been prepared from an FFPE block obtained within 6 months before screening.

Phase 2:

Cohort A1 (MEL):

4. Subjects with histologically confirmed unresectable Stage III or Stage IV MEL not amenable to local therapy who have received no prior systemic treatment (excluding adjuvant or neoadjuvant chemotherapy) for advanced or metastatic disease. Mucosal or cutaneous MEL is acceptable; however, subjects with ocular MEL are excluded.
   a. Must have documentation BRAF mutation status.

Cohort A2 (NSCLC):

5. Subjects with histologically or cytologically confirmed Stage IIIB, Stage IV, or recurrent squamous or nonsquamous NSCLC and who has received no more than 1 prior line of platinum-based chemotherapy for advanced or metastatic disease.
   a. Subjects with known driver mutations (including EGFR or BRAF mutations, or ALK or ROS1 rearrangements) are excluded.
   b. Prior adjuvant or neoadjuvant chemotherapy completed less than 6 months before study entry will be counted as 1 prior line of therapy.

Cohort B1 (SCCHN):

6. Subjects with histologically confirmed squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx that is not amenable to local therapy with curative intent (surgery or radiation with or without chemotherapy) and who have received no more than 1 prior line of platinum-based chemotherapy for recurrent or metastatic disease.
   a. Must have documentation of HPV status (eg, p16 status) of tumor (oropharyngeal only).
   b. Histologically confirmed recurrent or metastatic carcinoma of the nasopharynx and salivary gland or nonsquamous histologies are excluded.

Phase 2 (all cohorts):

7. Willingness to undergo serial pretreatment and on-treatment core or excisional tumor biopsies. Biopsy requirement may be omitted with medical monitor approval if it is not clinically feasible due to location of known disease or concomitant condition. Biopsies will be confirmed to contain adequate tumor tissue by a local pathology review.

   Note: If a subject is scheduled to have a tumor biopsy in the study and it is subsequently determined that tumor tissue cannot be safely obtained, then the subject may still enroll or continue in the study. The subject may be replaced in order to enroll sufficient number of subjects for biomarker evaluation.

All subjects (Phase 1 and Phase 2):

8. Ability to comprehend and willingness to sign an ICF.
9. Men or women aged 18 years or older.
10. Presence of measurable disease per RECIST v1.1 (Appendix E). Tumor lesions located in a previously irradiated area, or in an area subjected to other locoregional therapy, are considered measurable if progression has been demonstrated in the lesion following such therapy.
11. ECOG performance status of 0 or 1.
12. Expected survival of ≥ 12 weeks.
13. Willingness and ability to comply with the scheduled visits, treatment plan, and laboratory tests.
14. Willingness to avoid pregnancy or fathering children based on the following criteria:
    a. Woman of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea and at least 51 years of age).
    b. Woman of childbearing potential who has a negative serum pregnancy test at screening (within 72 hours of Day 1) and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through at least 5 months after the last dose of study treatment. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.
    c. Man who agrees to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through at least 7 months after the last dose of study treatment. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.

3.2. Subject Exclusion Criteria

A subject who meets any of the following criteria will be excluded from the study:

1. Laboratory and medical history parameters not within the Protocol-defined range; all screening laboratory tests should be performed within 7 days of Cycle 1 Day 1. If the screening laboratory tests outlined below were performed more than 7 days before Cycle 1 Day 1, the hematology, serum chemistry, and liver chemistry test results must be confirmed on Cycle 1 Day 1 before initiation of study treatment
    a. ANC < 1.5×10^9/L.
    b. Platelets < 100×10^9/L.
    c. Hemoglobin < 9 g/dL or < 5.6 mmol/L (transfusion is acceptable to meet this criterion).
    d. Serum creatinine ≥ 1.5 × institutional ULN, or measured or calculated CrCl < 50 mL/min for subjects with creatinine levels > 1.5 × institutional ULN (GFR can also be used in place of CrCl).
    e. **Phase 1 only:** AST or ALT ≥ 1.5 × institutional ULN.
    Phase 2 only: AST or ALT ≥ 2.5 × institutional ULN.

f. Total bilirubin ≥ 1.5 × institutional ULN or conjugated (direct) bilirubin ≥ institutional ULN. If an institutional ULN for conjugated bilirubin is not available, then conjugated bilirubin should be < 40% of total bilirubin to be considered eligible.
g. INR or PT > 1.5 × institutional ULN.
h. aPTT > 1.5 × institutional ULN unless subject is receiving anticoagulant therapy, as long as PTT is within therapeutic range of intended use of anticoagulants.
i. **Phase 1 only:** Albumin ≤ 3.0 g/dL or with medical monitor approval.

2. Receipt of anticancer medications or investigational drugs within the following interval before the first administration of study drug:

   a. ≤ 21 days for chemotherapy or targeted small molecule therapy.
   Note: Use of bisphosphonates is permitted.
   b. ≤ 28 days for previous monoclonal antibody used for anticancer therapy.
   Note: Use of denosumab is permitted.
   c. ≤ 28 days or 5 half-lives (whichever is longer) before Cycle 1 Day 1 for all other investigational agents or devices. For investigational agents with long half-lives (eg, > 5 days), enrollment before the fifth half-life requires medical monitor approval.

3. Previous radiotherapy within 7 days of Cycle 1 Day 1 (except for radiation to CNS, which requires a ≥ 28-day washout as described below). Subjects must also not require chronic use of corticosteroids and must not have had radiation pneumonitis as a result of treatment.

4. Known active CNS metastases and/or carcinomatous meningitis.

   Note: Subjects with previously treated brain metastases may participate provided that they are stable (without evidence of progression by imaging for at least 28 days before Cycle 1 Day 1 and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases or cerebral edema, and have not required steroids for at least 14 days before Cycle 1 Day 1.

5. Prior treatment with any immune checkpoint inhibitor (eg, anti–CTLA-4, anti–PD-1/PD-L1, anti–PD-2/PD-L2, anti-KIR, and any other antibody or drug specifically targeting T-cell costimulation) and/or an IDO inhibitor. Subjects who have received experimental vaccines or other immune therapies should be discussed with the medical monitor to confirm eligibility.

   Note: Subjects in Cohort A1 who received adjuvant anti–CTLA-4 therapy and had disease progression ≥ 6 months after completion of planned treatment may enroll.

6. Any unresolved toxicity > Grade 1 from previous anticancer therapy, except for stable chronic toxicities not expected to resolve, such as peripheral neurotoxicity, alopecia, and fatigue.

7. Subjects who are receiving an immunologically based treatment for any reason, including chronic use of systemic steroid or at doses ≥ 10 mg/day prednisone equivalent within 7 days before the first dose of study drug. Use of inhaled or topical steroids or systemic corticosteroids < 10 mg prednisone equivalent is permitted.

8. Receipt of a live vaccine within 30 days of planned start of study therapy.

   Note: Examples of live vaccines include but are not limited to the following: measles, mumps, rubella, chicken pox/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines are live attenuated vaccines and are not allowed.

9. Active infection requiring systemic therapy.
10. Subjects with any active or inactive autoimmune disease or syndrome (eg, rheumatoid arthritis, moderate or severe psoriasis, multiple sclerosis, inflammatory bowel disease) that has required systemic treatment in the past 2 years or who are receiving systemic therapy for an autoimmune or inflammatory disease (ie, with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs).

    Note: Exceptions include subjects with vitiligo or resolved childhood asthma/atopy, hypothyroidism stable on hormone replacement, controlled asthma, or Type I diabetes, Graves' disease, or Hashimoto's disease that are treated and controlled, or with medical monitor approval.

11. Evidence of interstitial lung disease or active, noninfectious pneumonitis, including symptomatic and/or pneumonitis requiring treatment.
12. History of organ transplant that requires use of immunosuppressive therapy.
13. Has known history of or is positive for hepatitis B (HBsAg reactive) or hepatitis C.
    a. HBV DNA must be undetectable and HBsAg negative at the screening visit.
    b. Hepatitis C antibody testing is allowed for screening purposes in countries where HCV RNA is not part of standard of care. In these cases, HCV antibody–positive subjects will be excluded.
    c. Subjects who have had definitive treatment for HCV are permitted if HCV RNA is undetectable at the screening visit.

    Note: Testing must be performed to determine eligibility.

14. Known history of HIV (HIV 1/2 antibodies).
15. History of other malignancy within 2 years of study entry, with the exception of cured basal cell or squamous cell carcinoma of the skin, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma in situ of the cervix, or other noninvasive or indolent malignancy, or cancers from which the subject has been disease-free for ≥ 1 year, following treatment with curative intent, with medical monitor approval.
16. Any history of SS after receiving 1 or more serotonergic drugs.
17. History or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful. Screening QTc interval > 480 milliseconds is excluded (corrected by Fridericia or Bazett formula). In the event that a single QTc is > 480 milliseconds, the subject may be enrolled if the average QTc for 3 consecutive ECGs is < 480 milliseconds. For subjects with an intraventricular conduction delay (QRS interval > 120 milliseconds), the JTc interval may be used in place of the QTc with medical monitor approval. The JTc must be < 340 milliseconds if JTc is used in place of the QTc. Subjects with left bundle branch block are excluded.

18. Clinically significant cardiac disease, including unstable angina, acute myocardial infarction within 6 months of Cycle 1 Day 1, New York Heart Association Class III or IV or congestive heart failure. Medically controlled arrhythmia stable on medication is permitted.
19. Known allergy or reaction to any components of epacadostat, nivolumab, ipilimumab, or lirilumab.
20. Presence of a GI condition (eg, inflammatory bowel disease, Crohn's disease, ulcerative colitis) that may affect drug absorption.

    Note: Subjects with feeding tubes must be approved for inclusion in the study by the medical monitor.
21. Use of MAOIs or drug that has significant MAOI activity (eg, meperidine, linezolid, methylene blue) within the 21 days before screening. See Appendix D for prohibited medications associated with MAO inhibition.
22. Use of any UGT1A9 inhibitor or inducer from screening through follow-up period, including the following: diclofenac, imipramine, ketoconazole, mefenamic acid, and probenecid. See Section 5.6.3 for a complete list of UGT1A9 inhibitor and inducers.
23. Bleeding associated with tumors that invade or are adjacent to major blood vessels, as shown unequivocally by imaging studies, or history of bleeding related to disease under study within 3 months of enrollment.
24. 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.
25. Women who are pregnant or breastfeeding.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

Note: Amendment 2 will serve to close the study to further enrollment; the primary purpose of the amendment is to provide an updated assessment schedule for subjects enrolled to date (Treatment Group A only). No subjects were enrolled into Treatment Group B.

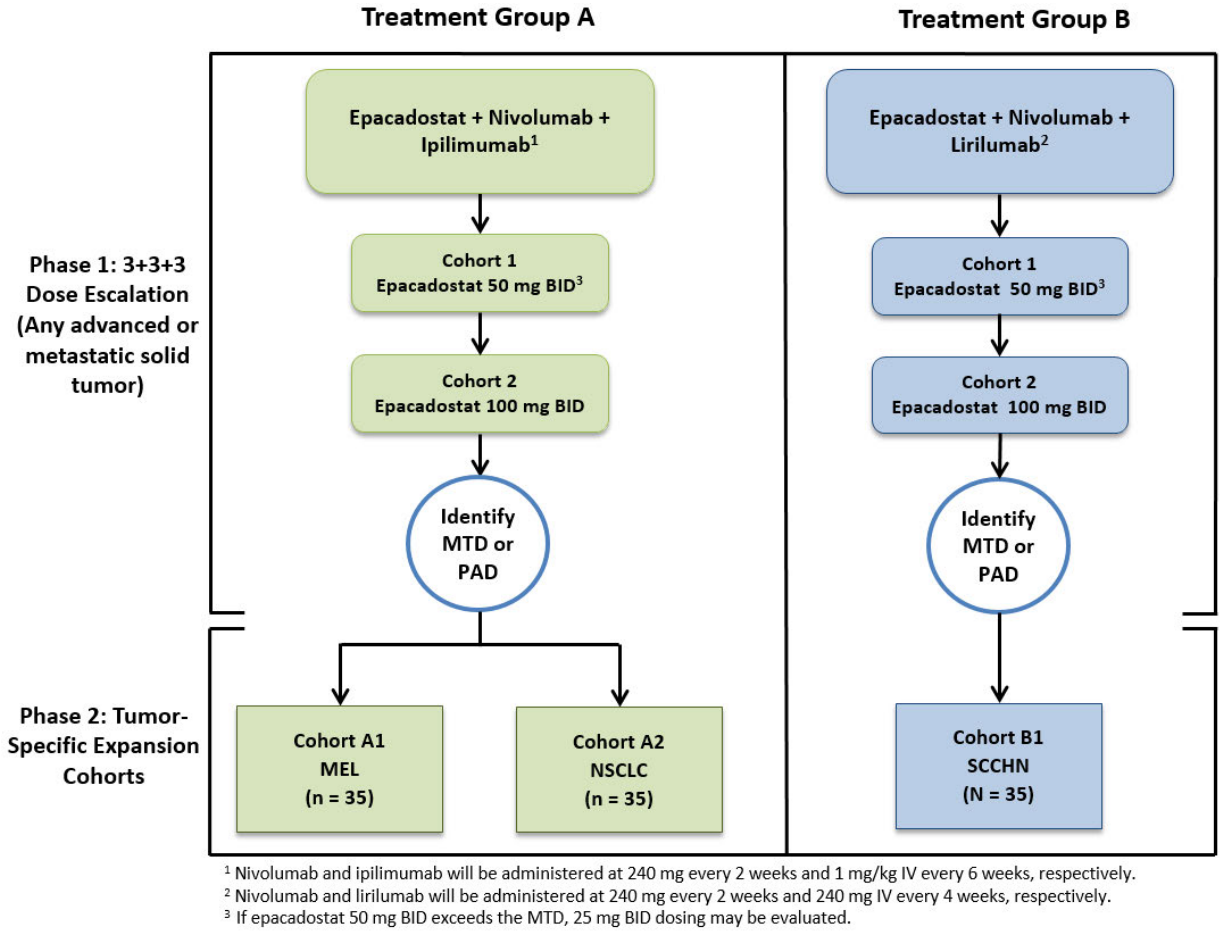
This is an open-label, nonrandomized, Phase 1/2 study to determine the safety, tolerability, and efficacy of epacadostat when given in combination with nivolumab and ipilimumab, and in combination with nivolumab and lirilumab. The study will be conducted in 2 independent treatment groups: Treatment Group A will evaluate the combination of epacadostat, nivolumab, and ipilimumab; Treatment Group B will evaluate the combination of epacadostat, nivolumab, and lirilumab. Each treatment group will be investigated in 2 phases:

- Phase 1 will consist of a standard 3 + 3 + 3 dose-escalation design to define the MTD or PAD of epacadostat with nivolumab and ipilimumab (Treatment Group A) and with nivolumab and lirilumab (Treatment Group B) in subjects with advanced or metastatic solid tumors; [redacted]
- Phase 2 will evaluate the efficacy of the MTD or PAD of epacadostat when given in combination with nivolumab and ipilimumab, and in combination with nivolumab and lirilumab, as determined in each of the Phase 1 treatment groups in select solid tumors, and will further evaluate the safety, [redacted] of the combinations.

Treatment Group A will enroll 2 tumor-specific expansion cohorts (Cohorts A1 and A2); Cohort A1 will include subjects with unresectable or metastatic MEL who have not received prior systemic therapy for advanced or metastatic disease; Cohort A2 will include subjects with advanced or metastatic NSCLC who have received no more than 1 prior line of platinum-based chemotherapy for advanced or metastatic disease.

Treatment Group B will enroll 1 expansion cohort (Cohort B1); Cohort B1 will include subjects with recurrent or metastatic SCCHN who have received no more than 1 prior line of platinum-based chemotherapy for recurrent or metastatic disease. See Figure 1 for overall study design.

Figure 1: Study Design



[1] Nivolumab and ipilimumab will be administered at 240 mg every 2 weeks and 1 mg/kg IV every 6 weeks, respectively.
[2] Nivolumab and lirilumab will be administered at 240 mg every 2 weeks and 240 mg IV every 4 weeks, respectively.
[3] If epacadostat 50 mg BID exceeds the MTD, 25 mg BID dosing may be evaluated.

4.1.1. Phase 1 – Dose Escalation

Dose escalation in Treatment Groups A and B will be conducted using a standard 3 + 3 + 3 design as per the dose-escalation schedule outlined in Table 3. A minimum of 3 evaluable subjects will be enrolled in each treatment group beginning with Dose Level 1 (starting dose of epacadostat 50 mg BID in Treatment Groups A and B).

In Treatment Group A, the first 3 evaluable subjects at each dose level will be observed for a minimum of 42 days before the next dose level begins enrollment. To be evaluable for tolerability, subjects must receive at least 75% of planned epacadostat doses (63/84) at the specified dose level, 3 doses of nivolumab, and 1 dose of ipilimumab, or subjects must experience a DLT during the DLT observation period.

In Treatment Group B, the first 3 evaluable subjects at each dose level will be observed for a minimum of 42 days before the next dose level begins enrollment. To be evaluable for tolerability, subjects must receive at least 75% of planned epacadostat doses (63/84) at the specified dose level, 3 doses of nivolumab, and 2 doses of lirilumab, or subjects must experience a DLT during the DLT observation period.

Subjects who discontinue for reasons other than a DLT (eg, events clearly associated with the underlying disease, disease progression, concomitant medication, comorbidity, or an AE clearly

unrelated to study treatment) during a DLT observation period will be considered nonevaluable for DLT evaluation and will be replaced.

Alternate doses or dose administration schedules, including sequenced (rather than concurrent) administration of treatment components, [redacted] and safety results.

For both treatment groups, the following dose-escalation rules apply:

- If 0 of the first 3 evaluable subjects at a dose level have a DLT, 3 subjects will be enrolled and treated at the next higher dose level (if applicable).
- If 1 of the first 3 evaluable subjects at a dose level has a DLT, that dose level will be expanded to 6 subjects. If ≤ 1 of 6 subjects in a dose level has a DLT, 3 subjects will be enrolled and treated at the next higher dose level (if applicable).
- If 2 of 6 subjects at a dose level have a DLT, that dose level will be expanded to include 9 subjects.
- If ≥ 2 of 3, ≥ 3 of 6, or ≥ 3 of 9 subjects have DLTs at a specific dose level, that dose level will be determined to have exceeded the MTD, and the previous dose level will be considered the MTD.

If Dose Level 1 in either treatment group (as specified in Table 3) exceeds the MTD, 3 additional subjects may be enrolled and treated at a lower dose (Dose Level -1).

If only 3 evaluable subjects were treated at the dose level selected for Phase 2, then a minimum of 3 additional evaluable subjects will be enrolled before the selected dose is deemed as the RP2D.

Dose interruptions and/or modifications may be implemented based on toxicity as described in Section 5.4.4. Dose modifications should not be made during the DLT observation period without consulting the study medical monitor. Intrasubject dose escalation is not permitted.

Table 3: Epacadostat Phase 1 Dose Levels

Treatment Group A			
Dose Level	**Epacadostat**	**Nivolumab**	**Ipilimumab**
-1	25 mg BID	240 mg Q2W	1 mg/kg IV Q6W
1 (starting dose)	**50 mg BID**[a]		
2	100 mg BID		
Treatment Group B			
Dose Level	**Epacadostat**	**Nivolumab**	**Lirilumab**
-1	25 mg BID	240 mg Q2W	240 mg IV Q4W
1 (starting dose)	**50 mg BID**[a]		
2	100 mg BID		

[redacted]

[a] If epacadostat 50 mg BID exceeds the MTD, 25 mg BID may be evaluated.

4.1.2. Phase 2 – Dose Expansion

The Phase 2 dose expansion cohorts will begin when the MTD or PAD of epacadostat has been determined in Phase 1 for the respective treatment group. This portion of the study will evaluate the efficacy of the MTD or PAD of epacadostat and will further evaluate the safety, [redacted] of the combinations.

Treatment Group A will enroll 2 expansion cohorts in parallel:

- **Cohort A1:** Approximately 35 subjects with unresectable or metastatic MEL who have not received prior systemic treatment for advanced or metastatic disease. Serial pretreatment and on-treatment biopsies are required for all subjects enrolled, if clinically feasible.
- **Cohort A2:** Approximately 35 subjects with advanced or metastatic NSCLC without known driver mutations (including EGFR, BRAF, ALK, and ROS1) who have received no more than 1 prior line of therapy for advanced or metastatic disease. Serial pretreatment and on-treatment biopsies are required for all subjects enrolled, if clinically feasible.

Treatment Group B will enroll 1 expansion cohort:

- **Cohort B1:** Approximately 35 subjects with recurrent or metastatic SCCHN who have received no more than 1 prior line of platinum-based chemotherapy for recurrent or metastatic disease. Serial pretreatment and on-treatment biopsies are required for all subjects enrolled, if clinically feasible.

