Clinical Study Protocol

INCB 24360-203

A Phase 1/2 Study Exploring the Safety, Tolerability, and Efficacy of Epacadostat in Combination With Durvalumab in Subjects With Selected Advanced Solid Tumors

Product:	**Epacadostat and Durvalumab**
IND Number:	[redacted]
EudraCT Number:	**2016-001911-19**
Phase of Study:	**1/2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Original Protocol (Version 0):	**18 AUG 2014**
Amendment (Version) 1:	**29 SEP 2014**
Amendment (Version) 2:	**20 FEB 2015**
Amendment (Version) 3:	**10 JUL 2015**
Amendment (Version) 4:	**12 JAN 2016**
Amendment (Version) 5:	**25 MAY 2016**
Amendment (Version) 6:	**28 JUN 2017**
Amendment (Version) 7:	**21 SEP 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 50, 54 56, 312, and Part 11 as well as ICH GCP consolidated guidelines (E6) and applicable regulatory requirements.

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for Epacadostat and Durvalumab. I have read the INCB 24360-203 Protocol Amendment 7 (Version 7 dated 21 SEP 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: INCB024360 (Epacadostat) and MEDI4736 (Durvalumab)

Title of Study: A Phase 1/2 Study Exploring the Safety, Tolerability, and Efficacy of Epacadostat in Combination With Durvalumab in Subjects With Selected Advanced Solid Tumors

Protocol Number: INCB 24360-203	**Study Phase:** 1/2

Primary Objectives:

- Phase 1: To evaluate the safety and tolerability, and define the maximum tolerated dose (MTD) or a pharmacologically active dose (PAD) of epacadostat administered in combination with durvalumab in subjects with select advanced solid tumors.
- Phase 2: To evaluate the efficacy of epacadostat administered in combination with durvalumab in subjects with select advanced solid tumors by assessing the objective response rate (ORR) per modified RECIST v1.1 (mRECIST v1.1) at the MTD or PAD.

Secondary Objectives:

- Phase 1: To evaluate the efficacy of epacadostat administered in combination with durvalumab in subjects with select advanced solid tumors by assessing ORR per mRECIST v1.1.
- Phase 2: To evaluate the safety and tolerability of the MTD or PAD of epacadostat administered in combination with durvalumab in subjects with select advanced solid tumors.
- Phases 1 and 2: To evaluate the efficacy of epacadostat administered in combination with durvalumab in subjects with select advanced solid tumors by assessing duration of response and progression-free survival (PFS).
- Phases 1 and 2: To evaluate the pharmacokinetics (PK) of epacadostat and durvalumab when administered in combination.
- Phases 1 and 2: To determine the immunogenicity of durvalumab when administered with epacadostat.
- [redacted]

Overall Study Design:

This is a Phase 1/2 open-label study of epacadostat administered in combination with durvalumab in subjects with advanced melanoma, non–small cell lung cancer (NSCLC), pancreatic cancer (Phase 1 only), squamous cell carcinoma of the head and neck (SCCHN), triple-negative breast cancer (TNBC), gastric or gastroesophageal (GE) junction cancer, and transitional cell carcinoma (TCC) of the genitourinary (GU) tract. The dose-escalation part of the study (Phase 1) uses a 3 + 3 design to identify the MTD or PAD of epacadostat in combination with durvalumab. Phase 2 will further explore the safety and efficacy of the MTD or PAD of epacadostat in combination with durvalumab determined in Phase 1. More than 1 PAD may be evaluated in Phase 2.

Phase 1 Dose Escalation

Phase 1 is the dose-escalation phase, which will include up to 6 cohorts of subjects treated with epacadostat at doses of 25 mg twice daily (BID), 50 mg BID, 75 mg BID, 100 mg BID, and 300 mg BID in combination with durvalumab 3 mg/kg or 10 mg/kg given on Day 1 of each 14-day cycle. A minimum of 3 subjects will be enrolled and treated in each cohort, and all 3 subjects will be observed for a minimum of 42 days before the subsequent cohort begins enrollment. Subjects must have received the cohort-specific dose of epacadostat for at least 75% of the doses (63 doses) and have received at least 3 doses of durvalumab during the 42-day dose-limiting toxicity (DLT) observation period, or have experienced a DLT to be evaluable for dose tolerability. Additional subjects will be enrolled in a cohort to achieve the minimum of 3 evaluable subjects if dropouts or dose interruptions/reductions occur that result in a subject being nonevaluable for DLTs.

The dose of epacadostat will be escalated if 0 of the first 3 evaluable subjects enrolled experience a DLT. If 1 of the first 3 evaluable subjects enrolled experience a DLT, the cohort will be expanded to include 3 additional evaluable subjects. If 2 or more of either 3 or 6 subjects enrolled experience a DLT, the prior dose level will be considered the MTD. If only 3 subjects were treated at this dose level, the dose will be confirmed as the MTD by evaluation of an additional 3 subjects before this dose is recommended for Phase 2 testing.

The cohorts and dose levels are shown in the table below.

Cohort	Maximum Daily Dose of Epacadostat	Dose of Durvalumab (Once Every 14 Days)
1	**25 mg BID orally**	**3 mg/kg IV**
2	25 mg BID orally	10 mg/kg IV
3	50 mg BID orally	10 mg/kg IV
4	75 mg BID orally	10 mg/kg IV
5	100 mg BID orally	10 mg/kg IV
6	300 mg BID orally[a]	10 mg/kg IV

IV = intravenous.
[a] Intermediate dose levels may be explored based on emerging PK or pharmacodynamic data.

Phase 2

Approximately 140 to 192 subjects with advanced melanoma, NSCLC, SCCHN, TNBC, gastric or GE junction cancer, or TCC of the GU tract will be enrolled at the MTD or PAD of epacadostat in combination with durvalumab. The approximate number of subjects needed for the melanoma, TNBC, and gastric and GE junction cancer cohorts will be determined using the Simon 2-stage design: Stage 1 will be the initial number of subjects per tumor type, and the decision to proceed with Stage 2 will be determined by the response rate observed in Stage 1. If more than 1 PAD is evaluated, the cohort may or may not be repeated for the specified tumor type as indicated in the table below. The sponsor may limit enrollment of a specific tumor type to Stage 1.

	No. of Subjects Enrolled		
Tumor Type	Stage 1	Stage 2 (If Study Proceeds to Stage 2)	Total (Stage 1 + 2)
Melanoma	15	25	40
TNBC	13	16	29
Gastric and GE junction cancer	9	11	20

Under Amendment 6, enrollment of the NSCLC, SCCHN, and TCC of the GU tract cohorts will be completed as expansion cohorts at the 300 mg BID dose level. The sample size for each cohort will be increased to account for the heterogeneity of PD-1 pathway–treated and PD-1 pathway–naive subjects within the selected tumor types. The approximate number of subjects per tumor type is listed in the table

below, and the number of PD-1 pathway–treated subjects in each cohort will be limited to 10 in order to reduce the risk of any cohort having a significant imbalance between PD-1 pathway–treated and PD-1 pathway–naive subjects, thereby preserving the predicted levels of baseline efficacy observed with PD-1 pathway monotherapy. Subjects enrolled at the 100 mg BID will be analyzed independently.