Enrollment into the Phase 2 expansion cohorts will begin when the MTD or PAD of epacadostat for the corresponding treatment group in Phase 1 has been determined; however, priority will be given to any open dose-escalation cohorts in Phase 1.

In Phase 2 of the study, toxicities will continue to be monitored. If the cumulative incidence of ≥ Grade 3 immune-related AEs is > 40% after a cumulative minimum of 10 subjects have been enrolled into the expansion cohorts within each treatment group, further enrollment in those expansions will be interrupted until the sponsor, investigators, and regulatory authorities (if applicable) determine the appropriate course of action. If an expansion cohort in a particular treatment group is discontinued because of toxicity, a new expansion may be initiated at a previously tested lower dose level of epacadostat.

The sponsor may elect to prioritize enrollment to specific treatment groups or expansion cohorts based on emerging safety or efficacy data in collaboration with investigational sites.

4.2. Measures Taken to Avoid Bias

This is an open-label study. Assessment of safety using CTCAE v4.03 and efficacy using RECIST v1.1 [redacted] are objective measurements, and only comparisons to pretreatment conditions will be made.

4.3. Number of Subjects

4.3.1. Planned Number of Subjects

Approximately 141 subjects may be enrolled into the study at approximately 15 to 20 sites.

Treatment Group A:

- **Phase 1:** Approximately 18 subjects.
- **Phase 2:** Cohort A1 – approximately 35 subjects
  Cohort A2 – approximately 35 subjects

Treatment Group B:

- **Phase 1:** Approximately 18 subjects.
- **Phase 2:** Cohort B1 – approximately 35 subjects.

4.3.2. Replacement of Subjects

Subjects may be replaced for any of the following reasons:

- In Phase 1, any subject who withdraws from treatment before the completion of the DLT observation period for any reason other than a DLT (ie, is not evaluable for DLTs; see Section 5.4.2) or who does not have the required exposure to the study drugs during the DLT evaluation period, may be replaced to ensure a minimum number of evaluable subjects.
- Subjects who do not meet the eligibility requirements of the study may be replaced.

Subjects who meet any of the criteria for replacement may remain on study for evaluation as outlined in Section 9.1 and Section 9.2.

4.4. Duration of Treatment and Subject Participation

After signing the ICF, screening assessments may be completed over a period of up to 28 days. Each subject enrolled in the study may continue to receive study treatment in continuous 14-day cycles for up to 2 years, as long as they are deriving benefit and have not met any of the Protocol-defined conditions for treatment withdrawal (see Section 5.5.1). If the subject discontinues study treatment, the treatment period will end and the subject will enter the safety follow-up period (see Section 6.4). Study participation, including post-treatment safety follow-up, is expected to average approximately 12 to 18 months per individual subject.

4.5. Overall Study Duration

The study begins when the first subject signs the ICF. The end of the study will occur when all subjects have discontinued treatment and the last follow-up visit has been performed.

If there have been ≤ 5 subjects on study for more than 6 months, a database lock of the study may occur to allow the analysis of the study data. Any remaining subjects may continue to receive study treatment and be seen by the investigator per usual standard of care for this population. The investigator will be expected to monitor for and report any SAEs, AEs of

special interest, and pregnancies, as detailed in Section 8. The remaining subjects are considered to be on study until a discontinuation criterion is met and written notification is provided to the sponsor.

4.6. Study Termination

The investigator retains the right to terminate study participation at any time according to the terms specified in the study contract. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination, send a copy of the notification to the sponsor or sponsor's designee, and retain 1 copy for the site study regulatory file.

The sponsor may terminate the study electively, if required by regulatory decision, or upon review of emerging data. If the study is terminated prematurely, the sponsor will notify the investigators, the IRBs and IECs, and regulatory bodies of the decision and reason for termination of the study.

5. TREATMENT

5.1. Treatment Assignment

5.1.1. Subject Numbering and Treatment Assignment

Each subject will be identified in the study by a subject ID number, which is a combination of the site ID and subject number. Site staff should contact the IRT to obtain the subject ID number during screening. This subject ID number will be maintained throughout the study and will not be reassigned. Subjects who fail screening and are repeating the screening process due to a change in eligibility status will be assigned a new subject ID number. For subjects who signed an ICF but are not treated, refer to the eCRF Completion Guidelines for instructions on which eCRFs to complete.

Site staff will contact the IRT to enroll the subject and obtain the initial assignment for the relevant treatments. The investigator or designee will select the assigned treatments from the stock that correspond to the number provided by the IRT, record the unique identifiers in the eCRF, and dispense the treatment to the subject. All subsequent dispensing of relevant treatments should follow this process. Full details will be provided in the IRT manual.

If a subject is mistakenly dispensed a bottle of study drug that is not the bottle assigned by the IRT, then the IRT help desk must be notified immediately. The reason for the misallocation of the study drug must be documented by the study site.

5.1.2. Randomization and Blinding

This is an open-label nonrandomized study; therefore, randomization and blinding do not apply.

5.2. Study Drugs

5.2.1. Epacadostat

For all subjects, epacadostat will be self-administered beginning on Cycle 1 Day 1 and continuously thereafter. Doses will be taken BID, in the morning and evening, approximately 12 hours apart without regard to food. If a dose is missed by more than 4 hours, then that dose should be skipped and the next dose should be taken at the next scheduled timepoint.

On Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 2 Day 1, the morning dose of epacadostat will be administered at the study site, as these study visits coincide [redacted]. On visit days when nivolumab and ipilimumab (Treatment Group A) or nivolumab and lirilumab (Treatment Group B) are administered, epacadostat should be taken before the start of any infusions.

Note: Subjects who are ongoing on study treatment as of the date of Amendment 2 may discontinue epacadostat at the discretion of the treating investigator (see Section 1.7).

5.2.1.1. Supply, Packaging, and Labeling

Epacadostat will be available as 25 mg and 100 mg tablets packaged in high-density polyethylene bottles. In Phase 1, subjects will receive epacadostat according to dose level assignment (Table 3). In Phase 2, all subjects will receive epacadostat at the MTD or PAD identified in Phase 1. All tablet excipients comply with the requirements of the applicable compendial monographs (Ph. Eur., USP/NF; refer to the epacadostat IB).

All Incyte investigational product labels will be in the local language and will comply with the legal requirements of each country.

5.2.1.2. Storage

Clinical supplies must be stored as described in the epacadostat IB.

5.2.2. Nivolumab

5.2.2.1. Description and Administration

Subjects will receive nivolumab 240 mg as a 30-minute IV infusion (± 5 minutes) on Day 1 of each 14-day cycle, starting at Cycle 1 Day 1. Intrasubject dose escalation of nivolumab is not permitted. Nivolumab will be administered after epacadostat. Sites are instructed to wait at least 30 minutes after the nivolumab infusion is completed before administering subsequent infusions of ipilimumab (Treatment Group A) or lirilumab (Treatment Group B).

Details on the preparation and administration are provided in the Pharmacy Manual.

5.2.2.2. Supply, Packaging, and Labeling

The investigator will take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of nivolumab in accordance with the protocol and any applicable laws and regulations. Nivolumab clinical supplies will be provided by BMS and will be labeled in accordance with local regulatory requirements.

The nivolumab product description is provided in Table 4. Refer to the nivolumab IB for additional details.

Table 4: Nivolumab Product Description

Product Description and Regimen Form	Potency	Primary Packaging Volume/ Label Type	Secondary Packaging/ Label Type	Appearance	Storage Conditions
Nivolumab (BMS-936558) solution for injection.	100 mg (10 mg/mL)	10 mg/mL vial/open-label	5 vials per carton/ open-label	Clear to opalescent colorless to pale yellow liquid, may contain particles.	2°C to 8°C. Protect from light and freezing.

5.2.3. Ipilimumab

5.2.3.1. Description and Administration

Subjects in Treatment Group A will receive ipilimumab 1 mg/kg as a 30-minute IV infusion (± 5 minutes) starting at Cycle 1 Day 1 and Q6W thereafter on Day 1 of every third treatment cycle (eg, Cycle 4, Cycle 7, etc). Intrasubject dose escalation of ipilimumab is not permitted. When administered on the same day, ipilimumab will be administered at least 30 minutes after the completion of the nivolumab infusion.

Details on the preparation and administration are provided in the Pharmacy Manual.

5.2.3.2. Supply, Packaging, and Labeling

The investigator will take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of ipilimumab in accordance with the protocol and any applicable laws and regulations. Ipilimumab clinical supplies will be provided by BMS and will be labeled in accordance with local regulatory requirements.

The ipilimumab product description is provided in Table 5. Refer to the ipilimumab IB for additional details.

Table 5: Ipilimumab Product Description

Product Description and Regimen Form	Potency	Primary Packaging Volume/ Label Type	Secondary Packaging/ Label Type	Appearance	Storage Conditions
Ipilimumab (BMS-734016) solution for injection.	200 mg/40 mL (5 mg/mL)	5 mg/mL vial/open-label	4 vials per carton/ open-label	Clear to slightly opalescent, colorless to pale yellow liquid, may contain particles.	2°C to 8°C. Protect from light and freezing.

5.2.4. Lirilumab

5.2.4.1. Description and Administration

Subjects in Treatment Group B will receive lirilumab 240 mg as a 60-minute IV infusion (± 5 minutes) starting at Cycle 1 Day 1 and Q4W thereafter on Day 1 of every other treatment cycle (eg, Cycle 3, Cycle 5, etc). Intrasubject dose escalation of lirilumab is not permitted. When administered on the same day, lirilumab will be administered at least 30 minutes after the completion of the nivolumab infusion.

Details on the preparation and administration are provided in the Pharmacy Manual.

5.2.4.2. Supply, Packaging, and Labeling

The investigator will take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of lirilumab in accordance with the protocol and any applicable laws and regulations. Lirilumab clinical supplies will be provided by BMS and will be labeled in accordance with local regulatory requirements.

The lirilumab product description is provided in Table 6. Refer to the lirilumab IB for additional details.

Table 6: Lirilumab Product Description

Product Description and Regimen Form	Potency	Primary Packaging Volume/ Label Type	Secondary Packaging/ Label Type	Appearance	Storage Conditions
Lirilumab (BMS-986015) solution for injection.	100 mg/10 mL (10 mg/mL)	10 mg/mL vial/open-label	6 vials per carton/ open-label	Clear to opalescent, colorless liquid, may contain few particles.	2°C to 8°C. Protect from light and freezing.

5.3. Treatment Compliance

Epacadostat is an oral medication, and compliance will be calculated by the sponsor based on the drug accountability documented by the site staff and monitored by the sponsor/designee (tablet counts). The objective is 100% compliance, and site staff should evaluate compliance at each visit and take appropriate steps to optimize compliance.

Nivolumab, ipilimumab, and lirilumab are administered as an IV infusion by site personnel. Receipt of infusions will be documented by the site staff and monitored by the sponsor/designee.

5.4. Treatment Interruptions and Adjustments

5.4.1. Dose Modifications

Modifications to epacadostat dosing are planned for the Phase 1 dose-escalation cohorts (see Section 4.1.1). Dose modifications in the form of interruption or discontinuation for any of the study treatment components (epacadostat, nivolumab, ipilimumab [Treatment Group A] or lirilumab [Treatment Group B]) may also be needed for individual subjects in the event of a DLT

or AE (related or unrelated to treatment). Intrasubject dose escalation for epacadostat, nivolumab, ipilimumab, or lirilumab is not permitted.

5.4.2. Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose

A DLT will be defined as the occurrence of any of the toxicities in Table 7 occurring from Cycle 1 Day 1 up to and including Day 42 for Treatment Groups A and B in Phase 1, except those with a clear alternative explanation (eg, disease progression) or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms based on investigator determination. Immune-related AEs of Grade 3 that improve to Grade 1 or lower within 14 days after the initiation of supportive care or corticosteroid therapy may be deemed a non-DLT. All DLTs will be assessed by the investigator using CTCAE v4.03 criteria.

To be evaluable for tolerability, subjects in Treatment Group A must receive at least 75% of planned epacadostat doses (63/84) at the specified dose level, 3 doses of nivolumab, and 1 dose of ipilimumab, or subjects must experience a DLT during the DLT observation period. Subjects in Treatment Group B must receive at least 75% of planned epacadostat doses (63/84) at the specified dose level, 2 doses of nivolumab, and 2 doses of lirilumab, or subjects must experience a DLT during the DLT observation period.

Individual subject dose reductions may be made based on events observed at any time during treatment with study drug; however, for the purposes of dose cohort escalation/de-escalation, expanding a dose cohort, and determining the MTD of epacadostat, decisions will be made based on events that are observed from the first day of study drug administration through the above-defined DLT observation period for each treatment group. A lower MTD may subsequently be determined based on relevant toxicities that become evident after the DLT observation period.

Table 7: Definition of Dose-Limiting Toxicity

Toxicity
Nonhematologic
• Any liver function abnormalities that meet the definition of Hy's law[a] • Any grade encephalopathy. • ≥ Grade 2 ocular irAEs. • Grade 4 irAEs will be considered a DLT regardless of duration. • Any ≥ Grade 3 nonhematologic toxicity EXCEPT: – Transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms. – Nausea, vomiting, and diarrhea adequately controlled with medical therapy within 48 hours. – Grade 3 rash in the absence of desquamation, with no mucosal involvement, that does not require systemic steroids and that resolves to Grade 1 in ≤ 14 days. – ≥ Grade 3 changes in amylase and lipase that is not associated with symptoms or clinical manifestations of pancreatitis. – Asymptomatic changes in lipid profiles. – Singular or nonfasting elevations in blood glucose (ie, blood glucose excursions will be considered toxicities if fasting blood glucose is elevated on 2 separate occasions). – Grade 3 irAE that improves to ≤ Grade 1 in ≤ 14 days by appropriate care or with corticosteroid therapy. – Grade 3 IRR that returns to Grade 1 in less than 6 hours
Hematologic
• ≥ Grade 3 thrombocytopenia with clinically significant bleeding (requires hospitalization, transfusion of blood products, or other urgent medical intervention). • Grade 4 neutropenia or thrombocytopenia lasting > 7 days. • ≥ Grade 3 febrile neutropenia (ANC < 1.0×10^9/L and fever > 101°F/38.3°C). • Grade 4 (life-threatening) anemia not explained by underlying disease.
General
• Subjects being unable to receive ≥ 75% of study drug doses during the DLT observation period because of toxicity, even if the toxicity does not meet DLT criteria defined above. ***Note:*** Exceptions include the DLT exclusions mentioned above. • Any death not clearly due to the underlying disease or extraneous causes.

Note: Transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms based on investigator determination will not be considered a DLT.

[a] Hy's law is defined as 1) ALT or AST elevation > 3 times ULN AND 2) total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase), AND 3) no other apparent possible causes of aminotransferase 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.

5.4.2.1. Management of Dose-Limiting Toxicities or Other Urgent Situations

In all cases, investigators may employ any measures or concomitant medications, after discussion with the sponsor (whenever possible), necessary to optimally treat the subject.

5.4.2.2. Follow-Up of Dose-Limiting Toxicities

Any DLT should be followed until it resolves to baseline or appears to have stabilized for a minimum of 30 days. During follow-up, subjects should be seen as often as medically indicated to assure safety.

5.4.3. Procedures for Cohort Review and Dose Escalation

Regular telephone conferences will be scheduled by the sponsor with study investigators in order to review cohort-specific data and overall safety data, to agree on dose escalation, adjudicate individual high-grade AEs as potentially dose-limiting, and guide other major study decisions.

5.4.4. Criteria and Procedures for Dose Interruptions and Adjustments of Study Treatment

General guidelines for management of toxicities are provided in Table 9. Study treatment may be delayed up to 4 weeks (28 days) to allow for resolution of toxicity. If a dose interruption is necessary, all study treatment components should be interrupted.

Subjects may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make further participation in the study unsuitable. The treating investigator should contact the sponsor to discuss the case of any subject whose treatment has been delayed for more than 4 weeks (28 days) before restarting treatment with the study drugs.

Individual decisions regarding dose interruption or reduction should be made using clinical judgment and in consultation with the sponsor's medical monitor, taking into account relatedness of the AE to the study drug and the subject's underlying condition. Adverse events that have a clear alternative explanation or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms may be exempt from dose-reduction rules.

Dose interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (eg, elective surgery, unrelated medical events, subject vacation, and/or holidays). Subjects should be placed back on study therapy within 4 weeks (28 days) of the scheduled interruption, unless otherwise discussed with the medical monitor. The reason for interruption should be documented in the subject's study record.

5.4.4.1. Epacadostat Dose Modifications

Table 8 describes epacadostat dose reductions that may occur due to any related AEs. Dose reductions should occur in a step-wise fashion from the initial starting dose of the cohort, and a maximum of 2 dose reductions of epacadostat are allowed for the management of an AE. If an AE recurs/does not return to baseline after the second dose reduction of epacadostat, then the subject must permanently discontinue epacadostat.

The lowest permissible dose of epacadostat is 25 mg BID. If a subject does not tolerate 25 mg BID, then the subject must permanently discontinue epacadostat. If epacadostat is discontinued after 2 dose reductions, or if a 25 mg BID dose is not tolerated, the subject may resume treatment with nivolumab monotherapy (or nivolumab with ipilimumab, if applicable) once criteria for restarting study treatment have been met with approval from the medical monitor.

Table 8: Dose Reductions of Epacadostat (Treatment Groups A and B)

Dose of Epacadostat	Dose Level -1 First Reduction of Epacadostat	Dose Level -2 Second Reduction of Epacadostat
100 mg BID	50 mg BID	25 mg BID
50 mg BID	25 mg BID	N/A – Discontinue Treatment
25 mg BID	N/A – Discontinue Treatment	N/A – Discontinue Treatment

5.4.4.2. Nivolumab, Ipilimumab, and Lirilumab Dose Modifications

There will be no dose reductions of nivolumab, ipilimumab, or lirilumab allowed for the management of toxicities of individual subjects. Doses of these agents are held for toxicity management, per Table 9. See Section 5.4.5 for dose modification and toxicity management guidelines pertaining to specific irAEs.

Table 9: General Guidelines for Interruption and Restarting of Study Treatment

CTCAE Grade/Severity	Hold Treatment (Y/N)	Timing for Restarting Treatment	Dose Level for Restarting Epacadostat	Dose Level for Restarting Nivolumab and Ipilimumab (Treatment Group A), or Nivolumab and Lirilumab (Treatment Group B)	Treatment Discontinuation
1-2 (Mild-moderate)	No	Continue treatment at the discretion of the investigator.	N/A – If held, restart at same dose.	NA - If held, restart at same dose.	N/A
3[a] (Severe)	Yes	Toxicity resolves to Grade 0-1.	Reduce by 1 dose level.[b]	Restart same dose.	Toxicity does not resolve within 4 weeks (28 days) of last dose, except by approval of the medical monitor. OR Second occurrence of previously resolved Grade 3 AE.
4[c] (Life-threatening)	Yes	Permanent discontinuation, except by approval of the medical monitor. If continuing, toxicity must resolve to Grade 0-1.	Permanent discontinuation, except by approval of the medical monitor. If continuing, reduce by 1 dose level.[b]	Permanent discontinuation, except by approval of the medical monitor.[c] If continuing, restart same dose.	Permanent discontinuation for any severe or life-threatening event, except by approval of the medical monitor.

[a] Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require a dose delay. It is recommended to consult with the medical monitor for Grade 3 amylase or lipase abnormalities.
[b] See Table 8 for epacadostat dose reduction guidelines. See Section 5.4.8 for study treatment withdrawal criteria.
[c] Isolated Grade 4 lipase or amylase abnormalities not associated with symptoms or clinical manifestations of pancreatitis may not require treatment discontinuation. Medical monitor should be consulted for any Grade 4 amylase or lipase abnormality.

5.4.5. Management of Immune-Related Adverse Events

Adverse events of a potential immunologic etiology or irAEs may be defined as an AE consistent with an immune phenomenon associated with drug exposure after all other etiologies have been eliminated. Immune-related AEs may be expected based on the nature of the study treatment, their mechanism of action, and reported experience with these and other immunotherapies. If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes before categorizing an AE as an irAE. Subjects who develop a ≥ Grade 2 irAE should be discussed immediately with the sponsor.

Elevations in amylase or lipase that are ≥ Grade 3 do not require dose interruption or reduction if the subject is asymptomatic or if the elevation is clinically insignificant or has been discussed with the medical monitor.

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested measures for the management of drug-related AEs with potential immunologic etiology are outlined in Table 10. Detailed management guidelines for specific irAEs can be in found in Section 5.4.5.1 through Section 5.4.5.7 and Appendix B. For each AE, attempts should be made to rule out other causes, including, but not limited to, metastatic disease or bacterial or viral infection, which might require specific supportive care.

Table 10: General Guidelines for Immune-Related Adverse Events

irAE	Guidance for Interrupting or Discontinuing Study Treatment	Guidance for Restarting Study Treatment	Supportive Care
Grade 1	No action.	Not applicable.	Provide symptomatic treatment.
Grade 2	May withhold study treatment per investigator's discretion.	May resume treatment if improves to Grade ≤ 1 within 6 weeks. If AE resolves within 4 weeks, subject may restart at the same dose and schedule. For an AE that does not resolve within 4 weeks, epacadostat should be reduced 1 dose level[a], but nivolumab and ipilimumab (Treatment Group A) or lirilumab (Treatment Group B) will be restarted at the same dose and schedule. If AE does not resolve within 6 weeks, study treatment with all study drugs should be discontinued or discussed with medical monitor.	Consider systemic corticosteroids in addition to appropriate symptomatic treatment.
Grade 3	Withhold study treatment until AE improves to Grade ≤ 1. Discontinue if unable to reduce corticosteroid dose to < 10 mg/day of prednisone or equivalent within 6 weeks of toxicity.	Any restart of study treatment must be discussed with medical monitor. Epacadostat should be reduced 1 dose level after AE has resolved to Grade ≤ 1.	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May use 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to ≤ Grade 1 and tapered over at least 4 weeks in most cases.
Grade 4	Discontinue study treatment.[a]	Not applicable. Any exceptions require medical monitor approval.	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May use 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to ≤ Grade 1 and tapered over at least 4 weeks in most cases.

[a] See Section 5.4.8 for study treatment withdrawal criteria.
Note: Detailed management guidelines for specific irAEs can be found in Sections 5.4.5.1 through 5.4.5.7.

5.4.5.1. Procedures and Guidelines for Pneumonitis

All study treatment should be interrupted in subjects with symptomatic pneumonitis and an immediate evaluation should be performed. The evaluation may include bronchoscopy to rule out other causes such as infection. If the subject is determined to have study drug−associated pneumonitis, the recommended treatment plan is detailed in Table 11.

Table 11: Guidelines for Management of Noninfectious Pneumonitis

Study Drug(s) Associated Pneumonitis	Withhold/Discontinue Nivolumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 1 (asymptomatic)	No action.	Not applicable.	Intervention not indicated.
Grade 2	Withhold study treatment.	**First episode of pneumonitis:** • If improves to near baseline: ○ Decrease the dose of epacadostat by 1 dose level; for nivolumab and ipilimumab (Treatment Group A) or lirilumab (Treatment Group B), restart at same dose and schedule subsequent cycles. • If not improved after 2 weeks or worsening permanently discontinue all study treatment. **Second episode of pneumonitis:** • Permanently discontinue all study treatment if, upon rechallenge, subject develops pneumonitis ≥ Grade 2.	Systemic corticosteroids are indicated. Taper if necessary.
Grade 3 and 4	Discontinue study treatment.	Not applicable. Any exceptions require medical monitor approval.	Systemic corticosteroids are indicated. The use of infliximab may be indicated as appropriate. See to Appendix B for additional recommendations.

Note: See Appendix B for additional guidance regarding management of noninfectious pneumonitis.

5.4.5.2. Procedures and Guidelines for Enterocolitis

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, mucus or blood in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic subjects, infectious etiologies should be ruled out and endoscopic evaluation should be considered for persistent or severe symptoms. All study treatment should be interrupted immediately for Grade ≥ 2 enterocolitis. Recommendations for management of enterocolitis are shown in Table 12, as well as additional information in Appendix B.

Table 12: Guidelines for Management of Enterocolitis

Study Drug(s) Associated Enterocolitis	Withhold/Discontinue Nivolumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 1	No action.	Not applicable.	All subjects who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. An antidiarrheal can be started.
Grade 2	Withhold study treatment.	May return to treatment if improves to ≤ Grade 1. If AE resolves within 4 weeks, subject may restart at the same dose and schedule for both nivolumab and ipilimumab (Treatment Group A) or lirilumab (Treatment Group B). For an AE that resolves to ≤ Grade 1 between 4 and 6 weeks after onset, epacadostat should be reduced 1 dose level, but nivolumab and ipilimumab (Treatment Group A) or lirilumab (Treatment Group B) may be restarted at the same dose and schedule. If AE does not resolve to ≤ Grade 1 within 6 weeks, all study treatment should be discontinued or discussed with medical monitor.	An antidiarrheal should be started. If symptoms are persistent for > 1 week, systemic corticosteroids should be initiated (eg, 0.5-1 mg/kg per day of prednisone or equivalent). When symptoms improve to ≤ Grade 1, corticosteroid taper should be started and continued over at least 1 month.
Grade 3 and 4	Discontinue study treatment.	Not applicable. Any exceptions require medical monitor approval.	Treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg per day of prednisone or equivalent. Systemic corticosteroids are indicated. The use of infliximab may be indicated as appropriate. When symptoms improve to ≤ Grade 1, corticosteroid taper should be started and continued over at least 1 month.

Note: See Appendix B for additional guidance regarding management of enterocolitis.

5.4.5.3. Procedures and Guidance for Hepatitis

Liver chemistry tests (hepatic transaminase and bilirubin levels) should be monitored and signs and symptoms of hepatotoxicity should be assessed before each dose of nivolumab and epacadostat. In subjects with hepatotoxicity, infectious or malignant causes should be ruled out and frequency of LFT monitoring should be increased until resolution. Recommendations for management of hepatitis are shown in Table 13 as well as additional information for management and follow-up in Appendix B.

Table 13: Recommended Approach for Handling Hepatitis

Study Drug(s) Associated Hepatitis	Withhold/Discontinue Nivolumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 1	No action.	Not applicable.	Increase frequency of LFT monitoring to twice per week until LFTs return to baseline, or consult with medical monitor. ***Note:*** Twice weekly testing is not required for subjects with Grade 1 LFT values at baseline until Grade ≥ 2 LFT elevations are observed.
Grade 2	Withhold study treatment.	If AE resolves to ≤ Grade 1 or baseline within 4 weeks, subject may restart at the same dose and schedule for both nivolumab and ipilimumab (Treatment Group A) or lirilumab (Treatment Group B). For an AE that resolves to ≤ Grade 1 between 4 and 6 weeks after onset, epacadostat should be reduced 1 dose level, but nivolumab and ipilimumab (Treatment Group A) or lirilumab (Treatment Group B) may be restarted at the same dose and schedule. If AE does not resolve to ≤ Grade 1 within 6 weeks, all study treatment should be discontinued.	Increase frequency of LFT monitoring to twice per week until LFTs return to baseline. If elevation persists for > 1 week, systemic corticosteroids should be initiated (eg, 0.5 mg/kg per day of prednisone or equivalent). When symptoms improve to ≤ Grade 1, corticosteroid taper should be started and continued over at least 1 month.
Grades 3 and 4	Discontinue study treatment.	Not applicable. Any exceptions require medical monitor approval.	Increase frequency of LFT monitoring to every 1-2 days. Treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg per day of prednisone or equivalent. When symptoms improve to ≤ Grade 1, corticosteroid taper should be started and continued over at least 1 month.

Note: See Appendix B for additional guidance regarding management of hepatitis.

5.4.5.4. Procedures for Immune-Mediated Dermatitis

Monitor subjects for signs and symptoms of dermatitis such as rash and pruritus. Unless an alternate etiology has been identified, signs or symptoms of dermatitis should be considered immune mediated. Recommendations for management of dermatitis are shown in Table 14 as well as additional information for management and follow-up in Appendix B.

Table 14: Recommended Approach for Handling Dermatitis

irAE	Withhold/Discontinue Nivolumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 1	No action.	Not applicable.	For mild to moderate dermatitis, such as localized rash and pruritus, treat symptomatically. Administer topical or systemic corticosteroids if there is no improvement of symptoms within 1 week.
Grade 2	No action.	Not applicable.	For mild to moderate dermatitis, such as localized rash and pruritus, treat symptomatically. Administer topical or systemic corticosteroids if there is no improvement of symptoms within 1 week.
Grades 3 and 4	Withhold study treatment in subjects with moderate to severe signs and symptoms of rash. Permanently discontinue study treatment in subjects with Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration or by necrotic, bullous, or hemorrhagic manifestations.	If AE resolves to baseline within 4 weeks, subject may restart at the same dose and schedule for both epacadostat and nivolumab and ipilimumab (Treatment Group A) or lirilumab (Treatment Group B). For an AE that resolves to ≤ Grade 1 between 4 and 6 after onset, epacadostat should be reduced 1 dose level, but nivolumab and ipilimumab (Treatment Group A) or lirilumab (Treatment Group B) may be restarted at the same dose and schedule. If AE does not resolve to ≤ Grade 1 within 6 weeks, all study treatment should be discontinued or discussed with medical monitor.	Administer systemic corticosteroids at a dose of 1 to 2 mg/kg per day of prednisone or equivalent. When dermatitis is controlled, corticosteroid tapering should occur over a period of at least 1 month.

Note: See Appendix B for additional guidance regarding management of dermatitis.

5.4.5.5. Procedures for Immune-Mediated Neuropathies

Subjects should be monitored for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. Recommendations for management of neuropathies are shown in Table 15 as well as additional information for management and follow-up in Appendix B.

Table 15: Recommended Approach for Handling Neuropathies

irAE	Withhold/Discontinue Nivolumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 1	No action.	Not applicable.	Provide symptomatic treatment.
Grade 2	May withhold study treatment.	If AE resolves to ≤ Grade 1 or baseline within 4 weeks, subject may restart at the same dose and schedule for epacadostat, nivolumab and ipilimumab (Treatment Group A) or lirilumab (Treatment Group B). For an AE that does not resolve within 4 weeks, epacadostat should be reduced 1 dose level but nivolumab ipilimumab (Treatment Group A) or lirilumab (Treatment Group B) may be restarted at the same dose and schedule. If AE does not resolve within 6 weeks, study treatment with both study drugs should be discontinued or discussed with medical monitor.	Consider systemic corticosteroids in addition to appropriate symptomatic treatment.
Grades 3 and 4	Discontinue study treatment.	Not applicable. Any exceptions require medical monitor approval.	Consider initiation of systemic corticosteroids at a dose of 1 to 2 mg/kg per day prednisone or equivalent for severe neuropathies. Institute medical intervention as appropriate for management of severe neuropathy.

Note: See Appendix B for additional guidance regarding management of neuropathies.

5.4.5.6. Procedures for Immune-Mediated Endocrinopathies

Subjects should be monitored for clinical signs and symptoms of hypophysitis, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism. Subjects may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension or with nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate etiology has been identified, signs or symptoms of endocrinopathies should be considered immune-mediated.

Thyroid function tests and clinical chemistries should be monitored at the start of treatment, before each dose, and as clinically indicated based on symptoms. In a limited number of subjects, hypophysitis has been diagnosed by imaging studies through enlargement of the pituitary gland. Recommendations for management of endocrinopathies are shown in Table 16. For additional information on detailed management of asymptomatic TSH elevation versus symptomatic endocrinopathy, see Appendix B.

Table 16: Recommended Approach for Handling Endocrinopathies

irAE	Withhold/Discontinue Nivolumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 1	No action.	Not applicable.	Provide symptomatic treatment.
Grade 2	May withhold study treatment.	If AE resolves within 4 weeks, subject may restart at the same dose and schedule for epacadostat, nivolumab, and ipilimumab (Treatment Group A) or lirilumab (Treatment Group B). For an AE that does not resolve within 4 weeks, epacadostat should be reduced 1 dose level but nivolumab and ipilimumab (Treatment Group A) or lirilumab (Treatment Group B) may be restarted at the same dose and schedule. If AE does not resolve within 6 weeks, study treatment should be discontinued.	Initiate systemic corticosteroids treatment at a dose of 1 to 2 mg/kg per day of prednisone or equivalent, and initiate appropriate hormone replacement therapy.
Grade 3	Withhold or discontinue study treatment.	If AE resolves or is controlled within 4 weeks, subject may restart at the same dose and schedule for epacadostat, nivolumab and ipilimumab (Treatment Group A) or lirilumab (Treatment Group B). For an AE that does not resolve within 4 weeks, epacadostat should be reduced 1 dose level, but nivolumab and ipilimumab (Treatment Group A) or lirilumab (Treatment Group B) may be restarted at the same dose and schedule. If AE does not resolve within 6 weeks, study treatment should be discontinued.	Consider initiating systemic corticosteroids treatment at a dose of 1 to 2 mg/kg per day of prednisone or equivalent, and initiate appropriate hormone replacement therapy.
Grade 4	Discontinue study treatment.	Not applicable. Any exceptions require medical monitor approval.	Consider initiation of systemic corticosteroids at a dose of 1 to 2 mg/kg per day of prednisone or equivalent, and initiate appropriate hormone replacement therapy.

Note: See Appendix B for additional guidance regarding management of endocrinopathies.

5.4.5.7. Procedures for Other Immune-Mediated Adverse Reactions, Including Ocular Manifestations

All study treatment should be permanently discontinued for severe immune-mediated adverse reactions. Systemic corticosteroids treatment should be initiated at a dose of 1 to 2 mg/kg per day of prednisone or equivalent for severe immune-mediated adverse reactions.

Corticosteroid eye drops should be administered to subjects who develop uveitis, iritis, or episcleritis. All study treatment should be permanently discontinued for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.

For additional management and follow-up guidance for renal immune events see Appendix B.

5.4.6. Procedure for Subjects Exhibiting Serotonin Syndrome

As noted in Section 1.2.1, there is a risk that epacadostat may cause an increase in serotonin levels in the brain that might trigger SS (Boyer and Shannon 2005) when administered in combination with other serotonergic agents. This syndrome has been most closely associated with use of MAOIs, meperidine, linezolid, or methylene blue; all of these agents are prohibited during the study. Selective serotonin reuptake inhibitors and SNRIs are permitted in the study. Serotonin syndrome usually manifests with autonomic changes, mental status changes, and neurological findings. These mild, moderate, and severe signs and symptoms of SS (summarized in Table 17) should be evaluated in the context of possible comorbid conditions as well.

The following procedures will be implemented if subjects exhibit the signs/symptoms of SS described in Table 17, including tremor; hyperreflexia; and spontaneous, ocular, or inducible clonus, together with agitation, fever, diaphoresis, or muscle rigidity:

- Immediately interrupt all treatment administration.
- Immediately interrupt any SSRI or SNRI administration.
- Provide appropriate medical management of the subject until all signs/symptoms are resolved (eg, IV fluids and/or sympathomimetic amines for hypotension, benzodiazepines for agitation, administration of 5-hydroxytryptamine antagonists, such as cyproheptadine).
- If etiologies other than SS are excluded, nivolumab and ipilimumab administration may be resumed unless other AE management guidelines apply for the specific event.
- If subject chooses to withdraw from the study or must restart treatment with SSRI or SNRI, the subject should be scheduled for a follow-up visit. Treatment with SSRI or SNRI may be initiated 2 weeks after resolution of signs and symptoms of SS.
- If a subject had experienced moderate or severe unconfounded SS in the opinion of the investigator, without concomitant SSRI or SNRI use, or serotonergic concomitant medications, only nivolumab/ipilimumab administration may be resumed; epacadostat treatment should be permanently discontinued.

Table 17: Sign and Symptoms of Serotonin Syndrome

Seriousness	Autonomic Signs	Neurological Signs	Mental Status	Other
Mild	Afebrile or low-grade fever Tachycardia Mydriasis Diaphoresis or shivering	Intermittent tremor Akathisia Myoclonus Mild hyperreflexia	Restlessness Anxiety	
Moderate	Increased tachycardia Fever (up to 41°C) Diarrhea with hyperactive bowel sounds Diaphoresis with normal skin color	Hyperreflexia Inducible clonus Ocular clonus (slow continuous lateral eye movements) Myoclonus	Easily startled Increased confusion Agitation and hypervigilance	Rhabdomyolysis Metabolic acidosis Renal failure Disseminated intravascular coagulopathy (secondary to hyperthermia)
Severe	Temperature often more than 41°C (Secondary to increased tone)	Increased muscle tone (lower limb > upper) Spontaneous clonus Substantial myoclonus or hyperreflexia	Delirium Coma	As above

Source: Boyer and Shannon 2005.

5.4.7. Management of Infusion Reactions

Table 18 shows treatment guidelines for subjects who experience an infusion reaction associated with administration of nivolumab, ipilimumab, or lirilumab. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 18: Infusion Reaction Treatment Guidelines

CTCAE Grade	Treatment	Premedication at Subsequent Dose Administration
Grade 1: Mild reaction; infusion interruption not indicated; intervention not indicated.	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable, in the opinion of the investigator.	None.
Grade 2: Requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	Stop infusion and monitor symptoms. Additional appropriate medical therapy may include, but is not limited to, the following: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate. Otherwise, dose administration will be held until symptoms resolve, and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study treatment.	Subject may be premedicated 1.5 h (± 30 min) before infusion with the following: • Diphenhydramine 50 mg orally (or equivalent dose of antihistamine). • Acetaminophen 500-1000 mg orally (or equivalent dose of antipyretic).
Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates). Grade 4: Life-threatening; pressor or ventilatory support indicated.	Stop infusion. Additional appropriate medical therapy may include, but is not limited to, the following: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable, in the opinion of the investigator. Hospitalization may be indicated. Subject is permanently discontinued from further study treatment.	No subsequent dose.

Note: Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.

5.4.8. Criteria for Permanent Discontinuation of Study Treatment

The occurrence of unacceptable toxicity not caused by the underlying malignancy will be presumed to be related to study treatment and will require that the study drug be permanently discontinued. Unacceptable toxicity is defined as follows:

- Grade 4 or life-threatening AEs, except with approval from the medical monitor.
- Toxicity requiring more than 2 dose reductions of epacadostat, or dose reductions below 25 mg BID.
- ≥ Grade 2 ocular irAE.
- Occurrence of an AE that is related to treatment with the study drug that, in the judgment of the investigator or the sponsor's medical monitor, compromises the subject's ability to continue study-specific procedures or is considered to not be in the subject's best interest.
- Persistent AE requiring a delay of therapy for more than 4 weeks (28 days) unless a greater delay has been approved by the sponsor.

5.5. Withdrawal of Subjects From Study Treatment

5.5.1. Withdrawal Criteria

Subjects may withdraw consent at any time for any reason or be withdrawn from study treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the sponsor if enrollment in the study is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

Subjects **must** be withdrawn from study treatment for the following reasons:

- The subject becomes pregnant.
- Consent is withdrawn. Subjects may choose to withdraw from the study at any time without penalty of jeopardizing their health care or loss of benefits to which the subject is otherwise entitled.

  Note: Consent withdrawn means that the subject can no longer be followed and no additional data can be collected.
- Further participation would be injurious to the subject's health or well-being, in the investigator's medical judgment.
- Unacceptable toxicity (see Section 5.4.8). Subjects with unacceptable toxicities must be withdrawn from study treatment but will continue in the safety follow-up period of the study (see Section 6.4).
- The subject has received study treatment for 2 years (ie, 24 months have elapsed since Cycle 1 Day 1).
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

A subject **may** be discontinued from study treatment as follows:

- Radiographic progression of disease per RECIST v1.1 (see Appendix E). A subject may continue on treatment after radiographic progression is confirmed per RECIST v1.1 if clinically stable or clinically improved, pending confirmation of disease progression [redacted] (see Sections 5.5.1.1 and 7.6.1).
- If, during the course of the study, a subject is found not to have met eligibility criteria (see Section 3), the medical monitor, in collaboration with the investigator, will determine whether the subject should be withdrawn from the study.
- If a subject is lost to follow-up or noncompliant with study procedures or study treatment in the investigator's opinion, the sponsor should be consulted for instruction on handling the subject.

5.5.1.1. Treatment After Initial Evidence of Radiologic Evidence of Disease Progression

Immunotherapeutic agents may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest as a clinical response after an initial increase in tumor burden or the appearance of new lesions.

[redacted]

Subjects may receive study treatment pending confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of clinically significant signs and symptoms (including worsening of laboratory values) indicating disease progression.
- No decline in ECOG performance status.
- No requirement for intensified management of disease-related symptoms.
- Absence of rapid progression of disease.
- Absence of progressive tumor at critical anatomical sites (eg, spinal cord compression) requiring urgent alternative medical intervention.

Subjects who are clinically unstable are not required to have repeat imaging for the confirmation of PD.

If a follow-up scan was not performed after unconfirmed PD (eg, due to patient refusal or patient death), the initial date of unconfirmed progression will be considered the date of PD.