	No. of Subjects Enrolled	
Tumor Type	**100 mg BID[a] (n = 19)**	**300 mg BID[b] (n = 84)**
NSCLC	8	28
SCCHN	7	28
TCC of the GU tract	4	28

[a] Subjects enrolled in the 100 mg BID dose level were enrolled before Amendment 5.
[b] All subjects in the 300 mg BID NSCLC, SCCHN, and TCC of the GU tract cohorts enrolled in Amendment 5 or earlier are included in the total sample size.

The study will consist of 3 periods:

Screening: Up to 28 days.

Treatment Period: The treatment period will continue every 14 days for up to 12 months as long as subjects are receiving benefit from treatment and have not met any criteria for study withdrawal. Once subjects complete 12 months of study treatment or permanently discontinue study treatment for any other reason, the end-of-treatment (EOT) visit should be conducted, and they should enter the safety follow-up period of the study.

Protocol Amendment 6 (28 JUN 2017) removed the option for subjects to receive epacadostat monotherapy once they completed 12 months of combination therapy with durvalumab. However, subjects already receiving epacadostat monotherapy prior to Amendment 6 were allowed to continue if they were receiving clinical benefit and their investigator felt it was in the best interest of the subject. These subjects will be allowed to continue epacadostat monotherapy for up to an additional 12 months, and their maximum overall study treatment duration should not exceed 24 months. Exceptions for these subjects to continue study treatment beyond 24 months will require medical monitor review and approval every 3 months.

Follow-Up Period: The safety follow-up visits will occur at 42 days and 90 days after the EOT visit or after the last dose of study treatment (if the EOT was not performed).

Study Drugs, Dosages, and Modes of Administration:

Epacadostat will be self-administered orally BID without regard to food and continued BID during each 14-day cycle. The MTD or PAD of epacadostat defined during Phase 1 will be used for Phase 2.

All BID doses will be taken morning and evening, approximately 12 hours apart. If a dose is missed by more than 4 hours, that dose should be skipped and the next dose should be taken at the scheduled time. If the subject vomits, an additional dose should not be taken. Intrasubject dose escalation of epacadostat is not allowed.

Durvalumab is an investigational agent and will be administered at 3 mg/kg or 10 mg/kg over 60 minutes on Day 1 of each 14-day cycle for up to 12 months. There will be an observation period of 3 hours after the first dose of durvalumab is administered. Intrasubject dose escalation of durvalumab is not allowed except as defined in the body of the Protocol.

Reference Therapy, Dosage, and Mode of Administration: Not applicable.

Duration of Participation: Subject participation is expected to average approximately 6 months.

Study Population:

Subjects with histologically or cytologically confirmed advanced melanoma, NSCLC, pancreatic cancer (Phase 1 only), SCCHN, TNBC, gastric or GE junction cancer, or TCC of the GU tract will be enrolled.

Key Inclusion Criteria:

- Male or female subjects, age 18 years or older.
- Histologically or cytologically confirmed diagnosis of melanoma, NSCLC, pancreatic cancer (Phase 1 only), SCCHN, TNBC, gastric or GE junction cancer, or TCC of the GU tract that is locally advanced (not amenable to curative therapy such as surgical resection) or metastatic.
- Must have failed at least 1 prior treatment regimen for locally advanced or metastatic disease or be intolerant to treatment or refuse standard treatment. Investigational agents used in combination with standard therapies are allowed. Adjuvant, neoadjuvant, or chemoradiation regimens given within 6 months of screening would be counted as having received 1 prior systemic regimen and would not require an additional systemic regimen for advanced or metastatic disease.
- For subjects with metastatic melanoma:
  - Must have known V600E activating BRAF mutation status or consent to BRAF V600E mutation testing during screening. Testing should be performed in a CLIA certified laboratory. BRAF mutation status determined as part of a panel of genetic tests performed in a gene expression analysis will also satisfy the inclusion criterion for BRAF mutation testing.
  - May be treatment-naive or have received prior treatment with an anti−cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) or anti−programmed cell death receptor 1 (anti–PD-1) targeted agent. ***Note:*** *In Phase 1, subjects who are BRAF mutation positive must have received prior treatment with a BRAF inhibitor with or without a MEK inhibitor.*
  - Ocular melanoma will be excluded.
- For subjects with NSCLC:
  - Subjects who have tumors with driver mutations (eg, epidermal growth factor receptor [EGFR] mutation positive or anaplastic lymphoma kinase fusion oncogene positive) must have received treatment with a targeted therapy and have progressed or be intolerant, if a targeted agent is available for the specific driver mutation.
  - Subjects may have received prior treatment with an anti−PD-1 targeted agent.
- For subjects with pancreatic cancer (Phase 1 only):
  - Subjects in Phase 1 must have an exocrine pancreatic neoplasm.
    Note: *Exocrine pancreatic neoplasms include all tumors related to the pancreatic ductal and ancinar cells and their stem cells.*
- For subjects with SCCHN:
  - Histology of squamous cell carcinoma.
    - Carcinoma of the nasopharynx and salivary gland will be excluded.
  - Prior systemic regimens must include a platinum-based therapy. Investigational agents used in combination with standard therapies are allowed. Subjects who relapse within 6 months of adjuvant therapy, including a platinum-containing regimen, may enroll.
- For subjects with TNBC:
  - Histologically or cytologically confirmed breast adenocarcinoma that is unresectable or metastatic.
  - Subjects with breast cancer history of different phenotypes (ie, estrogen receptor [ER]/progesterone receptor [PgR]/human epidermal growth factor receptor 2 [HER2] positive) must have pathologic confirmation of triple-negative disease from the most current biopsy.
  - Pathologically confirmed as triple negative, source documented, defined as both of the following:
    - ER and PgR negative: < 1% of tumor cell nuclei is immunoreactive in the presence of evidence that the sample can express ER or PgR (positive intrinsic controls).
    - HER2 negative as per American Society of Clinical Oncology/College of American Pathologists HER2 test guidelines.

Note: *HER2 test result should be reported as negative if a single test (or all tests) performed in a tumor specimen show the following:*

- *Immunohistochemistry (IHC) 1+ as defined by incomplete membrane staining that is faint/barely perceptible and within > 10% of the invasive tumor cells.*
- *IHC result is 0 as defined by no staining observed or membrane staining that is incomplete and is faint/barely perceptible and within ≤ 10% of the invasive tumor cells.*
- *In situ hybridization (ISH) assay is negative based on a single probe average HER2 copy number < 4.0 signals/cell or dual probe HER2/CEP17 ratio < 2.0 with an average HER2 copy number < 4.0 signals/cell.*
- *If results are equivocal, reflex testing (same specimen using the alternative test or new specimen, if available) should be performed using an alternative assay (IHC or ISH).*

- For subjects with TCC of the GU tract:
  - Histologically or cytologically confirmed TCC of the bladder, ureter, or renal pelvis or mixed histology bladder cancer.
  - Metastatic or locally advanced and not amenable to curative therapy with disease progression on or after platinum-based chemotherapy or alternative therapy if platinum-based therapy is not appropriate.
- For subjects with gastric or GE junction cancer:
  - Histologically or cytologically confirmed diagnosis of gastric or GE junction adenocarcinoma.
  - Progression on or after therapy containing platinum/fluoropyrimidine.
  - Documentation of HER2/neu status.
- Presence of measurable disease per RECIST v1.1 guidelines.
- ECOG performance status 0 to 1.
- Fresh baseline tumor biopsies (fresh baseline biopsy is defined as a biopsy specimen taken within 28 days prior to Cycle 1 Day 1) are required at baseline, except if inaccessible with medical monitor approval. Archival tissue should also be submitted if available.

  Note: *If a fresh baseline biopsy is inaccessible, an archival specimen should be submitted.*

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 treatment initiation.
  - Absolute neutrophil count < 1.5×10^9/L.
  - Platelets < 75×10^9/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 (glomerular filtration rate can also be used in place of creatinine or CrCl) < 50 mL/min for subjects with creatinine levels > 1.5 × institutional ULN.
  - AST or ALT > 2.5 × institutional ULN OR > 5 × ULN for subjects with liver metastases.
  - Total bilirubin > 1.5 × ULN OR direct bilirubin > institutional ULN for subjects with total bilirubin levels > 1.5 × ULN.
    - If there is no institutional normal range available for the direct bilirubin, the direct bilirubin should be < 40% of the total bilirubin.
    - In no case can total bilirubin exceed 3.0 × ULN.
  - International normalized ratio (INR) or prothrombin time (PT) > 1.5 × ULN (unless subject is receiving anticoagulant therapy, then subject may be included as long as PT or INR is within therapeutic range of intended use of anticoagulants).
  - Activated partial thromboplastin time (aPTT) > 1.5 × ULN (unless subject is receiving anticoagulant therapy, then subject may be included as long as aPTT is within therapeutic range of intended use of anticoagulants).

- Current pregnancy or breastfeeding.
- Participation in any other study in which receipt of an investigational study drug occurred within 28 days or 5 half-lives (whichever is longer) prior to first dose. For investigational agents with long half-lives (eg, 5 days), enrollment prior to the fifth half-life requires medical monitor approval.
- Receipt of prior immune checkpoint inhibitors (eg, anti–CTLA-4, anti–programmed cell death receptor 1 [anti–PD-1], anti–programmed cell death ligand 1 [anti–PD-L1], and any other antibody or drug specifically targeting T-cell costimulation) or an indoleamine 2,3-dioxygenase (IDO) inhibitor. Subjects who have received experimental vaccines or other immune therapies should be discussed with the medical monitor to confirm eligibility.

  Note: *The exception to this exclusion criterion would be subjects who have received a prior anti–CTLA-4 or PD-1 pathway targeted agent for indications in which an anti–CTLA-4 or PD-1 pathway targeted agent has been approved (eg, melanoma). In this case, the subject would be eligible to participate in the study.*
- Receipt of an immunologically based treatment for any reason, including chronic use of systemic steroid at doses ≥ 10 mg/day prednisone equivalent within 14 days prior to the first dose of study treatment. Use of inhaled or topical steroids or systemic corticosteroids < 10 mg is permitted.
- Receipt of any anticancer medication in the 21 days prior to receiving the first dose of study medication or any unresolved toxicity > Grade 1 from previous anticancer therapy, except for stable chronic toxicities not expected to resolve, such as peripheral neurotoxicity. Prior treatment with nitrosureas (eg, carmustine or lomustine) require a 6-week washout prior to the first dose of study treatment.
- Untreated central nervous system (CNS) metastases or carcinomatous meningitis, or CNS metastases that have progressed (eg, evidence of new or enlarging CNS metastasis or new neurological symptoms attributable to CNS metastases). Subjects with treated, clinically stable CNS metastases (defined as 2 brain images at least 4 weeks apart, both of which were obtained after treatment to the brain metastases) and who are off all corticosteroids for at least 2 weeks are eligible.
- Any active or inactive autoimmune process or inflammatory disorder (including rheumatoid arthritis, moderate or severe psoriasis, multiple sclerosis, sarcoidosis syndrome, diverticulitis [with the exception of diverticulosis], inflammatory bowel disease, systemic lupus erythematosus, Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, hypophysitis, uveitis, etc]) or receipt of systemic therapy for an autoimmune or inflammatory disease.

  Note: *Exceptions include subjects with vitiligo, hypothyroidism stable on hormone replacement, controlled asthma, Graves' disease, or Hashimoto's disease, celiac disease controlled by diet alone, or with medical monitor approval. Subjects without active disease in the last 5 years may be included but only after consultation with medical monitor.*
- Evidence of interstitial lung disease or active, noninfectious pneumonitis.
- Prior radiotherapy within 2 weeks of therapy. Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation to non-CNS disease with medical monitor approval.
- Receipt of monoamine oxidase inhibitors within the 21 days prior to the first dose of study treatment.
- History of serotonin syndrome after receiving 1 or more serotonergic drugs.
- History or presence of an abnormal electrocardiogram (ECG) that, in the investigator's opinion, is clinically meaningful. Screening QTc interval > 480 msec is excluded (corrected by Fridericia or Bazett's formula). In the event that a single QTc is > 480 msec, the subject may be enrolled if the average QTc for the 3 ECGs is ≤ 480 msec. For subjects with an intraventricular conduction delay (QRS interval ≥ 120 msec), the JTc interval may be used in place of the QTc with sponsor approval. The JTc must be < 340 msec if JTc is used in place of the QTc. Subjects with left bundle branch block are excluded.

Study Schedule/Procedures:

Subjects will have regularly scheduled study visits at the clinic site on Day 1 of every cycle (± 3 days) where laboratory assessments, vital sign collection, and physical examinations will be performed. Additional visits will be required during Cycle 1 for PK [redacted] assessment for subjects in Phase 1. Liver function (chemistry) tests will be performed every 14 days. Assessment of tumor size (by magnetic resonance imaging or computed tomography scan) will be performed at screening or baseline (prior to beginning therapy) and every 12 weeks until the end of treatment. Disease progression should be confirmed by a second, consecutive assessment at least 4 weeks after the first indication of progression per mRECIST v1.1 when the subject is clinically stable.

Fresh tumor biopsies will be required (except as indicated in the inclusion criteria) at baseline [redacted]

Standard PK parameters (eg, $t_{½}$, C_{ss}, V_{ss}, AUC, clearance) will be determined for durvalumab and epacadostat.

Primary Endpoints:

- Phase 1: MTD or PAD. The MTD is defined by the highest dose cohort where no more than 1 of 6 subjects experience a DLT, or the highest Protocol-defined dose for each agent in the absence of exceeding the MTD. Alternatively, the PAD is defined as a tolerated dose of epacadostat (in combination with durvalumab) that produces substantial pharmacologic target inhibition. Safety and tolerability will be assessed by monitoring the frequency, duration, and severity of adverse events (AEs), through physical examinations, by evaluating changes in vital signs and ECGs, and through clinical laboratory blood and urine sample evaluations.
- Phase 2: Objective response rate determined by radiographic disease assessments per mRECIST v1.1.

Secondary Endpoints:

- Phase 1: Objective response rate determined by radiographic disease assessments per mRECIST v1.1.
- Phase 2: Safety and tolerability of the combination as assessed by monitoring the 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.
- Phases 1 and 2: Durability of response determined by radiographic disease assessment defined as the time from earliest date of disease response until earliest date of disease progression.
- Phases 1 and 2: PFS determined from the date of randomization until disease progression or death.
- Phases 1 and 2: The endpoints for assessment of PK of durvalumab and epacadostat include individual durvalumab and epacadostat concentrations and PK parameters.
- Phases 1 and 2: The endpoints for assessment of immunogenicity of durvalumab include the number and percentage of subjects who develop detectable anti-drug antibodies.