Table 19: Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
Initial unconfirmed progressive disease (iUPD) OR subsequent iUPD after iSD, iPR or iCR.	Repeat imaging at ≥ 4 and ≤ 8 weeks to confirm PD.	May continue study treatment at the investigator's discretion while awaiting confirmatory scan.	Repeat imaging at ≥ 4 weeks to confirm PD if possible.	Discontinue treatment.
Next evaluable scan confirms PD (iCPD).	No additional imaging required.	Discontinue treatment.	No additional imaging required.	N/A
Repeat scan shows iUPD, iSD, iPR, or iCR.[a]	Continue regularly scheduled imaging assessments at 8 and 16 weeks after the start of treatment and then every 12 weeks (± 7 days) thereafter.	Continue study treatment at the investigator's discretion.	Continue regularly scheduled imaging assessments at 8 and 16 weeks after the start of treatment and then every 12 weeks (± 7 days) thereafter.	May restart study treatment if condition has improved and/or is clinically stable per investigator's discretion.

[a] iSD, iPR, and iCR is based on baseline or nadir.

In determining whether the tumor burden has increased or decreased, investigators should consider all baseline and any new target lesions as well as baseline and any new nontarget lesions.

Progressive disease (iCPD) is confirmed if further increase in tumor burden, compared to the last assessment, is seen as evidenced by one or more of the following:

- Continued increase in tumor burden (from iUPD) where RECIST 1.1 definitions of progression had been met (from nadir) in target, nontarget disease or new lesions
  - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum;
  - Continued unequivocal progression in nontarget disease with an increase in tumor burden;
  - Increase in size of previously identified new lesion(s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions
- RECIST v1.1 criteria are met in lesions types (target or nontarget or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR, or iCR if those criteria are met compared to baseline). As can be seen in Table 19, the prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response providing that iCPD is not documented at the next assessment after iUPD.

5.5.2. Withdrawal Procedures

In the event that the decision is made to permanently discontinue the study drug, the subject will be withdrawn from the study and the EOT visit should be conducted. Reasonable efforts should be made to have the subject return for the safety follow-up visit (see Section 6.4). The last date of the last dose of study drug and the reason for subject withdrawal will be recorded in the eCRF.

If a subject is withdrawn from all study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for withdrawal must be documented in the subject's medical record and in the eCRF.

  Note: The reason for withdrawal from treatment may be different than the reason for withdrawal from study.
- The EOT visit should be performed.
- The date of the EOT visit should be recorded in the eCRF and IRT.
- Subjects must be followed for safety until the time of the follow-up visit or until study drug–related toxicities resolve, return to baseline, or are deemed irreversible, or until the subject begins new anticancer therapy, whichever is longest.

If the subject discontinues study treatment and actively withdraws consent for collection of follow-up data (safety follow-up), then no additional data collection should occur; however, subjects will have the option of withdrawing consent for study treatment but continuing in the safety follow-up period.

5.6. Concomitant Medications

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the study. If there is a clinical indication for one of these or other medications, discontinuation from study therapy may be required. The investigator should discuss any questions regarding this with the sponsor. The final decision on any supportive therapy rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on study therapy requires the mutual agreement of the investigator, the sponsor, and the subject.

All concomitant medications received within 28 days before the first dose of study treatment and 30 days after the last dose of study treatment should be recorded. Concomitant medications administered in the 30 days after the last dose of study treatment should be recorded for SAEs and AEs as defined in Section 8.

5.6.1. Permitted Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the eCRF, including all prescription, over-the-counter, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug regimen, frequency, route, and date may also be included on the eCRF.

5.6.2. Restricted Medications

- Systemic steroids may be used at doses ≤ 10 mg/day prednisone or equivalents.
- Use of coumarin-based anticoagulants is discouraged. Low-dose warfarin (1 mg) is acceptable; however, doses that increase the INR are discouraged and will require dose modification. If an alternative to coumarin-based anticoagulants cannot be used, dose modifications of the warfarin may be needed. Based on the observed magnitude of epacadostat/warfarin PK interaction and PK/pharmacodynamic modeling results, for an epacadostat dose of 300 mg BID, the dose of warfarin should be reduced by approximately one-third after initiation of epacadostat administration based on approximately 30% to 40% reduction in S- and R-warfarin oral clearance values. Close INR monitoring is recommended for subjects on a stable dose of warfarin who are starting treatment with epacadostat. Based on PK/pharmacodynamic modeling, recommendations for warfarin dose modifications for subjects receiving other epacadostat doses are summarized in Table 20 based on the INR before starting epacadostat.

Table 20: Recommendations for Warfarin Dose Modifications

Stable Baseline INR	Epacadostat Dose		
	≤ 100 mg BID	**200 mg BID**	**300 mg BID**
INR ≤ 2.5	Close INR monitoring	Close INR monitoring	Reduce warfarin by ~33% and monitor INR
INR > 2.5	Close INR monitoring	Reduce warfarin by 20%-25% and monitor INR	Reduce warfarin by ~33% and monitor INR

- Use of the anticonvulsant carbamazepine (a UGT1A9 inducer) is prohibited; an alternative to carbamazepine should be used, if possible.

5.6.3. Prohibited Medications

Subjects are prohibited from receiving the following therapies starting from screening through EOT period of this study unless otherwise noted below:

- Any investigational medication other than the study drugs.
- Any anticancer medications, including chemotherapy or biologic therapy other than the study medications.
- Any chronic immunosuppressive treatment for any reason. (***Note:*** Inhaled or topical steroids are allowed, and systemic steroids at doses ≤ 10 mg/day of prednisone or equivalents are allowed, as described in Section 5.6.2, and immune suppressants are allowed for short-term treatment for immune toxicities or as prophylaxis for contrast allergy for imaging procedures.)
- Radiation therapy.

  Note: In the presence of a mixed response (some lesions improving or stable and other lesions progressing), radiation therapy to a symptomatic solitary lesion or to the brain is allowed.

- Administration of a live attenuated vaccine within 30 days before the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines are live attenuated vaccines and are not allowed.
- Any MAOI or drug associated with significant MAOI activity agents is prohibited from 21 days before Day 1 through 2 weeks after the final dose of epacadostat has been administered (see Appendix D).
- Any immunologic-based treatment for any reason from screening through follow-up visit is prohibited.

  Note: Completed adjuvant therapy (eg, vaccines) with medical monitor approval, inhaled or topical steroids, and systemic steroids at doses ≤ 10 mg/day prednisone equivalents are allowed, as described in Section 5.6.2.
- Any UGT1A9 inhibitor or inducer, including aceclofenac, acitretin, amitriptyline, androsterone, carbamazepine, cyclosporine, dasatinib, diclofenac, diflunisal, efavirenz, erlotinib, estradiol (17-beta), flutamide, gefitinib, gemfibrozil, glycyrrhetinic acid, glycyrrhizin, imatinib, imipramine, ketoconazole, lamotrigine, linoleic acid supplements, mefenamic acid, mycophenolic acid, niflumic acid, nilotinib, oxcarbazepine, phenobarbital, phenylbutazone, phenytoin, probenecid propofol, quinidine, rifampin, ritonavir, sorafenib, sulfinpyrazone, valproic acid, and verapamil.

  Note: Propofol, when used for short-term sedation during surgical/biopsy procedures, is allowed after consultation with the medical monitor. The epacadostat dose may be taken on the morning of the procedure, and the evening dose held following the procedure. Epacadostat may be resumed the next day.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. Subjects may receive other medications that the investigator deems to be medically necessary.

The exclusion criteria (Section 3.2) describe other medications that are prohibited during this study. There are no prohibited therapies during the post-treatment follow-up period.

6. STUDY ASSESSMENTS

All study assessments will be performed as indicated in the schedule of clinical assessments (Table 21 and Table 23), and all laboratory assessments will be performed as indicated in Table 22 and Table 24. Table 25 presents a summary of local clinical laboratory analytes to be assessed. The order of assessments is suggested by the order of mention within the schedule. See Section 7 for instructions on each assessment. Further details of study procedures and assessments can be found in the Study Reference Manual.

Table 21: Schedule of Clinical Assessments – Treatment Group A (Epacadostat + Nivolumab + Ipilimumab)

Visit	Screening	Treatment Period (14-Day Cycles)				EOT	Safety Follow-Up[b]		Comments
		Cycles 1 Through 3		Cycle 4 and Beyond	Disease Status[a]				
		Day 1	Day 8	Day 1	See Footnote a		30 Days After EOT	100 Days After EOT	
Evaluation/Window	**Days -28 to -1**	**± 3 Days**	**± 1 Day**	**± 3 Days**	**± 7 Days**	**+ 7 Days**	**+ 7 Days**	**± 7 Days**	
Administrative Procedures									
Informed consent	X								
Contact IRT	X	X		X		X			
Inclusion/exclusion criteria	X	X							
Prior medical and cancer history	X								
Prior and concomitant medications	X	X	X	X		X	X	X	
Reminder card		X	X	X		X	X		
Clinical Procedures/Assessments									
Comprehensive physical examination and height	X								
Targeted physical examination		X	X[b]	X		X	X	X	
Vital signs and weight	X	X	X	X		X	X	X	
ECOG performance status	X								
Laboratory assessments	X	X	X	X		X	X		See Table 22 for required laboratory assessments.
12-Lead ECG	X	X*				X			* Cycle 1 Day 1 and Cycle 2 Day 1. See Section 7.5.4 for details.
AE assessment	X	X	X	X		X	X	X	
Tumor tissue collection	X								**Only** Phase 1 subjects. See Table 22 for Phase 2 fresh biopsy collection timepoints.

Table 21: Schedule of Clinical Assessments – Treatment Group A (Epacadostat + Nivolumab + Ipilimumab) (Continued)

Visit	Screening	Treatment Period (14-Day Cycles)				EOT	Safety Follow-Up[b]		Comments
		Cycles 1 Through 3		Cycle 4 and Beyond	Disease Status[a]				
		Day 1	Day 8	Day 1	Q8W		30 Days After EOT	100 Days After EOT	
Evaluation/Window	**Days -28 to -1**	**± 3 Days**	**± 1 Day**	**± 3 Days**	**± 7 Days**	**+ 7 Days**	**+ 7 Days**	**± 7 Days**	
Study Drug Administration									
Administer epacadostat in clinic		X	X						[redacted] Epacadostat should be administered before nivolumab and ipilimumab.
Administer nivolumab		X		X					Nivolumab should be administered before ipilimumab at applicable visits.
Administer ipilimumab		X		X					Ipilimumab will be administered on Cycle 1 Day 1 and then on Day 1 of every 3rd cycle (Cycles 4, 7, 10, etc).
Efficacy Assessments									
Radiologic tumor assessments	X				X				The same imaging technique should be used in a subject throughout the study. If imaging shows PD, an imaging assessment should be performed at a minimum of 4 weeks and maximum of 8 weeks later to confirm PD [redacted] See Section 7.6 for complete details on imaging requirements.

[a] On-study imaging will be performed at 8 and 16 weeks (± 7 days) after the start of treatment and then every 12 weeks (± 7 days) thereafter until the end of study treatment. Imaging should follow calendar days starting with Day 1 of study treatment and should NOT be adjusted for delays in cycle starts.

[b] The mandatory safety follow-up visits should be conducted approximately 30 and 100 days after the last dose of study treatment or before the initiation of a new anticancer treatment, whichever comes first.

[c] Only required for Day 8 visits if there are ongoing AEs > Grade 2.

Table 22: Schedule of Laboratory Assessments – Treatment Group A (Epacadostat + Nivolumab + Ipilimumab)

Visit	Screening	Treatment Period (14-Day Cycles)			EOT	Follow-Up	Comments
		Cycles 1 Through 3		Cycle 4 and Beyond		30 Days After EOT	
		Day 1	Day 8	Day 1			
Evaluation/Window	**Days -28 to -1**	**± 3 Days**	**± 1 Day**	**± 3 Days**	**+ 7 Days**	**+ 7 Days**	
Local Laboratory Tests[a]							
Serum chemistry	X	X	X	X	X	X	Additional assessment of serum chemistry as clinically indicated.
Hematology with differential	X	X		X	X	X	Additional assessment of hematology as clinically indicated.
Liver chemistry tests	X	X	X	X	X	X	If baseline liver chemistry tests are WNL and increase to ≥ Grade 1, testing should be performed twice weekly until resolved to baseline. If baseline liver chemistry tests were Grade 1 at baseline and increase to ≥ Grade 2, twice weekly testing should be performed until resolved to ≤ Grade 1.
Coagulation panel	X			X	X		Screening, Cycle 4, and every 3rd cycle thereafter.
Endocrine function tests	X			X	X	X	Screening, Cycle 4, and every 3rd cycle thereafter.
Urinalysis	X				X		
Hepatitis B and C	X						
Serum pregnancy test[b] (childbearing females only)	X				X		Required for all women of childbearing potential during screening; must be within 72 hours before the first dose of study treatment.
[redacted]							

[a] All safety laboratory assessments will be performed locally.
[b] Urine pregnancy tests may be conducted at additional time points as medically indicated.

Table 23: Schedule of Clinical Assessments – Treatment Group B (Epacadostat + Nivolumab + Lirilumab)

Visit	Screening	Treatment Period (14-Day Cycles)				EOT	Follow-Up					Comments
		Cycles 1 Through 3		Cycle 4 and Beyond	Disease Status[a]		Safety[b]			Disease Status[c]	Survival	
		Day 1	Day 8	Day 1	Q8W		30 Days After EOT	100 Days After EOT	150 Days After EOT	Q8W	Q12W	
Evaluation/Window	**Days -28 to -1**	**± 3 Days**	**± 1 Day**	**± 3 Days**	**± 7 Days**	**+ 7 days**	**+ 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	**± 7 Days**	
Administrative Procedures												
Informed consent	X											
Contact IRT	X	X		X		X						
Inclusion/exclusion criteria	X	X										
Prior medical and cancer history	X											
Prior and concomitant medications	X	X	X	X		X	X	X	X			
Reminder card		X	X	X		X	X	X				
Poststudy anticancer therapy status							X	X	X	X	X	
Survival status											X	
Clinical Procedures/Assessments												
Comprehensive physical examination and height	X											
Targeted physical examination		X	X[d]	X		X	X	X	X			Only required for Day 8 visits if there are ongoing AEs > Grade 2.
Vital signs and weight	X	X	X	X		X	X	X	X			
ECOG performance status	X	X		X			X	X	X			
Laboratory assessments	X	X	X	X		X	X					See Table 22 for required laboratory assessments.
HPV status	X											Subjects with SCCHN (oropharyngeal only) must have documentation of HPV status (eg, p16 expression).
12-Lead ECG	X	X*				X						* Cycle 1 Day 1 and Cycle 2 Day 1. See Section 7.5.4 for details.
AE assessment	X	X	X	X		X	X	X	X			
Tumor tissue collection	X											**Only** Phase 1 subjects. See Table 24 for Phase 2 fresh biopsy collection timepoints.

Table 23: Schedule of Clinical Assessments – Treatment Group B (Epacadostat + Nivolumab + Lirilumab) (Continued)

		Treatment Period (14-Day Cycles)					Follow-Up					
		Cycles 1 Through 3		Cycle 4 and Beyond	Disease Status[a]		Safety[b]			Disease Status[c]	Survival	
Visit	Screening	Day 1	Day 8	Day 1	Q8W	EOT	30 Days After EOT	100 Days After EOT	150 Days After EOT	Q8W	Q12W	
Evaluation/Window	Days -28 to -1	± 3 Days	± 1 Day	± 3 Days	± 7 Days	+ 7 days	+ 7 Days	± 7 Days	± 7 Days	± 7 Days	± 7 Days	Comments
Study Drug Administration												
Administer epacadostat in clinic		X	X									Epacadostat will be administered in the clinic for visits [redacted] (Cycle 1 Day 1, Cycle 1 Day 8, Cycle 2 Day 1). Epacadostat should be administered before nivolumab and lirilumab.
Administer nivolumab		X		X								Nivolumab should be administered before lirilumab at applicable visits.
Administer lirilumab		X		X								Lirilumab will be administered on Cycle 1 Day 1 and then Day 1 of every other cycle (Cycles 3, 5, 7, etc).
Efficacy Assessments												
Radiologic tumor assessments	X				X					X		The same imaging technique should be used in a subject throughout the study. If imaging shows PD, an imaging assessment should be performed at a minimum of 4 weeks and maximum of 8 weeks later to confirm PD [redacted]. See Section 7.6 for complete details on imaging requirements.

[a] On-study imaging will be performed every 8 weeks (± 7 days) for the first 12 months and then every 12 weeks (± 7 days) thereafter. Imaging should follow calendar days starting with Day 1 of study treatment and should NOT be adjusted for delays in cycle starts.

[b] The mandatory safety follow-up visits should be conducted approximately 30, 100, and 150 days after the last dose of study treatment or before initiation of a new anticancer treatment, whichever comes first.

[c] For subjects who discontinue treatment for reasons other than disease progression, every effort should be made to continue monitoring their disease status every 8 weeks (± 7 days) for the first 12 months after the start of treatment and then every 12 weeks (± 7 days) thereafter by radiographic imaging until 1) start of new anticancer therapy, 2) confirmed disease progression, 3) death, 4) the end of the study, or 5) withdrawal of consent, whichever occurs first.

[d] Only required for Day 8 visits if there are ongoing AEs > Grade 2.

Table 24: Schedule of Laboratory Assessments – Treatment Group B (Epacadostat + Nivolumab + Lirilumab)

Visit	Screening	Treatment Period (14-Day Cycles)			EOT	Follow-Up	Comments
		Cycles 1 Through 3		Cycle 4 and Beyond		30 Days After EOT	
		Day 1	Day 8	Day 1			
Evaluation/Window	**Days -28 to -1**	**± 3 Days**	**± 1 Day**	**± 3 Days**	**+ 7 Days**	**± 7 Days**	
Local Laboratory Tests[a]							
Serum chemistry	X	X	X	X	X	X	Additional assessment of serum chemistry as clinically indicated.
Hematology with differential	X	X		X	X	X	Additional assessment of hematology as clinically indicated.
Liver chemistry tests	X	X	X	X	X	X	If baseline liver chemistry tests are WNL and increase to ≥ Grade 1, testing should be performed twice weekly until resolved to baseline. If baseline liver chemistry tests were Grade 1 at baseline and increase to ≥ Grade 2, twice weekly testing should be performed until resolved to ≤ Grade 1.
Coagulation panel	X			X	X		Screening, Cycle 4, and every 3rd cycle thereafter.
Endocrine function tests	X			X	X	X	Screening, Cycle 4, and every 3rd cycle thereafter.
Urinalysis	X				X		
Hepatitis B and C	X						
Serum pregnancy test[b] (childbearing females only)	X				X		Required for all women of childbearing potential during screening and must be within 72 hours before the first dose of study treatment.
[redacted]							

Table 24: Schedule of Laboratory Assessments – Treatment Group B (Epacadostat + Nivolumab + Lirilumab) (Continued)

Visit	Screening	Treatment Period (14-Day Cycles)			EOT	Follow-Up	Comments
		Cycles 1 Through 3		Cycle 4 and Beyond		30 Days After EOT	
		Day 1	Day 8	Day 1			
Evaluation/Window	Days -28 to -1	± 3 Days	± 1 Day	± 3 Days	+ 7 Days	± 7 Days	
[redacted]							

[a] All safety laboratory assessments will be performed locally.
[b] Urine pregnancy tests may be conducted at additional time points as medically indicated.

Table 25: Local Laboratory Tests: Required Analytes

Serum Chemistries	Hematology	Urinalysis	Hepatitis Screening	Endocrine Function Tests
Albumin Bicarbonate Blood urea nitrogen Calcium Chloride Creatinine Glucose Lactate dehydrogenase Phosphate Potassium Sodium Total protein Uric acid Amylase Lipase	Complete blood count, including: • Hemoglobin • Hematocrit • Platelet count • Red blood cell count • White blood cell count Differential count, including: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils Absolute values must be provided for: • Lymphocytes • Neutrophils	Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein	Hepatitis B surface antigen HBV-DNA HCV-RNA **or** HCV antibody where is HCV RNA is not SOC	Adrenocorticotropic hormone Serum cortisol (9 AM)[a] Luteinizing hormone[b] Prolactin TSH Free thyroxine (T4) Total triiodothyronine (T3) Serum testosterone (9AM)[a,b]
Liver Chemistry Tests			**Pregnancy Testing**	**Coagulation**
Alkaline phosphatase ALT AST Total bilirubin Direct bilirubin (if total bilirubin is elevated above ULN)			Female subjects of childbearing potential only require a serum test at screening. Pregnancy tests (serum or urine) should be repeated if required by local regulations.	PT or INR aPTT or PTT

[a] Serum cortisol and testosterone ideally should be drawn close to 9 AM but can be performed any time before 12 PM.
[b] Not needed in women, surgically castrated men, or men taking LH-releasing hormone agonist therapy.

6.1. Screening

Screening is the interval between signing the ICF and the day when the subject is enrolled and receives the first dose of study treatment (Cycle 1 Day 1); the total screening period must not exceed 28 days. Informed consent must be obtained before performing any study-specific procedures that are not considered standard of care. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process.