[redacted]

[redacted]

Planned Number of Subjects:

Phase 1: Approximately 36 subjects

Phase 2: Approximately 140 to 192 subjects

Principal Coordinating Investigator: TBD

Estimated Study Duration:

Estimated date first subject enrolled: 29 OCT 2014
Estimated date last subject completed: 25 OCT 2019

Statistical Methods:

Up to 36 subjects will be enrolled in the Phase 1 dose-escalation portion of the study and approximately 140 to 192 subjects will be enrolled in Phase 2 based on the Simon 2-stage design and expansion cohorts in select solid tumors. Descriptive statistics (eg, mean, standard deviation, range) will be derived where appropriate. Subject enrollment, disposition, demographics, and medical history will be summarized at baseline. The rate of DLTs will be summarized for each cohort. Dose exposure and density will be calculated for each cohort. Objective response rate will be summarized. Median duration of response and PFS will be analyzed by the Kaplan-Meier method. Pharmacokinetic [redacted] data will be analyzed with appropriate standard nonlinear analytic software.

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LIST OF ABBREVIATIONS

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

Term	Explanation
ADA	antidrug antibody
AE	adverse event
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
BID	twice daily
BRCA	breast cancer gene
CA19-9	carbohydrate antigen 19-9
CAP	College of American Pathologists
CFR	Code of Federal Regulations
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum concentration
C_{min}	minimum observed plasma or serum concentration over the dose interval
CNS	central nervous system
CR	complete response
CRF	case report form
C_{ss}	steady-state concentration
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated antigen 4
DC	dendritic cells
DLCO	diffusing capacity of the lung for carbon monoxide
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DM	diabetes mellitus
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eDMC	external data monitoring committee
EGFR	epidermal growth factor receptor
E_{max}	maximum effect
EOT	end of treatment

Term	Explanation
ER	estrogen receptor
FDA	Food and Drug Administration
FEF	forced expiratory flow
FEV_1	forced expiratory volume in 1 second
FT4	free thyroxine
5-FU	fluorouracil
FVC	forced vital capacity
GCP	Good Clinical Practice
GE	gastroesophageal
GI	gastrointestinal
gp100	glycoprotein 100
GU	genitourinary
HBV	hepatitis B virus
HCV	hepatitis C virus
HDPE	high-density polyethylene
HER2	human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act of 1996
HPV	human papillomavirus
HR	hazard ratio
I_{ave}	average inhibition
IB	Investigator's brochure
IC_{50}	concentration that results in 50% inhibition
ICF	informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDO1	indoleamine 2,3-dioxygenase 1
IEC	Independent Ethics Committee
Ig	immunoglobulin
IHC	immunohistochemistry
IN	Investigator Notification
INR	international normalized ratio
irAE	immune-related adverse event
IRB	Institutional Review Board
[redacted]	[redacted]
ISH	in situ hybridization
IV	intravenous
IVIG	intravenous immunoglobulin
LFT	liver function (chemistry) test
LLN	lower limit of normal
MAOI	monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities

Term	Explanation
mRECIST v1.1	Modified Response Evaluation Criteria in Solid Tumors Version 1.1
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PAD	pharmacologically active dose
PCP	pneumocystis pneumonia
PD-1	programmed cell death receptor 1
PD-L1	programmed cell death ligand 1
PD	progressive disease
PFS	progression-free survival
PgR	progesterone receptor
PK	pharmacokinetic(s)
PO	orally
PR	partial response
PT	prothrombin time
QD	once daily
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SNRI	serotonin/norepinephrine reuptake inhibitor
SS	serotonin syndrome
SSRI	selective serotonin reuptake inhibitor
$t_{½}$	half-life
TCC	transitional cell carcinoma
T_{max}	time to maximum concentration
TNBC	triple-negative breast cancer
Treg	regulatory T cell
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
VA	alveolar volume
V_{ss}	volume of distribution at steady state

1. INTRODUCTION

INCB 24360-203 is a Phase 1/2 study of epacadostat administered in combination with durvalumab in subjects with advanced melanoma, NSCLC, pancreatic cancer (Phase 1 only), SCCHN, TNBC, gastric or GE junction cancer, and TCC of the GU tract. Phase 1 will be an open-label dose escalation to identify the MTD or PAD of epacadostat in combination with durvalumab. Phase 2 will further explore the safety and efficacy of the MTD or PAD of epacadostat in combination with durvalumab determined in Phase 1. Epacadostat represents a novel, potent, and selective inhibitor of the enzyme IDO1 in both human tumor cells and human DCs.

Durvalumab is a human IgG1κ monoclonal antibody directed against human PD-L1. The antibody is composed of 2 identical heavy chains of approximately 49,670 Da each, and 2 identical light chains of approximately 23,390 Da each. The fragment crystallizable domain of durvalumab contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to the complement component C1q and the fragment crystallizable gamma receptors responsible for mediating antibody-dependent cell-mediated cytotoxicity.

For a thorough discussion of the pharmacology of epacadostat and durvalumab, refer to the epacadostat Investigator's Brochure (iIB) and the current durvalumab Investigator's Brochure (mIB).

1.1. Pharmaceutical and Therapeutic Background

The immune system has the innate ability to detect and eliminate aberrant cells, including tumor cells. This occurs through T cells by recognizing the aberrant proteins of malignant cells and coordinating an immune response against them. Tumor cells have been shown to evade the immune system by exploiting the immune checkpoint pathways that down regulate the immune response to avoid healthy tissue damage (Davies 2014). Immune therapies targeting the immune checkpoint pathways have recently become an important therapeutic strategy for harnessing the immune system's ability to control malignancy. The PD-1 pathway and the tryptophan-catabolizing enzyme, IDO1, are 2 components of the checkpoint pathways that have been shown to be present in the tumor microenvironment and appear to be valid immunotherapy targets for generating a successful immune response (Creelan 2014, Spranger et al 2014).

1.1.1. Inhibition of PD-1 Signaling as a Target for Cancer

The PD-1 receptor-ligand interaction is a key component to the immune checkpoint pathway. The normal function of PD-1, expressed on the cell surface of activated T cells under normal conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. Similar to CTLA-4, PD-1 is a surface receptor member of the B7-CD28 superfamily. It has been shown to induce T-cell tolerance by negatively regulating antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (Talmadge et al 2007, Creelan 2014). The mechanism by which PD-1 down-modulates T-cell responses is similar to but distinct from that of CTLA-4, as both molecules regulate an overlapping set of signaling proteins (Hiraoka 2010, Nobili et al 2008). PD-1 has been shown to be expressed on activated lymphocytes, including peripheral CD4+ and CD8+ T cells, B cells, Tregs, and natural killer

cells (Hodi and Dranoff 2010, Kloor 2009). The ligands for PD-1 (PD-L1 and PD-L2) are expressed in several cell types, including nonhematopoietic tissues and many tumors (Lee et al 2008, Leffers et al 2009, Nishimura et al 2000, Hiraoka 2010). Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various nonhematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues (Hiraoka 2010). PD-L1 is expressed in many human tumors and has been associated with a poor prognosis (Thompson et al 2007, Konishi et al 2004, Hamanishi et al 2007, Nomi et al 2007, Boland et al 2013). This evidence suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and that upregulation of this pathway contributes to immune tolerance and tumor progression and should be considered as a target for the therapeutic intervention of cancer.

1.1.2. Inhibition of IDO1 as a Target for Cancer

Recent interest has focused on the role of IDO1 as a mechanism of immune tolerance in malignancy (Godin-Ethier et al 2011). 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 breakdown 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). IDO1 activity also promotes the differentiation of naive T cells to Tregs (Fallarino et al 2006). Since 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 expansion of Tregs may provide an additional mechanism whereby IDO1 could promote an immunosuppressive environment.

A critical role for IDO1 in immune modulation 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), [redacted]

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 melanoma, ovarian, colorectal, and pancreatic cancers (Okamoto et al 2005, 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 advanced malignancies either alone or in combination with chemotherapeutics and/or immunotherapy-based strategies.

1.1.3. Epacadostat

Epacadostat represents a novel, potent, and selective inhibitor of the enzyme IDO1. In cell-based assays, epacadostat potently inhibits IDO1 in both human tumor cells and human DCs, resulting in reduced tryptophan to kynurenine conversion (IC_{50} values = 7.1-12.7 nM). Epacadostat does not significantly inhibit other proteins that could impact tryptophan catabolism.

To assess its selectivity profile, epacadostat was evaluated in a broad panel of approximately 55 different receptors, ion channels, transporters, and nonkinase enzymes. Epacadostat demonstrated activity at the human vasopressin 1a receptor (IC_{50} value = 0.67 μM) and weak activity at the human dopamine transporter (22% and 71% inhibition at 1 and 10 μM, respectively) and human carbonic anhydrase II enzyme (IC_{50} = 5.3 μM). In cell culture, epacadostat reverses the strongly inhibitory effect on the development of T-cell–mediated responses that IDO1 activity imparts, resulting in enhanced T-cell and natural killer cell proliferation, enhanced interferon γ production, reduced Treg differentiation, reduced DC apoptosis, and enhanced expression of DC activation markers.

Epacadostat reversal of the IDO1-mediated suppression of T-cell proliferation is dose-dependent with a potency consistent with its inhibition of tryptophan to kynurenine conversion

(half maximal effective concentration = 17.7 nM). The in vivo data demonstrate that epacadostat can inhibit IDO1 systemically and, importantly, in tumors and tumor-draining lymph nodes. Epacadostat was efficacious in mouse models of colon and pancreatic cancer, and its ability to reduce tumor growth was dependent on a functional immune system, consistent with its proposed mechanism of action. Moreover, epacadostat enhanced lymphocyte function in tumors and tumor-draining lymph nodes. [redacted] Finally, epacadostat improved the tumor growth control of cytotoxic chemotherapy when used in combination. These data support the evaluation of epacadostat in patients with malignant diseases.

1.1.4. Durvalumab

Durvalumab, an anti–PD-L1 antibody, is a potential anticancer therapy for patients with advanced solid tumors. Durvalumab is a human monoclonal antibody of the IgG1κ subclass that inhibits binding of PD-L1 to PD-1 and CD80. Durvalumab is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 149 kDa. Durvalumab contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to complement protein C1q and the Fcγ receptors involved in triggering effector function (Oganesyan et al 2008).

1.1.5. Combined Immune Checkpoint Inhibition

Blockade of immune inhibitory pathways is emerging as an important therapeutic modality for the treatment of cancer as evidenced by the clinical responses observed with antibodies to CTLA-4 and PD-1/PD-L1. Ipilimumab, a fully human, IgG1 monoclonal antibody blocking CTLA-4, improved OS in patients with advanced melanoma (Hodi et al 2010, Robert et al 2011). Subsequently, both nivolumab (BMS-936558) and pembrolizumab (MK-3475), which are IgG4 monoclonal antibodies targeting PD-1, have shown preliminary efficacy in multiple tumor types. Nivolumab and pembrolizumab (MK-3475) have been shown to produce durable objective responses in patients with melanoma, renal cell cancer, and NSCLC (Topalian et al 2012, Hamid et al 2013, Garon et al 2015). Targeting PD-L1 with MPDL3280A has also shown Phase 1 responses in multiple tumor types, including NSCLC, renal cell carcinoma, melanoma, colorectal carcinoma, and gastric cancer (Herbst et al 2013). More recently, the anti–PD-L1 antibody durvalumab has shown Phase 1 responses in subjects with NSCLC, SCCHN, gastroesophageal cancer, and pancreatic adenocarcinoma (Segal et al 2014).

Although these single agents have all exhibited antitumor activity, multiple immune inhibitory mechanisms are present concurrently within the tumor microenvironment, [redacted] (Quezada and Peggs 2013, Spranger et al 2014). For example, CTLA-4 and PD-1 appear to play complementary roles in regulating adaptive immunity. Whereas PD-1 contributes to T-cell exhaustion in peripheral tissues, CTLA-4 inhibits at earlier points in T-cell activation. In preclinical models, combined blockade of PD-1 and CTLA-4 achieved more pronounced antitumor activity than blockade of either pathway alone (Curran et al 2010, Selby et al 2013).

On the basis of these observations, both a Phase 1 and Phase 2 study were conducted to investigate the safety and efficacy of combined CTLA-4 and PD-1 blockade (with the use of

ipilimumab and nivolumab, respectively) in subjects with advanced melanoma. In the Phase 1 open-label, dose escalation study of nivolumab in combination with ipilimumab, ORR (according to the modified World Health Organization criteria) for all subjects in the concurrent regimen group was 40%. Evidence of clinical activity (conventional, unconfirmed, or immune-related response or SD for ≥ 24 weeks) was observed in 65% of subjects. In 17 subjects treated at the maximum doses that were associated with an acceptable level of AEs, 53% of subjects had an objective response compared with ipilimumab monotherapy (10.9%), all with tumor reduction of ≥ 80%. Grade 3 or 4 AEs related to therapy occurred in 53% of subjects in the concurrent-regimen group but were qualitatively similar to previous experience with monotherapy and were generally reversible (Wolchok et al 2013).

In the Phase 2 randomized, double-blinded study of nivolumab in combination with ipilimumab versus ipilimumab alone in subjects with previously untreated, unresectable or metastatic melanoma, the investigator-assessed ORR among subjects with *BRAF* wild-type tumors was 61% (95% CI, 49 to 72) in the combination group versus 11% in the ipilimumab monotherapy group. A CR was observed in 16 subjects (22%) in the combination group and no subjects in the ipilimumab monotherapy group. In subjects with *BRAF* wild-type tumors, median PFS was not reached with the combination and was 4.4 months (95% CI, 2.8 to 5.7) with ipilimumab monotherapy (HR, 0.40; 95% CI, 0.23 to 0.68; $p < 0.001$). Among subjects with *BRAF* mutation positive tumors, the ORR was 52% (12 of 23 subjects) in the combination group. Median PFS for the combination was 8.5 months (95% CI, 2.8 to not estimable) and 2.7 months (95% CI, 1.0 to 5.4) in the ipilimumab monotherapy group. The rate of treatment-related AEs was 91% in the combination group and 93% in the ipilimumab monotherapy group. Drug-related AEs of Grade 3 or 4 were reported more frequently in the combination group than in the ipilimumab monotherapy group (54% vs 24%). Select AEs with potential immunological causes were consistent with the Phase 1 study, and most of the events resolved with immune-modulating medication (Postow et al 2015).

As described above, IDO1 is another negative regulatory mechanism that contributes to tumor-derived immune suppression. In preclinical models, IDO1 inhibition has been shown to synergize with blockade of either anti–CTLA-4 or anti–PD-1/PD-L1 in delaying tumor growth and increasing OS (Holmgaard et al 2013, Spranger et al 2014). This effect was shown to be T-cell–dependent, leading to enhanced T-cell proliferation and interleukin-2 production within the tumor and to a marked increase in the effector-to-regulatory T-cell ratios in the tumors.