Procedures conducted as part of the subject's routine clinical management (eg, blood count, imaging) and obtained before the signing of informed consent may be used for screening or baseline purposes, provided the procedure meets the Protocol-defined criteria and has been performed in the timeframe of the study. All information associated with eligibility requirements must be entered into the appropriate eCRF pages.

Results from the screening visit evaluations will be reviewed to confirm subject eligibility before enrollment or administration of study treatment. Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the results to be in error. For screening assessments that are repeated, the most recent available result before enrollment will be used to determine subject eligibility. Additionally, a subject who fails screening may repeat the screening process 1 time if the investigator believes there has been a change in eligibility status.

6.2. Treatment

The treatment period begins on the day the subject receives the first dose of study treatment (Cycle 1 Day 1) through the point at which the investigator determines the subject will be permanently discontinued from study treatment. Cycle 1 Day 1 must be no more than 28 days after the subject has signed the ICF and no more than 3 days after the date of enrollment into the study (ie, enrollment in the IRT system). At Cycle 1 Day 1, results from screening visit evaluations should be reviewed to determine whether the subject continues to meet the eligibility requirements as specified in the Protocol. Subjects will have regularly scheduled study visits as outlined in Table 21 and Table 22 (as applicable to treatment group assignment), and toxicities will be monitored continuously and will be graded using NCI CTCAE v4.03.

6.3. End of Treatment

When the subject permanently discontinues all components of study treatment, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data from the EOT visit should be entered into the eCRF. The subject should be encouraged to return for the safety follow-up visit.

6.4. Follow-Up

6.4.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visits, which should occur approximately 30 days (+ 7 days), 100 days (± 7 days), and 150 days

(± 7 days; Treatment Group B only) after the EOT visit (or after the last dose of study treatment if the EOT visit was not performed). Adverse events and SAEs must be reported up until at least 100 days after the last dose of study treatment for Treatment Group A, up until at least 150 days after the last dose of study treatment for Treatment Group B, or until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the subject return for the follow-up visits and to report any AEs that may occur during this period. If a subject is scheduled to begin a new anticancer therapy before the end of the safety follow-up period, the applicable safety follow-up visit should be performed before new anticancer therapy is started. After the safety follow-up period, there will be no additional assessments and the study will be considered complete.

6.5. End of Study

Subjects will be considered as having completed the study if they meet any of the following criteria:

- Subject dies, and a date of death is available.
- Subject is known to have died; however, the date of death cannot be obtained.

  Note: Every effort must be made to obtain the date of death.
- Consent is withdrawn for any further contact related to this study.
  - Subjects may choose to withdraw from the study at any time without penalty of jeopardizing their health care or loss of benefits to which they are otherwise entitled. Every reasonable effort should be made to determine the reason a subject withdraws prematurely, and this information should be recorded in the eCRF.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.
- The subject completes the safety follow-up period.

6.6. Unscheduled Visits

Unscheduled study visits may occur at any time if medically warranted. Any assessments performed at those visits should be recorded in the eCRF.

7. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

7.1. Administration of Informed Consent Form

Valid informed consent must be obtained from the study subject before conducting any study-specific procedures using an ICF approved by the local IRB/IEC that contains all elements required by ICH E6, and describes the nature, scope, and possible consequences of the study in a form understandable to the study subject. Local and institutional guidelines for ICF content and administration must be followed; the original signed ICF must be retained by the investigator, and a copy of the signed ICF must be provided to the study subject. The informed consent process for each subject must be documented in writing within the subject source documentation. Subjects of childbearing potential must agree to take appropriate measures to avoid pregnancy in order to participate in the study (see Appendix A).

7.2. Interactive Response Technology Procedure

IRT will be contacted to obtain a subject identification number when a subject enters the screening period. Upon determining that the subject is eligible for study entry, IRT will be contacted to enroll the subject and obtain treatment group assignment. Additionally, IRT will be contacted at each Day 1 visit during the treatment period, as appropriate, to update the relevant treatment supply. IRT will also be contacted at the last dose of study treatment.

7.3. Demography and Medical History

7.3.1. Demographics and General Medical History

Demographic data and a complete medical and medication history will be collected at screening by the investigator or qualified designee and will include date of birth, race, ethnicity, medical and surgical history, and current illnesses. Medical history should include all active conditions and any condition considered to be clinically significant by the investigator.

7.3.2. Disease Characteristics and Treatment History

Details regarding the disease for which the subject has enrolled in this study (eg, date of diagnosis, primary tumor histology, previous systemic therapies, surgeries, radiation therapy, and stage of cancer) will be collected at screening. In addition, disease-relevant biomarker information is required where available (eg, NSCLC: EGFR, BRAF, ALK, and ROS1 status; MEL: V600-activating BRAF mutation status; SCCHN: HPV status, p16 status [if primary tumor location is oropharynx]; PDAC: CA 19-9 level; CRC: MSI status, CEA level; gastric cancer: EBV status, H. pylori status, CA 19-9 level; ovarian cancer: BRCA1 and BRCA2 status, CA 125 level). These items will be recorded separately and will not be listed in medical history.

7.4. Prior and Concomitant Medications and Procedures

Prior and concomitant medications and procedures will be reviewed to determine subject eligibility. Any medication received or procedure performed within 28 days before Cycle 1

Day 1 up to the end of the safety follow-up period or until the subject starts a new anticancer therapy, whichever occurs first, will be recorded in the eCRF. The medication record will be maintained after signing the ICF to document concomitant medications, including any changes to the dose or regimen. Concomitant medications include any prescription, over-the-counter, or natural/herbal preparations taken or administered during the study period. Concomitant treatments and/or procedures that are required to manage a subject's medical condition during the study will also be recorded in the eCRF. See Section 5.6 for details regarding restricted and prohibited medications.

7.5. Safety Assessments

7.5.1. Adverse Events

Adverse events will be monitored from the time the subject signs the ICF. Subjects will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study. In order to avoid bias in eliciting AEs, subjects will be asked general, nonleading questions such as "How are you feeling?" All AEs (serious and nonserious) must be recorded on the source documents and eCRFs regardless of the assumption of a causal relationship with the study drug. The definition, reporting, and recording requirements for AEs are described in Section 8.

7.5.2. Physical Examinations

Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

Physical examinations must be performed by a medically qualified individual such as a licensed physician, physician's assistant, or an advanced registered nurse practitioner, as local law permits.

7.5.2.1. Comprehensive Physical Examination

The comprehensive physical examination will include height and the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; lymph nodes; and a brief neurologic examination. Clinically significant abnormal findings before Cycle 1 Day 1 should be recorded as medical history. New clinically significant abnormal findings observed after Cycle 1 Day 1 should be recorded as AEs.

7.5.2.2. Targeted Physical Examination

The targeted physical examination will be a symptom-directed evaluation conducted by the investigator or a medically qualified designee. The targeted physical examination will include assessment(s) of the body systems or organs, as indicated by subject symptoms, AEs, or other findings.

7.5.3. Vital Signs and Weight

Vital sign measurements include blood pressure, pulse, respiratory rate, body temperature, and weight. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

7.5.4. 12-Lead Electrocardiograms

Baseline 12-lead ECGs will be obtained at screening, with additional ECGs obtained at EOT, and as clinically indicated for all subjects. Additional triplicate ECGs will also be obtained at Cycle 1 Day 1 predose and 2 hours after the first dose of epacadostat, and at Cycle 2 Day 1 predose and 2 hours after administration of epacadostat (see Table 26). [redacted] Clinically significant abnormal findings at screening will be recorded as medical history. Clinically significant abnormal findings after the first dose of study treatment should be recorded as an AE. All 12-lead ECGs will be performed with the subject in a recumbent or semirecumbent position after 5 minutes of rest.

The 12-lead ECG readings will be interpreted by the investigator at the site to be used for immediate subject management. The decision to include or exclude a subject or to withdraw a subject from the study treatment based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the medical monitor, as appropriate. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs. In the event that a single QTc is > 480 msec at screening, the subject may enroll if the average QTc for 3 consecutive ECGs is < 480 msec or with approval from the medical monitor. Prolonged QTc intervals must be read by a cardiologist. For subjects with an intraventricular conduction delay (QRS interval > 120 msec) at screening, the JTc interval may be used in place of the QTc with medical monitor approval. In addition, the JTc interval should be used for all subsequent assessments.

Table 26: Schedule of ECG Assessments

Timepoint	Screening	Cycle 1 Day 1	Cycle 2 Day 1	EOT
Predose	X	X – triplicate	X - triplicate	X
2 hours (± 5 min) after epacadostat dose	N/A	X – triplicate	X - triplicate	N/A

7.5.5. Laboratory Assessments

Screening laboratory assessments must be performed within 7 days of Cycle 1 Day 1. If performed more than 7 days before Cycle 1 Day 1, then the tests must be repeated and eligibility confirmed before study drug administration on Cycle 1 Day 1. Laboratory samples collected on Study Day 1 must be performed before study drug administration. After Cycle 1, predose laboratory procedures can be conducted up to 72 hours before study drug administration (within the 3-day study visit window), and results should be reviewed by the investigator or qualified designee and found to be acceptable before a new cycle of treatment is initiated.

7.5.5.1. Serum Chemistry

A comprehensive serum chemistry will be performed as indicated in Table 22 and Table 24; required analytes for this panel are listed in Table 25. Additional assessment of serum chemistry may be conducted as clinically indicated (ie, if results are abnormal). Appropriate monitoring intervals should be discussed with the medical monitor in these circumstances. Serum chemistry tests will be performed by the site's local laboratory.

7.5.5.2. Liver Chemistry

Liver chemistry tests will be performed as indicated in Table 22 and Table 24; required analytes for this panel are listed in Table 25. Liver chemistry testing will be performed weekly during the first 3 treatment cycles. If liver chemistry tests are elevated, see the guidance in Section 5.4.5.3. Liver chemistry test monitoring for persistent low-grade abnormalities does not need to be monitored on a biweekly basis indefinitely. Appropriate LFT monitoring intervals should be discussed with the medical monitor for these circumstances. Liver chemistry tests will be performed by the site's local laboratory.

7.5.5.3. Hematology

Hematology with differential will be performed as indicated in Table 22 and Table 24; required analytes for this panel are listed in Table 25. Additional assessment of hematology with differential may be conducted as clinically indicated (ie, if results are abnormal). Appropriate monitoring intervals should be discussed with the medical monitor in these circumstances. Hematology with differential will be performed by the site's local laboratory.

7.5.5.4. Coagulation Panel

A coagulation panel will be performed as indicated in Table 22 and Table 24; required analytes for this panel are listed in Table 25. The coagulation panel will be analyzed by the site's local laboratory.

7.5.5.5. Endocrine Function

Endocrine function tests will be performed as indicated in Table 22 and Table 24; required analytes for this panel are listed in Table 25. The endocrine function tests will be analyzed by the site's local laboratory.

7.5.5.6. Urinalysis

Urinalysis will be performed as indicated in Table 22 and Table 24; required analytes for this panel are listed in Table 25. The urinalysis results will be analyzed by the site's local laboratory.

7.5.5.7. Hepatitis Screening Tests

Hepatitis screening assessments will be performed at the screening visit to rule out hepatitis infection; required analytes are shown in Table 25. Generally, hepatitis tests should be performed early in the screening process due to the length of time needed to obtain the results. Additional tests may be performed if clinically indicated.

7.5.5.8. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential at screening and at the EOT visit. The serum pregnancy test performed at screening must be performed within 72 hours before the first dose of study treatment. Urine pregnancy tests will be conducted as outlined in Table 12 and Table 24, as medically indicated, or per country-specific requirements. Urine pregnancy tests will be done locally. If a urine pregnancy test is positive, the results should be confirmed with a serum pregnancy test.

If the serum pregnancy test is negative after a urine test was positive, the investigator will assess the potential benefit/risk to the subject and determine whether it is in the subject's best interest to resume study drug and continue participation in the study.

7.6. Efficacy Assessments

7.6.1. Assessment of Disease

Overall tumor response will be assessed using RECIST v1.1 [redacted] may be used to guide treatment decisions for discontinuation of therapy due to disease progression. See Section 5.5.1.1 for specific guidance regarding continuation of therapy after iUPD is observed.

7.6.2. Initial Tumor Imaging

Initial tumor imaging must be performed within 28 days before the first dose of treatment. The site study team must review prestudy images to confirm that the subject has measurable disease per RECIST v1.1.

Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days before the first dose of treatment. The same imaging technique should be used for an individual subject throughout the study. The baseline scan must be a contrast CT or MRI except in circumstances where there is a contrast allergy or with medical monitor approval. When the CT component of a PET/CT uses higher energy and thinner slices, it may be acceptable with medical monitor approval. A standard, full assessment for lesions should be conducted at baseline, including CT or MRI scans of chest, abdomen, and pelvis; subjects with SCCHN should also have imaging of the neck performed. Computed tomography or MRI scan of the brain will be performed at screening if there are signs or symptoms suggesting that the subject has disease involvement in the CNS. An MRI of the brain will also be required at screening for all subjects with MEL. Brain MRIs should also be considered when disease burden due to any targeted tumor types is extensive (ie, when ≥ 3 metastatic disease sites are involved). The same modality (CT or MRI) should be used for follow-up assessments, including radiologic assessments of all sites of disease present at baseline, at 8 and 16 weeks (± 7 days) after the start of treatment, and then 12 weeks (± 7 days) thereafter until the end of study treatment. In addition to radiologic monitoring, all other lesions observed at the screening visit should be followed.

For selection of target lesions, RECIST v1.1 should be followed. For example, RECIST v1.1 discourages selection of target lesions inside the field of previous irradiation. Lesions situated in a previously irradiated area or in an area subjected to other locoregional therapy are usually not considered measurable, unless the area is the solitary site of measurable disease, AND there has

been demonstrated progression in the lesion. Also, if a subject has only 1 measurable lesion, this lesion should not be biopsied.

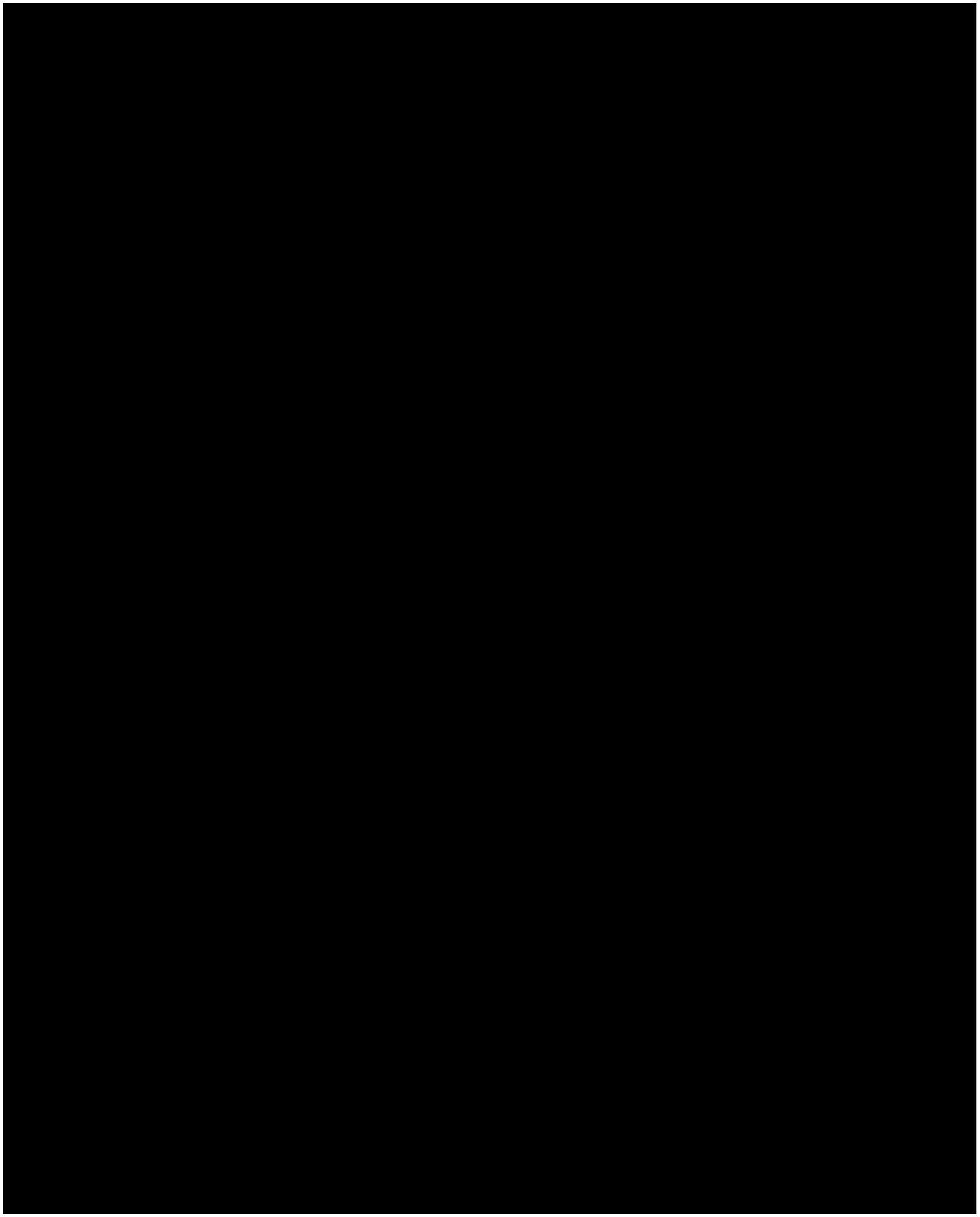
7.6.3. Tumor Imaging During the Study

Tumor imaging, including photographs, should be continued on-treatment if skin lesion is present and assessed clinically, and the same imaging technique should be used to assess disease status throughout the study. Imaging should be performed at 8 and 16 weeks (± 7 days) from the first dose of treatment and then every 12 weeks (± 7 days) thereafter or more frequently if clinically indicated until the end of study treatment. Imaging should follow calendar days starting with Day 1 of study treatment and should not be adjusted for delays in cycle starts.

Per RECIST v1.1 [redacted], response should be confirmed by a repeat radiographic assessment not less than 4 weeks from the date the response was first documented. The scan for confirmation of response may be performed at the earliest of 4 weeks after the first indication of response or at the next scheduled scan, whichever is clinically indicated.

Imaging should continue to be performed until documented iCPD (see Section 5.5.1.1), discontinuation of all study treatment, withdrawal of consent, death, or the end of the study, whichever occurs first.

[redacted]



7.8. Other Study Procedures

7.8.1. Distribution of Subject Reminder Cards and Subject Diaries

Subjects will be provided with reminder cards at each visit. All necessary instructions, such as administration instructions for epacadostat, concomitant medications, and reminders of visits to conduct laboratory tests, should be provided to the subject in writing on this reminder card, or on accompanying written materials. Subject diaries will be provided for the purpose of documenting epacadostat administration and AEs. The subject diary will have an area on which the date and time of the last dose of epacadostat taken before each visit will be recorded as well as the time (and content, if applicable to the visit) of the last meal. On Cycle 1 Day 1, subjects will also be given an SS information sheet for signs and symptoms of SS. This information sheet also instructs subjects to seek immediate medical care if any of these symptoms are observed.

8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events

8.1.1. Definitions

For the purposes of this Protocol, an adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related, that occurs after a subject provides informed consent. Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically meaningful, require therapy (eg, hematologic abnormality that requires transfusion), or require changes in the study drug(s).

8.1.2. Reporting

Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events form of the eCRF. Conditions that were already present at the time of informed consent should be recorded on the Medical History form in the eCRF. Monitoring for the occurrence of new AEs should be continued for at least 100 days after the last dose of study treatment for Treatment Group A, and 150 after the last dose of study treatment for Treatment Group B. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

The term "disease progression" should be recorded as an AE/SAE only if there are no other identifiable AEs/SAEs associated with the disease progression at the time of reporting. For events associated with disease progression, the relevant signs and symptoms should be reported using a diagnosis whenever possible rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE. If the events resulting from disease progression meet the criteria for an SAE (eg, resulted in hospitalization, a life-threatening event, or death), the specific event(s) should be reported as an SAE(s) as described in Section 8.3.2. In both cases (ie, AEs or SAEs related to disease progression), it should be indicated that each event (reported as a diagnosis or as signs and symptoms) is related to disease progression on the Adverse Events form of the eCRF.

The severity of AEs will be assessed using CTCAE v4.03 Grades 1 through 5. If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity:

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 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 due to AE

The occurrence of AEs should be sought by nondirective questioning of the subject during the screening process after signing the ICF and at each visit during the study. Adverse events may also be detected when they are volunteered by the subject during the screening process or between visits, or through physical examination, laboratory test, or other assessments. To the extent possible, each AE should be evaluated to determine:

- The severity grade (CTCAE Grade 1 to 5).
- Whether there is at least a reasonable possibility that the AE is related to the study treatment: suspected (yes) or not suspected (no).
  - ***Note:*** causality assessment for each agent administered per study must be indicated.
- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to study drug.
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per serious adverse event (SAE) definition provided in Section 8.3.1.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements (see Section 8.3.2).