In an ongoing Phase 1/2 open-label dose-escalation study of epacadostat in combination with ipilimumab (3 mg/kg IV), daily doses of epacadostat have been evaluated in 21-day cycles. In the initial Phase 1 dose-escalation portion, 5 of 7 subjects receiving epacadostat 300 mg BID in combination with 4 doses of ipilimumab (3 mg/kg every 3 weeks) developed clinically significant ALT elevations; therefore, the study was amended to evaluate lower epacadostat doses. At the 300 mg BID dose level, 6 of 7 subjects had evaluable scans and all showed SD as assessed by irRC. Enrollment was restarted at 25 mg BID (n = 8), where 1 subject with progression of prior extensive liver metastases had a dose-limiting toxicity (DLT; Grade 3 AST elevation). Subsequent cohorts received 50 mg BID continuous, 50 mg BID intermittent (2 weeks on, 1 week off), and 75 mg BID (50 mg every morning/25 mg every evening) in combination with 4 doses of ipilimumab 3 mg/kg every 3 weeks. Eighteen subjects were enrolled in the 50 mg BID continuous dosing cohort, and 4 DLTs were reported (1 Grade 3

diarrhea, 1 Grade 3 AST/ALT elevation, 1 Grade 3 colitis, 1 Grade 3 pneumonitis). At the 50 mg BID intermittent dose level, 1 of the 9 subjects enrolled experienced a DLT of Grade 3 colitis, and in the 75 mg total daily dose cohort, 1 DLT of Grade 3 rash was reported in the 7 subjects enrolled. Epacadostat doses of ≤ 50 mg BID in combination with ipilimumab were generally well tolerated, and all immune-related AEs were reversible with appropriate management (Gibney et al 2015).

In summary, both IDO1 and PD-1/PD-L1 have been shown to suppress T-cell–mediated antitumor immunity. [redacted] Preclinical and clinical data indicate that these pathways are important in various cancers.

1.1.6. Melanoma

For a number of years, the standard of care for advanced melanoma included dacarbazine. Similar response rates were subsequently demonstrated in advanced disease for both dacarbazine and temozolomide, and both were considered standard-of-care options. Response rates are generally in the range of 10% to 20% with median response durations of 3 to 4 months.

Ipilimumab was approved by the FDA and in the EU in 2011 for the treatment of unresectable or metastatic melanoma on the basis that it has been shown to improve survival of previously treated subjects with advanced melanoma (Hodi et al 2010). Ipilimumab is a fully humanized IgG1κ monoclonal antibody against CTLA-4, and was evaluated in 676 subjects with unresectable Stage 3 to 4 melanoma, with comparisons between ipilimumab alone, ipilimumab + gp100 peptide vaccine, or gp100 alone. The median OS with ipilimumab + gp100 was 10.0 months compared to 6.4 months for gp100 alone (HR 0.68; $p < 0.001$). No difference in OS was seen among the 2 ipilimumab groups. This study was preceded by a number of Phase 2 studies that evaluated dose ranging, single-agent activity in a nonrandomized setting, and the addition of a steroid in an attempt to ameliorate the immunologic toxicities (O'Day et al 2010, Weber et al 2009, Wolchok et al 2010). Response rates in these Phase 2 studies ranged from 6% to 15% with some suggestion for improved 1- and 2-year survival rates. Monotherapy ipilimumab has also recently been approved for use as adjuvant therapy for patients with Stage III melanoma to reduce the risk of recurrence following surgery (Eggermont et al 2015).

Other therapies for advanced melanoma include a BRAF inhibitor (vemurafenib, RG7204) that has demonstrated promising results among subjects whose tumors exhibit the V600E BRAF mutation (Flaherty et al 2010, Chapman et al 2011). Recent results from a Phase 3 study that compared vemurafenib to dacarbazine among 675 subjects with advanced melanoma carrying the V600E mutation demonstrated improved efficacy for vemurafenib and supported approval in the United States (Chapman et al 2011) and in the EU. Median OS was 13.6 months (95% CI: 12.0, 15.3) in the vemurafenib group and 10.3 (95% CI: 9.1, 12.8) in the dacarbazine group. In the interim analysis for OS and final analysis for PFS, vemurafenib was 5.3 months (95% CI: 4.9, 6.6) as compared with dacarbazine 1.6 months (95% CI: 1.6, 1.7), with a p-value of < 0.0001 for both comparisons.

More recently, the FDA and the EU have approved the use of multiple combination regimens for BRAF-mutant metastatic melanoma. Dabrafenib in combination with trametinib was approved for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600

mutation. This indication was based on the demonstration of durable response rate. The median duration of response was 10.5 months for the dabrafenib plus trametinib combination compared to 5.6 months for trametinib alone. Dabrafenib and trametinib are also approved for monotherapy use in patients with unresectable or metastatic melanoma with BRAF V600. The FDA and EU also approved cobimetinib for use in combination with vemurafenib for the treatment of advanced melanoma carrying the V600E mutation (Larkin et al 2014). In the Phase 3 study by Larkin et al (2014), 495 patients with previously untreated unresectable locally advanced or metastatic melanoma carrying the BRAF V600 mutation received vemurafenib and cobimetinib or vemurafenib and placebo. Median PFS was 9.9 months in the combination group and 6.2 months in the control group (hazard ratio for death or disease progression, 0.51; 95% CI, 0.39 to 0.68, $p < 0.001$).

The unmet medical need remains high for advanced melanoma, with only 10-month median survival expected for subjects treated with ipilimumab alone, and 1-year survival rates < 50%.

Malignant melanoma can be considered an immunogenic tumor and activity with anti–PD-1 and anti–PD-L1 antibodies is encouraging and well documented in this tumor type. MK-3475 (pembrolizumab) was approved by FDA and the EU for the treatment of patients with advanced (unresectable or metastatic) melanoma in adults. Opdivo® (nivolumab) monotherapy and in combination with ipilimumab was also approved by FDA and the EU for treatment of patients with advanced (unresectable or metastatic) melanoma. PD-1 inhibitors are rapidly becoming the treatment of choice in this disease setting as evidenced by the expansive list of recent approvals and committee recommendations noted above.

Studies exploring the OS of these agents are ongoing, and early data are encouraging. Expression of IDO and interleukin-10 have been found to be increased in melanoma as the disease progresses, and expression of IDO in tumor cells has been associated with shorter subject survival (Polak et al 2007, Brody et al 2009, Liu et al 2009). Other studies have shown that decreased serum tryptophan concentrations are associated with poor prognosis for melanoma subjects (Weinlich et al 2007). [redacted]

1.1.7. Non–Small Cell Lung Cancer

Lung cancer is the most common cause of death from cancer worldwide, estimated to be responsible for nearly 1 in 5 (18%), or 1.38 million, cancer deaths in 2008 (Ferlay et al 2010). In the United States, it was estimated that 226,160 people will be diagnosed with and 160,340 will die from cancer of the lung and bronchus in 2012 (Howlader et al 2013).

Non–small cell lung cancer accounts for approximately 80% of all cases of lung cancer. Many patients present with early-stage disease and are treated with curative intent using surgery or radiation therapy, sometimes combined with concurrent or adjuvant chemotherapy (Goldstraw et al 2007). In contrast, systemic therapy is generally appropriate for patients with more advanced disease at presentation. Systemic therapy is also used for patients who have relapsed with advanced disease after definitive treatment.