All AEs should be treated appropriately. If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on Adverse Event form and the treatment should be specified on the Prior/Concomitant Medications or Procedures and Non-Drug Therapy form in the eCRF.

Once an AE is detected, it should be followed until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat the event, and the outcome.

When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE until the event resolves. For example, 2 separate AEs will be reported if a subject has Grade 1 diarrhea, meeting the definition of an AE, that lasts for 3 days before worsening to a Grade 3 severity. The Grade 1 event will be reported as an AE with a start date equal to the day the event met the Grade 1 AE definition and a stop date equal to the day that the event increased in severity from Grade 1 to Grade 3. The Grade 3 event will also be reported as an AE, with the start date equal to the day the event changed in intensity from Grade 1 to Grade 3 and a stop date equal to the day that the event either changed severity again or resolved.

8.2. Laboratory Test Abnormalities

Laboratory abnormalities that constitute an AE in their own right (considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug) should be recorded on the Adverse Event form in the eCRF. Whenever possible, a diagnosis rather than a symptom should be provided (eg, "anemia" instead of "low hemoglobin"). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory test result corresponds to a sign or symptom of a previously reported AE, it is not necessary to separately record the laboratory test result as an additional event.

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A Grade 3 or 4 AE does not automatically indicate an SAE unless it meets the definition of serious, as defined in Section 8.3.1. A dose modification for the laboratory abnormality may be required (see Section 5.4) and should not contribute to the designation of a laboratory test abnormality as an SAE.

8.3. Serious Adverse Events

8.3.1. Definitions

An SAE is defined as an event that meets at least 1 of the following criteria:

- Is fatal or life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is a result of:
  - A routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
  - An elective surgery or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF.
  - A treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE and not resulting in hospital admission.
  - Any social reasons and respite care, in the absence of any deterioration in the subject's general condition.

- Results in persistent or significant disability, incapacity, or a substantial disruption of a person's ability to conduct normal life functions.
- Constitutes a congenital anomaly or birth defect.
- Is considered to be an important medical event or a medically significant event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above.

8.3.2. Reporting

Every SAE, regardless of suspected causality (eg, relationship to study drug(s) or study procedure or disease progression), occurring after the subject has signed the ICF through the last study visit (or 100 days after the last dose of study treatment, or until the subject receives a new anticancer therapy, whichever occurs earlier) must be reported to the sponsor (or designee) within **24 hours** of learning of its occurrence, unless otherwise specified by the Protocol. Any SAEs occurring more than 100 days for Treatment Group A and 150 days for Treatment Group B after the last dose of study drug should be reported to the sponsor or its designee only if the investigator suspects a causal relationship to the study drugs.

Information about all SAEs is collected and recorded on the Adverse Event form of the eCRF. The investigator must assess and record the causal relationship of each SAE to the study treatment. The investigator must also complete the Incyte Serious Adverse Event Report Form, in English, and send the completed and signed form to the sponsor or designee within 24 hours of becoming aware of the SAE. The investigator must provide a causality assessment, that is, assess whether there is at least a reasonable possibility that the SAE is related to the study treatment: suspected (yes) or not suspected (no). Refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.

The contact information of the sponsor's study-specific representatives is listed in the investigator manual provided to each site. The original copy of the SAE Report Form and the confirmation sheet must be kept at the study site.

Investigational site personnel must report any new information regarding the SAE within 24 hours of becoming aware of the information in the same manner that the initial SAE Report Form was sent. Follow-up information is recorded on an amended or new SAE Report Form, with an indication that it is follow-up to the previously reported SAE and the date of the original report. The follow-up report should include information that was not provided on the previous SAE Report Form, such as the outcome of the event (eg, resolved or ongoing), treatment provided, action taken with study drug because of the SAE (eg, dose reduced, interrupted, or discontinued), or subject disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.

If the SAE is not documented in the IB for the study drug (new occurrence) and is thought to be related to the sponsor's study drug, the sponsor or its designee may urgently require further information from the investigator for reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification (IN) to inform all investigators involved in any

study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC, or as per national regulatory requirements in participating countries.

8.4. Emergency Unblinding of Treatment Assignment

Not applicable.

8.5. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study drug may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed in a subject during maternal or paternal exposure to study drug, the following procedures should be followed in order to ensure subject safety:

- The study drug must be discontinued immediately (female subjects only).
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Trial Pregnancy form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the sponsor's study drug to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Form.

Any SAE occurring during pregnancy must be recorded on the SAE report form and submitted to the sponsor or designee.

8.6. Warnings and Precautions

Special warnings or precautions for the study drug, derived from safety information collected by the sponsor or its designee, are presented in the Investigator's Brochure (IB). Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. Any important new safety information should be discussed with the subject during the study, as necessary. If new significant risks are identified, they will be added to the ICF.

8.7. Safety Monitoring Committee

For Phase 1, approximately weekly, the sponsor will conduct telephone conferences with investigators to review dose level–specific data, overall safety data from prior dose levels (if applicable), and to agree on dose escalation, dose de-escalation, and cohort expansion decisions. For Phase 2, a safety monitoring committee (SMC) will review safety data at regular intervals throughout the study. The frequency of meetings will be contingent upon enrollment and

availability of safety data for analysis and review. Details regarding membership, roles, and responsibilities of the committee are specified in the SMC charter.

8.8. Product Complaints

The sponsor collects product complaints on study drugs and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

All product complaints associated with material packaged, labeled, and released by the sponsor or its designee will be reported to the sponsor. All product complaints associated with other study material will be reported directly to the respective manufacturer.

The investigator or his/her designee is responsible for reporting a complete description of the product complaint via email or other written communication to the sponsor contact or respective manufacturer as noted in the packaging information. Any AE associated with a product complaint should be reported as described in Section 8.1.2 of this Protocol.

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint communication with the product.

9. STATISTICS

9.1. Study Populations

The safety population includes all subjects enrolled in the study who received at least 1 dose of combination therapy (epacadostat, nivolumab, ipilimumab for Treatment Group A, or epacadostat, nivolumab, lirilumab for Treatment Group B). All safety analyses will be based on the safety population.

The full analysis set includes all subjects enrolled in the study who received at least 1 dose of combination therapy (epacadostat, nivolumab, ipilimumab for Treatment Group A, or epacadostat, nivolumab, lirilumab for Treatment Group B). The full analysis set will be used for the summary of demographics, baseline characteristics, subject disposition, and analyses of all efficacy data.

The PP population includes all subjects in the full analysis set that are considered to be sufficiently compliant with the Protocol. More details of the PP population will be provided in the Statistical Analysis Plan. The PP population may be used in the sensitivity analysis of efficacy endpoints. The determination of subjects being considered for exclusion from the PP population by the clinical team will be prepared and signed before database freeze.

9.2. Selection of Sample Size

9.2.1. Sample Size in Phase 1

A 3 + 3 + 3 dose escalation design will be used in Phase 1 to determine the MTD or PAD and DLT(s) of epacadostat when given in combination with nivolumab and ipilimumab (Treatment Group A) and nivolumab and lirilumab (Treatment Group B). The total number of subjects will depend on the frequency of DLTs and number of dose levels tested before MTD or PAD is established. Based on 3 + 3 + 3 design algorithm, within each treatment group, a minimum of 3 subjects and up to 9 subjects will be enrolled at each dose level.

9.2.2. Sample Size in Phase 2

The Phase 2 dose expansions will evaluate the efficacy and further evaluate the safety, tolerability, [redacted] of the MTD or PAD of epacadostat determined in each of the Phase 1 treatment groups in select solid tumors. A sample size of 35 subjects is expected to be enrolled in Cohorts A1, A2, and B1 (Table 30). The sample size for the Cohort A1 (MEL) yields a power of 80% to detect a target ORR of about 20% increase (Ha: 79%) from historical response rate (H0: 59%). For Cohort A2 (NSCLC), this yields a power of 80% to detect a target ORR of about 22% increase (Ha: 52%) from historical response rate (H0: 30%). For Cohort B1 (SCCHN), this yields a power of 80% to detect a target ORR of about 22% increase (Ha: 46%) from historical response rate (H0: 24%). This assumes a 1-sided alpha of 5%. Subjects who undergo serial prestudy and on-treatment tumor biopsies in expansion Cohorts A1, A2, and B1 may be at risk of being nonevaluable for response; therefore, additional subjects may be enrolled in a specific efficacy expansion cohort to achieve a minimum 35 response-evaluable subjects.

Table 30: Sample Size Calculation for Each Phase 2 Cohort: Comparing to a Known Proportion

Efficacy Expansion Cohort	H0	Ha	Sample Size
MEL (A1)	59%	79%	35
NSCLC (A2)	30%	52%	35
SCCHN (B1)	24%	46%	35

9.3. Level of Significance

Phase 1 of the study is exploratory and no formal statistical tests will be performed. Unless otherwise specified, all CIs will be at the 95% confidence level.

The level of significance for each of the Phase 2 cohorts (A1, A2, and B1) is 1-sided 5% for the analysis of the primary endpoint of ORR.

9.4. Statistical Analyses

Note: As Amendment 2 will serve to discontinue the study to further enrollment, limited safety and efficacy analyses will be performed. Listings will be substituted for summary tables for efficacy analyses. Summary tables will only be provided for selected safety analyses.

9.4.1. Efficacy Analyses

The ORR will be summarized in accordance with both RECIST v1.1 [redacted]. It is defined as the percentage of subjects having CR or PR per RECIST v1.1; [redacted] The ORR as determined by the investigator and their 95% exact binomial CIs will be summarized.

Progression-free survival will be summarized per RECIST v1.1 [redacted]. It is defined as the time from the start of combination therapy until the earliest date at which progression criteria are met (as determined by investigator evaluation of objective radiographic disease assessment per RECIST v1.1 [redacted]) or death due to any cause, if occurring sooner than disease progression. Censoring of PFS will follow FDA guidance (FDA 2007). Details will be provided in the Statistical Analysis Plan. Total number of subjects who progressed or died and number of subjects censored will be summarized. Kaplan-Meier estimate of PFS will be provided with 95% CIs.

Duration of response will be summarized per RECIST v1.1 [redacted] It is defined as the time from the earliest date of CR/PR per RECIST v1.1, [redacted], until the earliest date at which progression criteria are met (as determined by investigator evaluation of radiographic disease assessment per RECIST v1.1 [redacted] or death due to any cause, if occurring sooner than disease progression. Censoring of DOR will follow the same algorithm as the censoring of PFS noted above. Total number of objective responders, number of subjects who progressed or died, and number of subjects censored will be summarized. Kaplan-Meier estimates of DOR will be provided with 95% CIs.

[redacted]

9.4.2. Safety Analyses

The clinical safety data (vital signs, physical examinations, ECGs, laboratory tests, and AEs) will be summarized using descriptive statistics (eg, mean, frequency) using the safety population. Summary tables may be replaced with listings when appropriate. For example, an AE frequency table may be replaced with a listing if it only contains a few unique preferred terms reported on relatively few subjects.

9.4.2.1. Adverse Events

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first dose of study treatment. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing to study drug administration. Adverse events will be tabulated by the MedDRA preferred term and system organ class. Severity of AEs will be based on the NCI CTCAE v4.03 using Grades 1 through 5.

The subset of AEs considered by the investigator to have a relationship to study drug will be considered to be treatment-related AEs. If the investigator does not specify the relationship of

the AE to study drug, the AE will be considered treatment-related. The incidence of AEs and treatment-related AEs will be tabulated.

9.4.2.2. Clinical Laboratory Tests

Laboratory data will be classified into Grades 1 through 4 using CTCAE v4.03. The following summaries will be produced for the laboratory data:

- Number and percentage of subjects with worst postbaseline CTCAE grade (regardless of baseline value). Each subject will be counted only for the worst grade observed postbaseline.
- Shift tables from baseline to the worst postbaseline value using CTCAE grade.
- For laboratory parameters where CTCAE grades are not defined, shift tables to the worst postbaseline value using the low/normal/high classifications based on laboratory reference ranges.

9.4.2.3. Vital Signs

Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, pulse, respiratory rate, and body temperature) at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities (see Table 31), and subjects exhibiting clinically notable vital sign abnormalities will be listed. A value will be considered an "alert" value if it is outside the established range and shows a > 25% change from baseline.

Table 31: Criteria for Clinically Notable Vital Sign Abnormalities

Parameter	High Threshold	Low Threshold
Systolic blood pressure	> 155 mmHg	< 85 mmHg
Diastolic blood pressure	> 100 mmHg	< 40 mmHg
Pulse	> 100 bpm	< 45 bpm
Temperature	> 38ºC	< 35.5ºC
Respiratory rate	> 24/min	< 8/min

9.4.2.4. Electrocardiograms

Descriptive statistics and mean change from baseline will be determined for each ECG parameter at each assessment time. Electrocardiogram results will be reviewed for clinically notable abnormalities according to predefined criteria (Table 32). Subjects exhibiting clinically notable ECG abnormalities will be listed.

Table 32: Criteria for Clinically Notable Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold
QTcF	> 480 ms	< 295 ms
PR	> 220 ms	< 75 ms
QRS	> 120 ms	< 50 ms
QT	> 500 ms	< 300 ms

QTcF = Fridericia correction.

9.4.2.5. Adverse Events of Special Interest

Adverse events of special interest include irAEs that are seen with immunotherapy and any other observed autoimmune phenomenon.

An overall summary of irAEs will include number (%) of subjects reporting any irAEs, any Grade 3 or 4 irAEs, any treatment-related irAEs, any fatal irAEs, and any irAEs leading to treatment interruption/dose reduction/discontinuation.

[redacted]

9.5. Analyses for the Safety Monitoring Committee

An SMC will review safety data at regular intervals throughout Phase 2 of the study. The frequency of meetings will be contingent upon enrollment and availability of safety data for analysis and review. Details regarding the analyses needed for the committee will be specified in the SMC charter.

9.6. Interim Analysis

No interim analysis is planned.

10. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

10.1. Investigator Responsibilities

This study will be performed in accordance with ethical principles that originate in the Declaration of Helsinki and conducted in adherence to the study Protocol; GCPs as defined in Title 21 of the US CFR Parts 11, 50, 54, 56, and 312; ICH E6 GCP consolidated guidelines; and local regulatory requirements as applicable to the study locations.

The investigator will be responsible for:

- Permitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and subject records at each monitoring visit.
  - Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all subjects.
  - Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.
- Obtaining informed consent and ensuring that the study subjects' questions have been answered and the subjects fully understand study procedures:
  - Informed consent must be obtained before any study-related procedures are conducted, unless otherwise specified by the Protocol.
  - Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the subject. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to subject records.

- Obtaining approval from the IRB/IEC before the start of the study and for any changes to the clinical study Protocol, important Protocol deviations, routine updates, and safety information in accordance with institutional requirements and local law.
  - The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by the IRB/IEC.
- Adhering to the Protocol as described in this document and agreeing that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its designee and, second, by the IRB/IEC. Each investigator is responsible for enrolling subjects who have met the specified eligibility criteria.
- Retaining records in accordance with all local, national, and regulatory laws, but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.
  - All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

10.2. Accountability, Handling, and Disposal of Study Drug

The investigator is responsible for drug accountability at the study site; however, some of the drug accountability duties may be assigned to an appropriate pharmacist or other designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities. The investigator or designee must maintain records that document:

- Delivery of study drug to the study site.
- Inventory of study drug at the site.
- Subject use of the study drug including pill or unit counts from each supply dispensed.
- Return of study drug to the investigator or designee by subjects.

The investigational product must be used only in accordance with the Protocol. The investigator will also maintain records adequately documenting that the subjects were provided the specified

study drug. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the investigational product and study subjects.

Completed accountability records will be archived by the site. The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee shipment of any remaining study drug back to the sponsor or its designee for destruction according to institutional standard operating procedures. If local procedures mandate on-site destruction of investigational supply, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study drug is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

10.3. Data Management

Data management will be performed in a validated database via an Electronic Data Capture (EDC) system. All data entry, verification, and validation will be performed in accordance with the current standard operating procedures of the Data Management Department at the sponsor or its designee. The database will be authorized for lock once all defined procedures are completed.

The investigator will be provided with access to an EDC system so that an eCRF can be completed for each subject. Entries made in the eCRF must be verifiable against source documents; if updates to the database are not possible, any discrepancies should be explained and documented. The investigator will be responsible for reviewing all data and eCRF entries, and will sign and date the designated forms in each subject's eCRF, verifying that the information is true and correct. The investigator is responsible for the review and approval of all query responses.

Protocol deviations will be identified and recorded in the Protocol Deviation form of the eCRF. The study monitor will reference the Monitoring Plan in order to ensure that each issue identified is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements.

10.4. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor or its designee must adhere to applicable data privacy laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that sensitive information is handled in accordance with local requirements (eg, HIPAA). Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of protected information must be obtained.

Subject names will not be supplied to the sponsor or its designee, if applicable. Only the subject number and subject's initials (subject's initials will only be recorded if allowable by local regulations) will be recorded in the eCRF, where permitted; if the subject's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed that representatives of the sponsor or its designee, IRB or IEC, or regulatory authorities may inspect their medical

records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

10.5. Financial Disclosure

Before study initiation, all clinical investigators participating in clinical studies subject to FDA Regulation Title 21 Code of Federal Regulations (CFR) Part 54 – Financial Disclosure by Clinical Investigators (ie, "covered studies") are required to submit a completed Clinical Investigator Financial Disclosure form that sufficiently details any financial interests and arrangements that apply. For the purpose of this regulation, "clinical investigator" is defined as any investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects, including the spouse and each dependent child of the clinical investigator or subinvestigator. These requirements apply to both US and foreign clinical investigators conducting covered clinical studies.

Any new clinical investigators added to the covered clinical study during its conduct must also submit a completed Investigator Financial Disclosure Form. During a covered clinical study, any changes to the financial information previously reported by a clinical investigator must be reported to the sponsor or its designee. At the conclusion of the covered clinical study, the clinical investigators will be reminded of their obligations. In the event that the clinical investigator is not reminded, they nevertheless will remain obligated to report to the sponsor or its designee any changes to the financial information previously reported, as well as any changes in their financial information for a period of 1 year after completion of the covered clinical study.

10.6. Publication Policy

By signing the study Protocol, the investigator and his or her institution agree that the results of the study may be used by the sponsor, Incyte Corporation (Incyte), for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. Study results will be published in accordance with applicable local and national regulations. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. The terms regarding the publication of study results are contained in the agreement signed with the sponsor or its designee. A signed agreement will be retained by the sponsor or its designee.

11. REFERENCES

Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicenter, open-label, phase 1/2 trial. Lancet Oncol 2016;17:883-895.

Beatty GL, O'Dwyer PJ, Clark J, et al. Phase I study of the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of the oral inhibitor of indoleamine 2,3-dioxygenase (IDO1) INCB024360 in patients (pts) with advanced malignancies. J Clin Oncol 2013;31(suppl):Abstract 3025.

Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med 2005;352:1112-1120.

Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol 2010;28:3167-3175.

Brandacher G, Perathoner A, Ladurner R, et al. Prognostic value of indoleamine 2,3-dioxygenase expression in colorectal cancer: effect of tumor-infiltrating T cells. Clin Cancer Res 2006;12:1144-1151.

Clinical Trial Facilitation Group (CTFG). Recommendations related to contraception and pregnancy testing in clinical trials. September 15, 2014. http://www.hma.eu/ctfg.html. Accessed July 7, 2017.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-247.

Epacadostat Investigator's Brochure (IB). Wilmington, DE: Incyte Corporation.

Fallarino F, Grohmann U, You S, et al. The combined effects of tryptophan starvation and tryptophan catabolites down-regulate T cell receptor zeta-chain and induce a regulatory phenotype in naive T cells. J Immunol 2006;176:6752-6761.

Frumento G, Rotondo R, Tonetti M, Damonte G, Benatti U, Ferrara GB. Tryptophan-derived catabolites are responsible for inhibition of T and natural killer cell proliferation induced by indoleamine 2,3-dioxygenase. J Exp Med 2002;196:459-468.

Gangadhar TC, Hamid O, Smith DC, et al. Epacadostat (INCB024360) plus pembrolizumab in patients with advanced melanoma and select solid tumors: updated phase 1 results from ECHO 202/KEYNOTE-037. Ann Oncol 2016;27(suppl 6):Abstract 1110PD.

Gangadhar TC, Schneider BJ, Bauer TM, et al. Epacadostat plus pembrolizumab treatment of NSCLC: preliminary Phase 1/2 results of ECHO-202/KEYNOTE-037. Poster presented at: ASCO Annual Meeting 2017; June 2-6, 2017; Chicago, IL; Abstract 9014.