Initial systemic therapy (chemotherapy or targeted agents) may delay disease progression and prolong survival in patients with advanced NSCLC; however, almost all patients eventually develop PD. Therapy should be individualized based on molecular and histologic features of the

tumor. Whenever possible, patients should have tumor tissue assessed for the presence of a driver mutation that stimulates tumor growth. These mutations define subsets of patients likely to respond to specific inhibitors (NCCN Guidelines). Patients with a known driver mutation in the EGFR are initially managed with an EGFR tyrosine kinase inhibitor (Moran and Sequist 2012, Gridelli et al 2012). Those with an anaplastic lymphoma kinase fusion oncogene in their tumor are preferentially treated with crizotinib (Kwak et al 2010, Camidge et al 2012, Shaw et al 2013). Patients without a driver mutation are generally treated with chemotherapy.

Most patients with advanced NSCLC eventually develop PD and require additional treatment after their initial treatment with either chemotherapy or targeted therapy. Currently approved cytotoxic chemotherapies for previously treated patients with NSCLC demonstrate few objective responses, which are generally of short duration, with limited impact on PFS and OS.

Phase 1 studies of anti–PD-1 agents have demonstrated promising results. The FDA granted approval for pembrolizumab for the treatment of metastatic NSCLC. Pembrolizumab was approved for patients whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing regimens (Garon et al 2015). Patients with EGFR or ALK genomic tumor aberrations should have disease progression on an FDA-approved therapy for these aberrations before receiving pembrolizumab. In the Phase 1 study by Garon et al (2015), an ORR of 19.4% was reported in the 495 NSCLC patients who received monotherapy pembrolizumab. Median duration of response was 12.5 months, median PFS was 3.7 months, and OS was 12 months. Nivolumab was also approved by the FDA and the EU for patients with locally advanced or metastatic NSCLC with progression after chemotherapy. In the United States, patients with EGFR or ALK genomic tumor aberrations should also have disease progression on an FDA-approved therapy for these agents. The Phase 3 study comparing nivolumab to docetaxel resulted in an OS of 12.2 months (95% CI, 9.7 to 15.0) among 292 subjects in the nivolumab group and 9.4 months among the 290 subjects in the docetaxel group (HR, 0.73; 96% CI, 0.59 to 0.89; p = 0.002). The response rate with nivolumab was 19% as compared with 12% in the docetaxel group (p = 0.02) (Borghaei et al 2015).

In addition to PD-1 inhibition, drugs targeting PD-L1 have also shown promising data. MPDL3280A, a humanized monoclonal antibody that blocks PD-L1 from binding to its receptors, including PD-1 and B7.1, has shown similar efficacy. In a Phase 1 study that included subjects with both squamous and nonsquamous NSCLC; ORR was 24% (9/37), and at the time of the abstract publication, all responses were ongoing and improving (Soria et al 2013). The 24-week PFS was 46%. Analysis of biomarker data from tumor samples demonstrated a correlation between PD-L1 status and efficacy in both the MPDL3280A and pembrolizumab (MK-3475) studies.

Targeting the IDO1 enzyme has been studied in subjects with metastatic NSCLC as well in the form of vaccination with an epitope derived from IDO1. In the Phase 1 study, no severe toxicities occurred. One of 15 HLA-A2−positive subjects treated developed a PR after 1 year of vaccine treatment, and SD of ≥ 8.5 months was reported in another 6 subjects. The median survival was 25.9 months, and long-lasting PR + SD was seen in 47% of the subjects. Expression of IDO was detected in 9 of 10 tumor biopsy specimens by IHC (Iversen et al 2014).

1.1.8. Pancreatic Cancer

Cancer of the exocrine pancreas is a highly lethal malignancy. Pancreatic cancer is the 13th most common form of cancer worldwide, with 279,000 people diagnosed in 2008 (Ferlay 2008). Most die from the disease because it commonly presents in an advanced state.

Chemotherapy represents the cornerstone of initial therapy for patients with advanced disease. Until recently, single-agent gemcitabine or gemcitabine in combination with erlotinib was considered the standard of care for most patients in the first-line advanced disease setting (Burris et al 1997, Moore et al 2007). Two combination regimens have recently emerged as new standards of care based on Phase 3 studies in which the combinations were compared to gemcitabine monotherapy.

Subjects treated with gemcitabine in combination with *nab*-paclitaxel showed a statistically significant improvement in OS compared with subjects receiving gemcitabine alone (median of 8.5 months vs 6.7 months; HR 0.72, $p = 0.000015$). Based on these results, the combination of gemcitabine plus *nab*-paclitaxel was approved by the FDA for the first-line treatment of metastatic adenocarcinoma of the pancreas and has emerged as a standard of care for the treatment of patients with advanced disease and good performance status (NCCN Guidelines).

The superiority of FOLFIRINOX (a regimen that combines leucovorin-modulated 5-FU with irinotecan and/or oxaliplatin) over gemcitabine monotherapy was initially suggested in a randomized Phase 2 study that showed FOLFIRINOX was associated with a high ORR (39% vs 11%) and manageable toxicity (Ychou et al 2007). The study was expanded to a Phase 3 study in which chemotherapy-naive subjects with metastatic pancreatic cancer were randomly assigned to gemcitabine alone versus the FOLFIRINOX regimen (Conroy et al 2011). The study was stopped when a preplanned interim analysis demonstrated that the primary endpoint of OS had been met (median 11.1 months vs 6.8 months; HR 0.57; $p < 0.001$). These data establish FOLFIRINOX as another standard-of-care option in treatment-naive patients with advanced pancreatic cancer with a good performance status (NCCN Guidelines).

The future role of immunotherapy in pancreatic cancer is less clear than the evidence shown in melanoma and NSCLC. Experience in the clinical setting with immunotherapies is limited. A Phase 2 study evaluated the efficacy of ipilimumab in subjects with pancreatic cancer. Twenty-seven subjects were enrolled, and although no responses by RECIST v1.1 were seen, 1 subject did experience a delayed response and regression of the primary lesion and several hepatic metastases. The subject also had an improvement in tumor markers and performance status (Royal et al 2010). Pancreatic cancers have been shown to express PD-L1, which may be contributing to immune suppression and evasion. PD-L1 expression in pancreatic cancer has also been shown to be associated with decreased tumor-infiltrating lymphocytes and poor prognosis (McDermott and Atkins 2013).

As there are currently no approved standard of care for patients with pancreatic cancer who have PD despite first-line therapy, guidelines established by the NCCN in the United States and the European Society of Medical Oncology encourage the participation of patients with recurrent or refractory advanced pancreatic cancer and satisfactory performance status in clinical studies (NCCN Guidelines, Seufferlein et al 2012). Because of the lack of effective therapies for this highly lethal malignancy, it is reasonable to provide an experimental therapy to patients who have failed approved first-line therapies in this setting.

1.1.9. Squamous Cell Carcinoma of the Head and Neck

In the United States alone, approximately 55,070 people will develop head and neck cancer in the next year (Cancer.net 2014). Tobacco use and drinking alcohol greatly increase the risk of developing head and neck cancer. In addition, infection with HPV is associated with the development of head and neck cancer, and the incidence of HPV-associated SCCHN is on the rise. Many patients present with localized disease that may be treated with either surgery or radiation therapy with curative intent (Vermorken and Specenier 2010). Unfortunately, most patients will develop local recurrent disease, and about 20% to 30% of these patients will be diagnosed with distant metastases. Treatment for recurrent/metastatic disease is typically not considered curative and includes chemotherapy or targeted agents. Single agents most commonly used as monotherapy in this setting (eg, methotrexate, cisplatin, and 5-FU) typically have a short duration of response of only approximately 3 to 5 months. Combination chemotherapy may be selected in patients with selected characteristics such as a good performance status (NCCN Guidelines). Response rates of combination therapy are generally improved over monotherapy; however, clinical study data have not proven an OS benefit when compared to methotrexate, cisplatin, or 5-FU monotherapy (Vermorken and Specenier 2010), and these combinations may cause a significant increase in toxicity.