Goldman JW, Antonia SJ, Gettingger SN, et al 2017 Nivolumab plus ipilimumab as first-line treatment for advanced NSCLC: 2-yr OS and long-term outcomes from CheckMate 012. Poster presentation at: ASCO Annual Meeting 2017; June 2-6, 2017; Chicago, IL; Abstract 9093.

Hamid O, Chasalow SD, Tsuchihashi S, Alaparthy S, Galbraith S, Berman D. Association of baseline and on-study tumor biopsy markers with clinical activity in patients with advanced melanoma treated with ipilimumab. J Clin Oncol 2009;27(suppl):15s [abstr 9008].

Hamid O, Bauer TM, Spira AI, et al. Epacadostat plus pembrolizumab in patients with SCCHN: Preliminary Phase 1/2 Results From ECHO-202/KEYNOTE-037. Poster presented at: ASCO Annual Meeting 2017; June 2-6, 2017; Chicago, IL; Abstract 6010.

Hellmann MD, Gettinger SN, Goldman J, et al. CheckMate 012: Safety and efficacy of first-line nivolumab and ipilimumab in advanced NSCLC. J Clin Oncol 2016;34(suppl):Abstract 3001.

Huang L, Baban B, Johnson BA 3rd, Mellor AL. Dendritic cells, indoleamine 2,3 dioxygenase and acquired immune privilege. Int Rev Immunol 2010;29:133-155.

Ino K, Yoshida N, Kajiyama H, et al. Indoleamine 2,3-dioxygenase is a novel prognostic indicator for endometrial cancer. Br J Cancer 2006;95:1555-1561.

Ipilimumab Investigator's Brochure (IB). Princeton, NJ: Bristol-Myers Squibb Company; 2017.

Kohrt HE, Thielens A, Marabelle A, et al. Anti-KIR antibody enhancement of anti-lymphoma activity of natural killer cells as monotherapy and in combination with anti-CD20 antibodies. Blood 2014;123:678-686.

Laimer K, Troester B, Kloss F, et al. Expression and prognostic impact of indoleamine 2,3-dioxygenase in oral squamous cell carcinomas. Oral Oncology 2011;5:352-357.

Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015;373:23-34.

Leidner R, Kang H, Haddad R, et al. Preliminary efficacy from a phase 1/2 study of the natural killer cell–targeted antibody, lirilumab in combination with nivolumab in squamous cell carcinoma of the head and neck. SITC Annual Meeting; November 9-13, 2016; National Harbor, MD; Abstract 456.

Lirilumab Investigator's Brochure (IB). Princeton, NJ: Bristol-Myers Squibb Company; 2017.

Ljunggren HG, Kärre K. In search of 'missing self': MHC molecules and NK cell recognition. Immunol Today 1990;11:237-244.

Long GV, Dummer R, Hamid O, et al. Epacadostat (E) plus pembrolizumab (P) versus pembrolizumab alone in patients (pts) with unresectable or metastatic melanoma: results of the phase 3 ECHO-301/KEYNOTE-252 study. J Clin Oncol 2018;36(suppl):108. [abstr]

Mellor AL, Baban B, Chandler P, et al. Cutting edge: induced indoleamine 2,3, dioxygenase expression in dendritic cell subsets suppresses T cell clonal expansion. J Immunol 2003;171:1652-1655.

Mellor AL, Munn DH. Tryptophan catabolism and T-cell tolerance: immunosuppression by starvation? Immunol Today 1999;20:469-473.

Mellor AL, Munn DH. IDO expression by dendritic cells: tolerance and tryptophan catabolism. Nat Rev Immunol 2004;4:762-774.

Muller AJ, DuHadaway JB, Donover PS, Sutanto-Ward E, Prendergast GC. Inhibition of indoleamine 2,3-dioxygenase, an immunoregulatory target of the cancer suppression gene Bin1, potentiates cancer chemotherapy. Nat Med 2005;11:312-319.

Munn DH, Mellor AL. Indoleamine 2,3-dioxygenase and tumor-induced tolerance. J Clin Invest 2007;117:1147-1154.

Munn DH, Sharma MD, Hou D, et al. Expression of indoleamine 2,3-dioxygenase by plasmacytoid dendritic cells in tumor-draining lymph nodes. J Clin Invest 2004;114:280-290.

Nakamura T, Shima T, Saeki A, et al. Expression of indoleamine 2,3-dioxygenase and the recruitment of Foxp3-expressing regulatory T cells in the development and progression of uterine cervical cancer. Cancer Sci 2007;98:874-881.

Nivolumab Investigator's Brochure (IB). Lawrenceville, NJ & Chuo-Ku, Osaka: Bristol-Myers Squibb Research and Development & Ono Pharmaceutical Co., Ltd.

[redacted]

Opdivo (nivolumab) [summary of product characteristics]. Princeton, NJ: Bristol-Myers Squibb Pharma EEIG; 2015.

Opdivo [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2017.

Perez RP, Riese MJ, Lewis KD, et al. Epacadostat plus nivolumab in patients with advanced solid tumors: preliminary Phase 1/2 results of ECHO-204. Oral presentation at: ASCO Annual Meeting 2017; June 2-6, 2017; Chicago, IL; Abstract 3003.

Purdy AK, Campbell KS. Natural killer cells and cancer: regulation by the killer cell Ig-like receptors (KIR). Cancer Biol Ther 2009;8:2211-2220.

Quezada SA, Peggs KS. Exploiting CTLA-4, PD-1 and PD-L1 to reactivate the host immune response against cancer. Br J Cancer 2013;108:1560-1565.

[redacted]

Uhrberg M, Valiante NM, Young NT, Lanier LL, Phillips JH, Parham P. The repertoire of killer cell Ig-like receptor and CD94:NKG2A receptors in T cells: clones sharing identical alpha beta TCR rearrangement express highly diverse killer cell Ig-like receptor patterns. J Immunol 2001;166:3923-3932.

US Food and Drug Administration (FDA). Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. 2007. https://www.fda.gov/downloads/Drugs/Guidances/ucm071590.pdf. Accessed July 11, 2017.

Uyttenhove C, Pilotte L, Théate I, et al. Evidence for a tumoral immune resistance mechanism based on tryptophan degradation by indoleamine 2,3-dioxygenase. Nat Med 2003;9:1269-1274.

Weber JS, Yang JC, Atkins MB, Disis ML. Toxicities of immunotherapy for the practitioner. J Clin Oncol 2015;33:2092-2099.

Weinlich G, Murr C, Richardsen L, Winkler C, Fuchs D. Decreased serum tryptophan concentration predicts poor prognosis in malignant melanoma patients. Dermatology 2007;214:8-14.

Witkiewicz A, Williams TK, Cozzitorto J, et al. Expression of indoleamine 2,3-dioxygenase in metastatic pancreatic ductal adenocarcinoma recruits regulatory T cells to avoid immune detection. J Am Coll Surg 2008;206:849-854.

Wolchok JD, Saenger Y. The mechanism of anti-CTLA-4 activity and the negative regulation of T-cell activation. Oncologist 2008;13(suppl 4):2-9.

Zou W. Regulatory T cells, tumour immunity and immunotherapy. Nat Rev Immunol 2006;6:295-307.

Yervoy [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2017.

Zhang Y, Li Y, Diamond S, Yeleswaram S. Effects of Epacadostat with Co-Administration of Linezolid on Brain Extracellular Fluid Concentrations of Serotonin: An Intracerebral Microdialysis Study in Sprague-Dawley Rats.AAPS Meeting 2016; November 13-17, 2016; Denver, CO. Abstract/poster#19M0400.

APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For Subjects Participating in the Study:

The following methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods.

Such methods include:

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

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.
[2] Contraception methods that in the context of this guidance are considered to have low user dependency.
[3] Vasectomised partner is a highly effective method provided of avoiding pregnancy that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
[4] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Source: CTFG 2014.

APPENDIX B. MANAGEMENT GUIDELINES FOR IMMUNE-RELATED ADVERSE EVENTS

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 (I-O) agents and regimens.

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

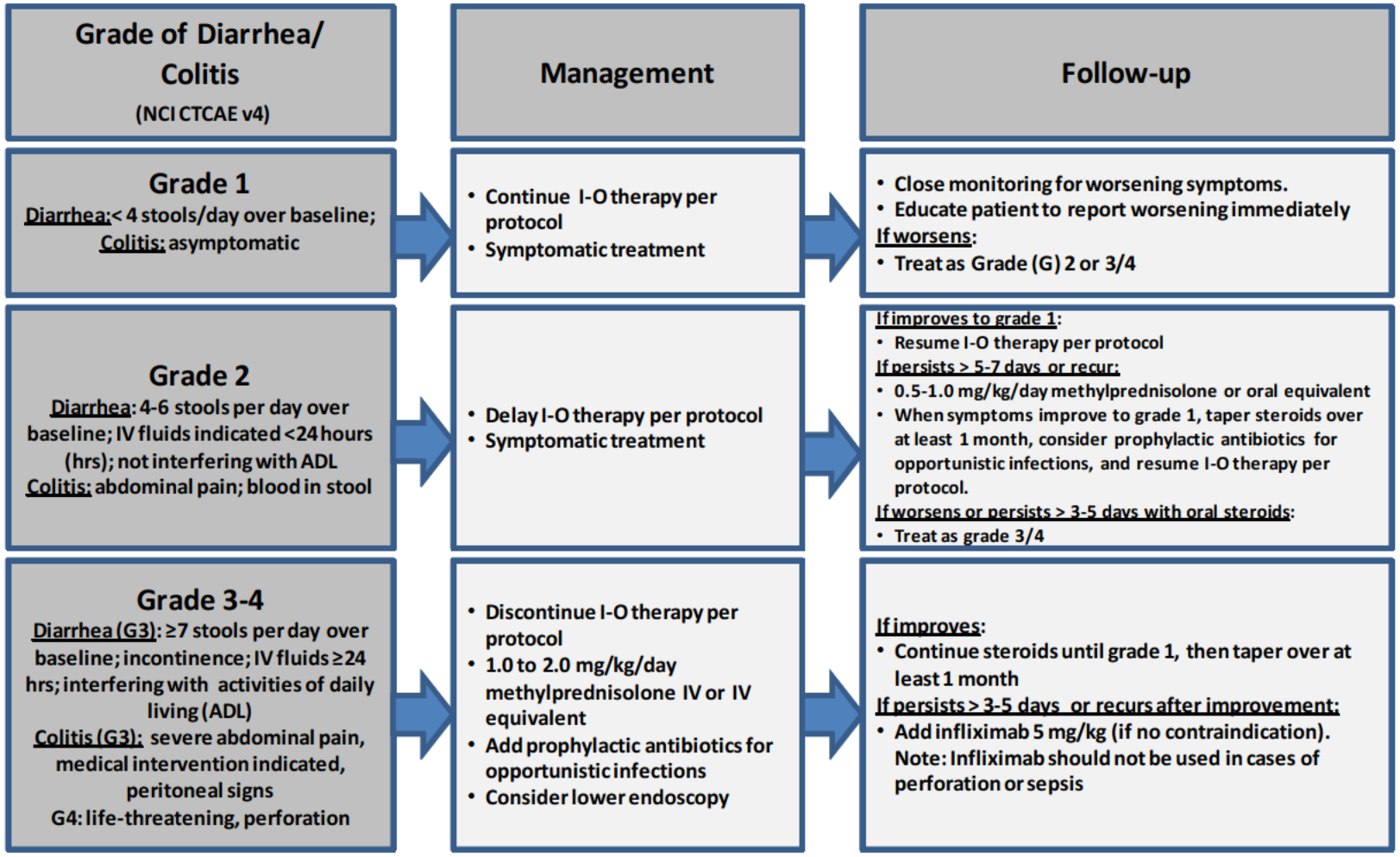
Corticosteroids are a primary therapy for I-O drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent 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 I-O agent or regimen being used.

GI Adverse Event Management Algorithm

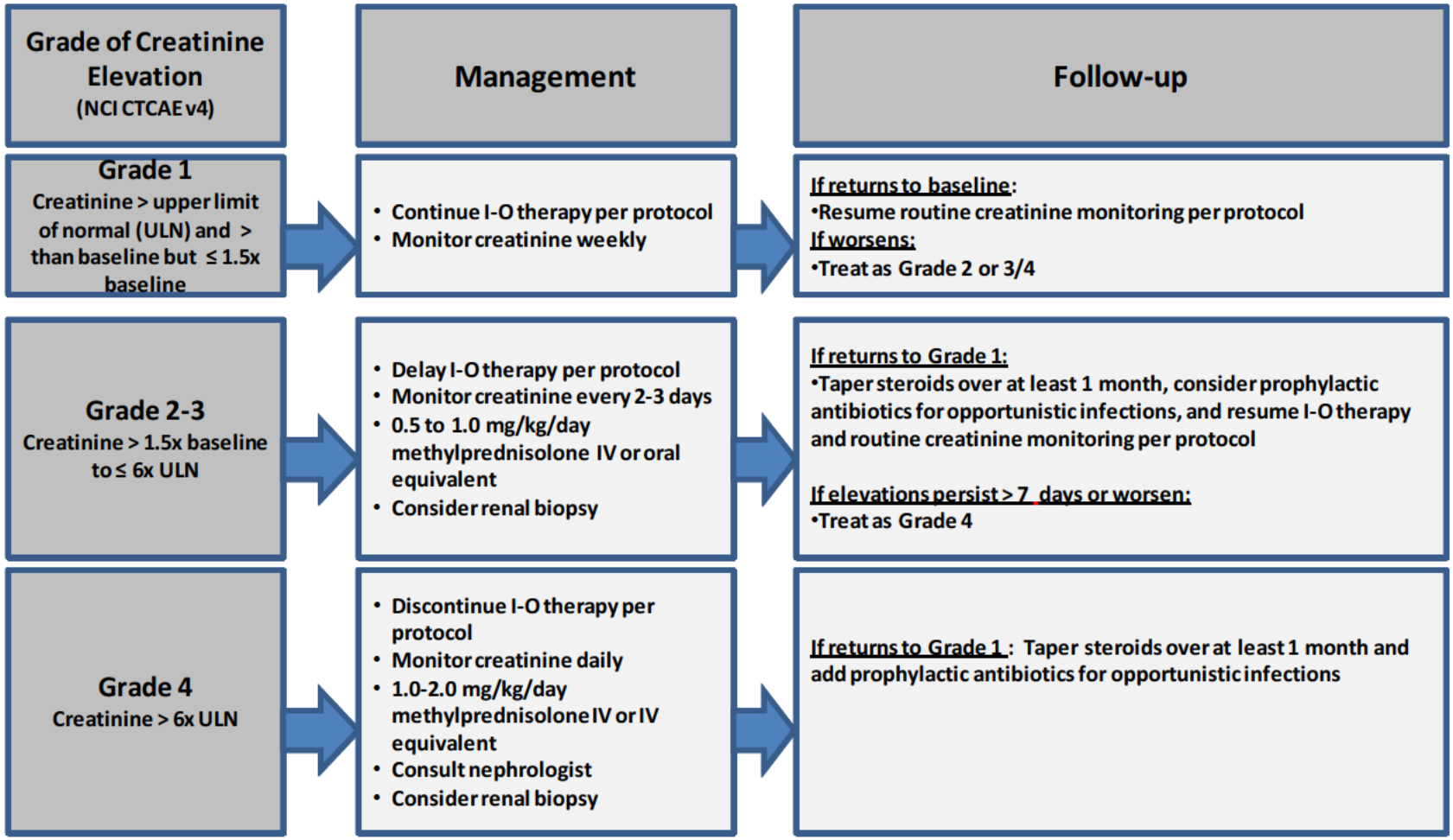
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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

Renal Adverse Event Management Algorithm

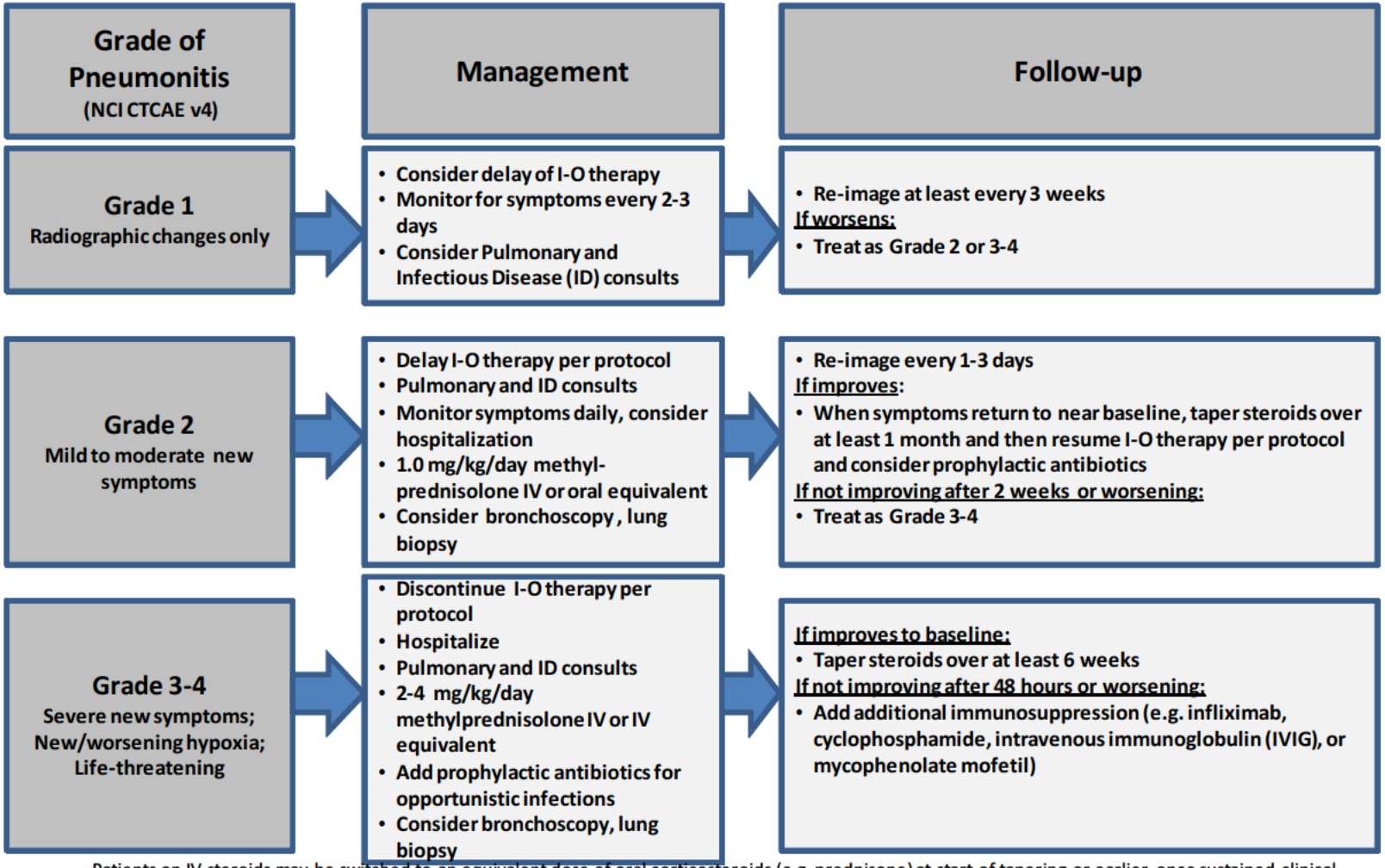
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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

Pulmonary Adverse Event Management Algorithm

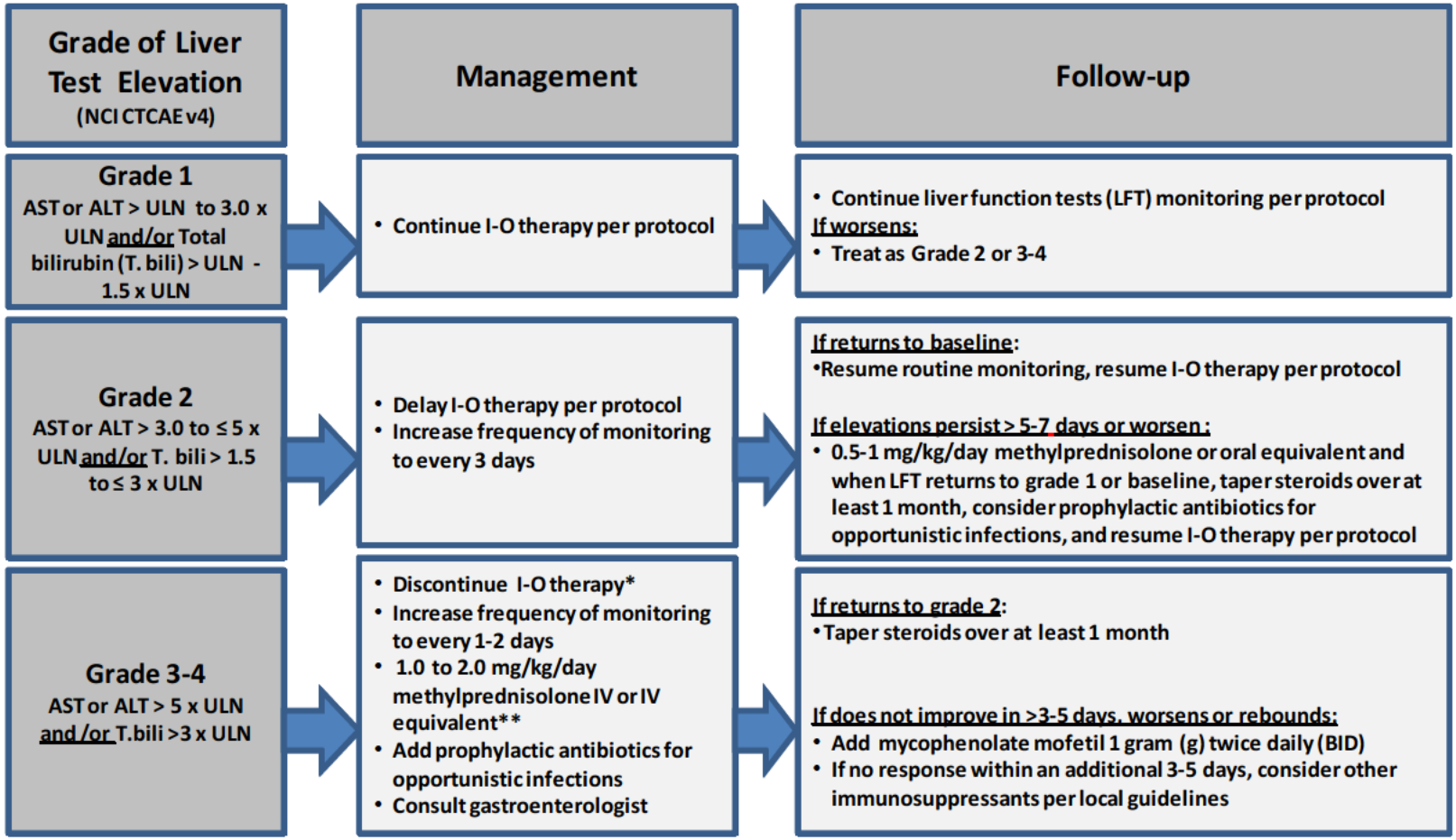
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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.



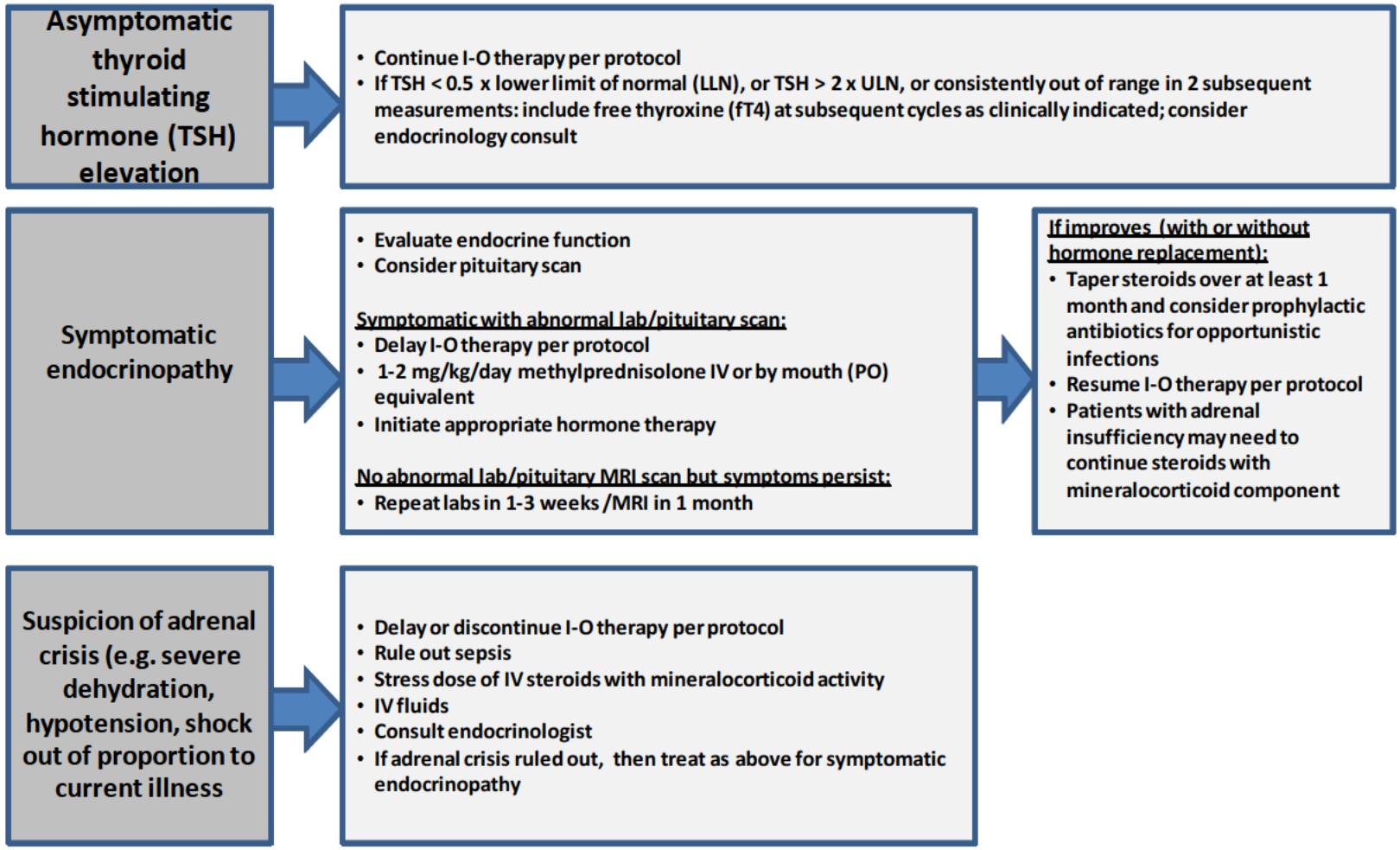
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

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

Endocrinopathy Management Algorithm

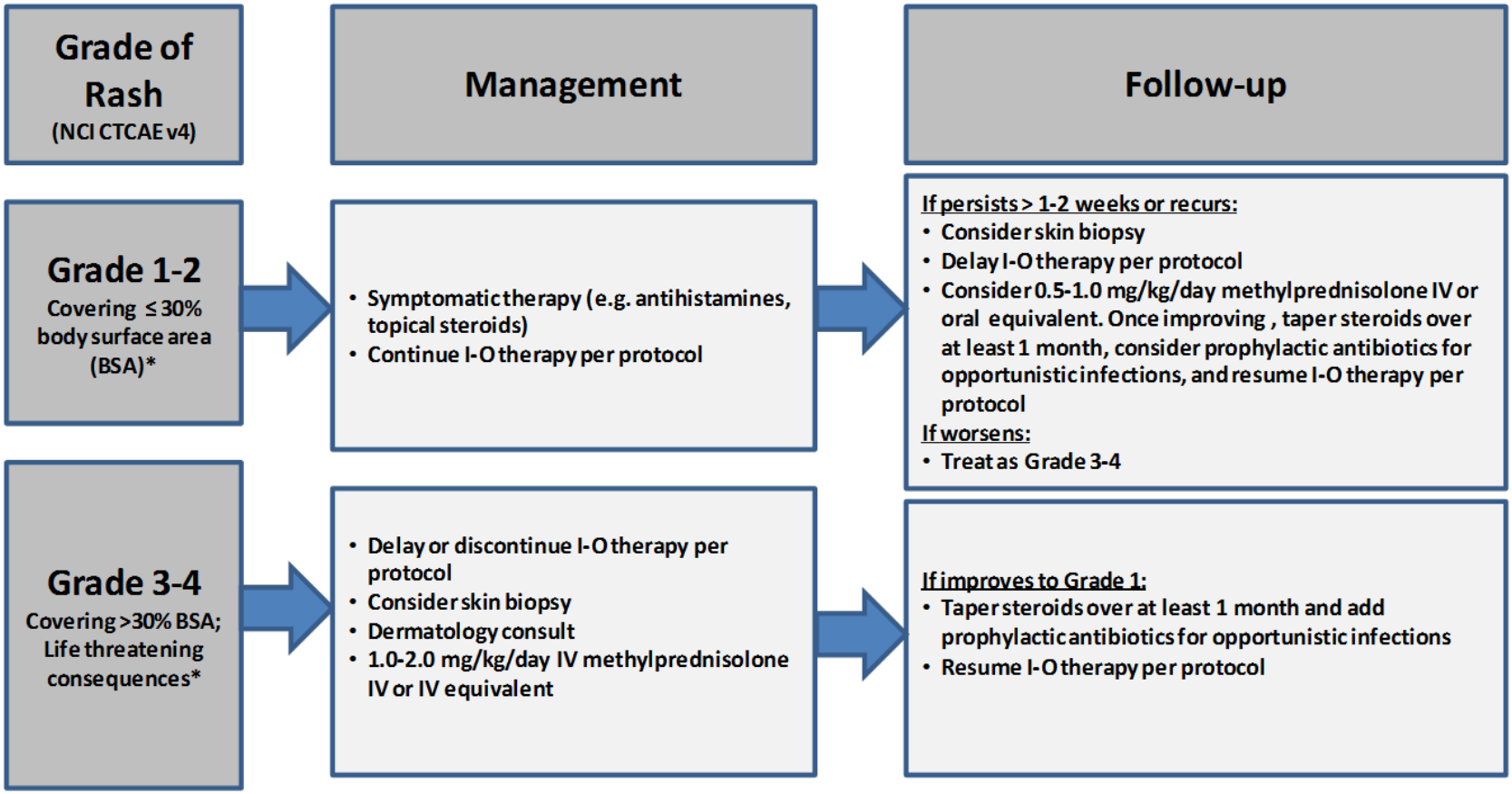
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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.

Skin Adverse Event Management Algorithm

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

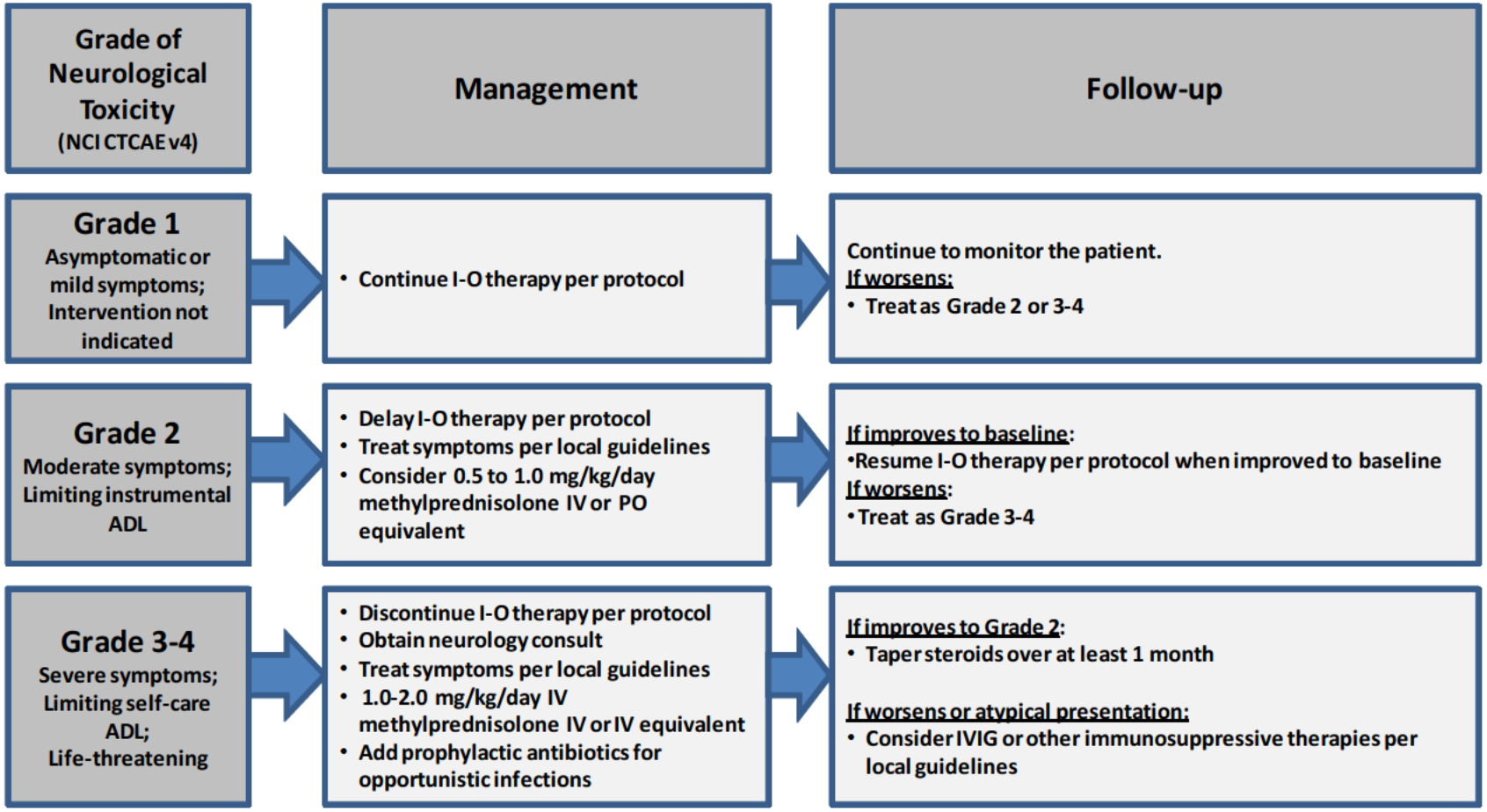


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

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.

APPENDIX D. MONOAMINE OXIDASE INHIBITORS AND DRUGS ASSOCIATED WITH SIGNIFICANT MONOAMINE OXIDASE INHIBITORY ACTIVITY

Monoamine Oxidase Inhibitors	Drugs Associated With Significant Monoamine Oxidase Inhibitory Activity
Hydrazines (eg, phenelzine)	Meperidine
Caroxazone	Linezolid
Echinopsidine	Methylene blue
Furazolidone	
Tranylcypromine	
Brofaromine	
Metralindole	
Minaprine	
Moclobemide	
Pirlindole	
Toloxatone	
Lazabemide	
Pargyline	
Rasagiline	
Selegiline	

APPENDIX E. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS V1.1

RECIST v1.1* will be used in this study for assessment of tumor response. While either computed tomography or magnetic resonance imaging may be used, as per RECIST v1.1, computed tomography is the preferred imaging technique in this study.

* As published in the *European Journal of Cancer*:

Source: Eisenhauer et al 2009.

APPENDIX F. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment (Version) 1:	31 JUL 2017
Amendment (Version) 2:	05 DEC 2018

Amendment 2 (05 DEC 2018)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to close the study to future enrollment and provide guidance for subjects continuing on study treatment under a simplified assessment schedule, and to allow for the discontinuation of epacadostat while continuing treatment with nivolumab and ipilimumab.

1. **Synopsis; Section 4.1, Overall Study Design; Section 9.4, Statistical Analyses**

   Description of change: Note was added indicating that Amendment 2 will serve to close the study to further enrollment and update the assessment schedule for subjects enrolled to date in Treatment Group A, and that limited safety and efficacy analyses will be performed.
   Rationale for change: To state the purpose of Amendment 2.

2. **Synopsis; Section 1.7, Rationale for Dose and Schedule of the Combination Therapies; Section 5.2.1, Epacadostat**

   Description of change: The option to discontinue epacadostat treatment while continuing nivolumab and ipilimumab treatment was added.

   Rationale for change: In the Phase 3 ECHO-301/KEYNOTE-252 study evaluating pembrolizumab plus epacadostat 100 mg BID versus pembrolizumab alone, the combination of pembrolizumab and epacadostat did not result in greater clinical benefit than pembrolizumab alone. Thus, it is unlikely that doses of epacadostat being evaluated in the ECHO-208 study in combination with nivolumab and ipilimumab will result in clinical benefit.

3. **Synopsis; Section 6, Study Assessments (Table 21); Section 5.5, Withdrawal of Subjects From Study Treatment; Section 6.3, End of Treatment; Section 6.4, Follow-Up; Section 6.5, End of Study; Section 7.5, Poststudy Anticancer Therapy; Section 7.10.2, Data Collection for Survival Follow-Up**

   Description of change: The post-treatment disease status and survival follow-up periods have been removed from the Protocol.

   Rationale for change: The sponsor has determined that post-treatment disease status and survival follow-up data are no longer needed.

4. **Synopsis; Section 5.5.1.1, Treatment After Initial Evidence of Radiologic Evidence of Disease Progression (Table 19); Section 6, Study Assessments; Section 7.6.2, Initial Tumor Imaging; Section 7.6.3, Tumor Imaging During the Study**

   Description of change: Imaging schedule was updated to specify that should be assessed at 8 and 16 weeks after the start of treatment and then every 12 weeks thereafter, and that no additional imaging is required after end of treatment.

   Rationale for change: To perform fewer, less frequent imaging assessments for subject convenience and to relieve site staff burden while still evaluating disease status at clinically appropriate intervals.

5. **Synopsis; Section 4.4, Duration of Treatment and Subject Participation**

   Description of change: The allowance for re-treatment in subjects who discontinue treatment after 2 years and subsequently develop disease progression within 1 year of the last dose of study medication was removed.

   Rationale for change: There is no evidence to suggest that treatment with nivolumab with or without ipilimumab beyond 2 years or re-treatment after subsequent progressive disease provides clinical benefit.

[redacted]

7. **Section 5.2.1.2, Storage (Epacadostat)**

   Description of change: The section was changed to "Clinical supplies must be stored as described in the epacadostat IB."

   Rationale for change: To provide consistent storage instructions for epacadostat.

8. **Section 5.4.6, Procedure for Subjects Exhibiting Serotonin Syndrome (including Table 17)**

   Description of change: The epacadostat risk language and serotonin syndrome management guidelines were updated to reflect current language.

   Rationale for change: To incorporate updated information regarding the risk and management of serotonin syndrome.

9. **Section 6, Study Assessments (Table 25, Local Laboratory Tests: Required Analytes)**

   Description of change: Table 25 should indicate the following required coagulation analytes:

   - PT or INR
   - aPTT or PT**T**

   Rationale for change: To correct a typographical error and clarify the required analyte.

10. **Section 7.6, Efficacy Assessments; Appendix E, Response Evaluation Criteria in Solid Tumors v1.1**

    Description of change: Deleted text regarding collection of radiographic tumor assessments for central review.

    Rationale for change: Independent central review is no longer planned.

11. **Synopsis, Section 6, Study Assessments; Section 7.8, Performance and Quality of Life Assessments**

    Description of change: Deleted ECOG performance status assessments.

    Rationale for change: ECOG performance status assessments are no longer needed.

[redacted]

13. **Section 9.4.2.4, Electrocardiograms (Table 32)**

    Description of change: RR interval was deleted from Table 32 (Criteria for Clinically Notable Electrocardiogram Abnormalities).

    Rationale for change: RR interval will not be collected in the case report form or used in the analysis of clinically notable ECG abnormalities. Heart rate itself will be collected and summarized along with the intervals listed in Table 32.

14. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 1 (31 JUL 2017)

The primary purpose of this amendment is to address Food and Drug Administration (FDA) review comments received on 26 JUL 2017.

This amendment includes the changes to the Protocol INCB 24360-208 (12 JUL 2017) summarized below. A redline version of the amendment depicting the updated and previous text is also provided.

1. **Synopsis; Section 6, Study Assessments (Tables 21 and 23, Schedule of Clinical Assessments); Section 7.6.4, 12-Lead Electrocardiograms (including Table 26, Schedule of ECG Assessments)**

   Description of change: The electrocardiogram (ECG) monitoring schedule was modified to perform triplicate ECGs at the anticipated maximal concentrations on Cycle 1 Day 1 and Cycle 2 Day 1.

   Rationale for change: To incorporate requested change from the FDA.

2. **Section 3.2, Subject Exclusion Criteria; Section 5.6.2, Restricted Medications; Section 5.6.3, Prohibited Medications**

   Description of change: UGT1A9 inducers were added to exclusion criterion 22 and the list of prohibited medications.

   Rationale for change: To incorporate requested change from the FDA.

[redacted]

4. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.