Cetuximab, an agent targeting EGFR, is widely used in the United States and the EU in the setting of recurrent/metastatic disease. In the United States and EU, cetuximab is approved for use in recurrent locoregional or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with 5-FU. In the United States, cetuximab is also approved for patients whose disease has progressed after platinum-based therapy. A study of 442 first-line subjects with SCCHN showed that the addition of cetuximab to platinum-based (cisplatin or carboplatin) therapy with 5-FU significantly improved OS from 7.4 months to 10.1 months (HR = 0.80; p = 0.04). Significant benefits were also seen in PFS and ORR; however, approximately 20% of subjects in each arm discontinued due to AEs.

PD-L1 has been shown to be expressed in the tumor microenvironment of SCCHN. PD-L1 staining by IHC is seen in both HPV-positive tumors and HPV-negative tumors, although HPV positivity does appear to correlate with a higher probability of PD-L1 expression in the tumor microenvironment (Lyford-Pike et al 2013). In early clinical studies, a subject with metastatic SCCHN was treated with the anti–PD-L1 monoclonal antibody MDPL3280A experienced a response by the second cycle of treatment (Herbst et al 2013). More recent data studying the anti–PD-1 antibody MK-3475 in subjects with PD-L1–positive SCCHN has shown a best ORR of 19.6% using RECIST v1.1 (Seiwert et al 2014). Additional studies of anti–PD-1 and anti–PD-L1 agents in the setting of metastatic SCCHN are ongoing.

1.1.10. Triple-Negative Breast Cancer

Triple-negative breast cancer accounts for approximately 20% of breast cancers diagnosed worldwide, or about 200,000 cases each year (Swain 2008). A strong association has been found with African-American race, younger age, higher grade, premenopausal status, more advanced stage at diagnosis, and positive BRCA mutation status. More than 75% of tumors displaying a positive BRCA mutation status are triple negative (Bayraktar et al 2011). Despite initial responses to chemotherapy, TNBC has a poor prognosis as defined by low 5-year survival and high recurrence rates after adjuvant therapy.

Triple negative status is defined as tumors that lack expression of the ER and PgR but express HER2 at normal levels. The ASCO/CAP panel guidelines for determining ER, PgR, and HER2 status were created to improve the accuracy of testing and are commonly used in clinical practice (Hammond et al 2010, Wolff et al 2013).

Triple-negative breast cancer is described as "paradoxical" because of the relatively high likelihood of response and pathologic CR but poorer overall outcomes. The risk of distant recurrence in TNBC and death peaks approximately 3 years after diagnosis and declines rapidly thereafter (Liedtke et al 2008). As compared with ER-positive breast cancers, TNBC has a higher rate of relapse and a higher risk for metastases to the lung and brain (Lin et al 2012). Unfortunately, since endocrine therapy and HER2-directed therapies are ineffective, the only approved option for metastatic TNBC is chemotherapy, which is associated with a median survival of < 1 year.

Recent studies suggest that PD-L1 is expressed in approximately 20% of patients with TNBC (Chawla et al 2014), and immunotherapy agents, including the anti-PD-1 antibody pembrolizumab, appear to be active in heavily pretreated patients with metastatic TNBC. In a Phase 1b study, subjects with PD-L1+ metastatic TNBC were treated with monotherapy pembrolizumab every 2 weeks. Approximately 50% of subjects on study had received ≥ 3 lines of therapy. Of the 27 evaluable subjects, the ORR was 18.5%, median time to response was 18 weeks, and the median duration of response had not been reached (range, 15-40+ weeks). Three of 5 responders at the time of analysis were on treatment for ≥ 11 months (Buisseret et al 2015). Additional studies of both anti–PD-1 and anti–PD-L1 targeted agents are ongoing.

1.1.11. Gastric and Gastroesophageal Junction Cancer

In 2015, an estimated 24,590 and 16,980 patients will be diagnosed with gastric and esophageal cancer, respectively, and approximately 26,310 men and women will eventually succumb to their disease (NCCN 2015). The prognosis for both gastric and GE junction cancers remains overwhelmingly poor. Five-year survival rate rates for patients with proximal gastric cancer are only 10% to 15%. Locally advanced unresectable and metastatic gastroesophageal cancers are not curable, and typically care is managed through a multidisciplinary approach including surgery, radiotherapy, and chemotherapy.

Cisplatin is one of the most active agents for locally advanced metastatic esophageal cancer, with single-agent response rates of approximately 20% or higher. Single-agent activity has also been observed with irinotecan, docetaxel, paclitaxel, and etoposide; however, cisplatin in combination with fluorouracil is the most commonly used regimen, resulting in response rates of approximately 20% to 50%. Other combination chemotherapy regimens including oxaliplatin, carboplatin, mitomycin, and gemcitabine have been evaluated in advanced or metastatic esophageal cancer in the clinical trial setting; however, no consistent benefit was seen for any specific chemotherapy regimen (NCCN 2015).

Recently, targeted therapies have shown clinical activity in the locally advanced or metastatic setting. Ramucirumab, a vascular endothelial growth factor receptor-2 antibody, as a single agent or in combination with paclitaxel, was approved by the FDA and the EU for the treatment of patients with advanced gastric or adenocarcinoma of the esophagogastric junction for whom treatment in combination with paclitaxel is not appropriate or for patients who have progressed after therapy with platinum- or fluropyrimidine-based chemotherapy. In the REGARD trial,

355 subjects were randomized to receive best supportive care plus ramucirumab or placebo. Median OS was 5.2 months in subjects treated in the ramucirumab group compared to 3.8 months for those in the placebo group (p = 0.047) (Fuchs et al 2014). In a second study of ramucirumab in combination with paclitaxel, the combination resulted in significantly higher OS, PFS, and ORR than paclitaxel alone. The median OS for the combination was 9.63 months as compared to 7.63 months in the paclitaxel-alone arm (p = 0.0001) (NCCN 2015).

In the near future, molecular characterization of upper GI tumors is expected to lead to additional treatment options for patients with advanced disease. *HER2*-neu testing is currently recommended if metastatic disease is documented or suspected. In the ToGA study, the addition of trastuzumab to chemotherapy in patients with *HER2*-neu overexpression or amplification resulted in a significant improvement in OS (13.8 vs 11.1 months, p = 0.046) (Bang et al 2010). This study established trastuzumab in combination with chemotherapy as a new standard of care for patients with *HER2*-neu–positive or metastatic gastric and esophagogastric junction adenocarcinoma.

Recent clinical studies suggest that PD-1 and PD-L1 inhibitors may also have clinical activity in gastric and GE junction tumors. In a Phase 1b study, subjects with metastatic adenocarcinoma of the stomach or GE junction received the anti–PD-1 treatment pembrolizumab every 2 weeks. The ORR was 22% (95% CI, 10-39) by central review and 33% by investigator review. Median time to response was 8 weeks (range, 7-16 weeks), median duration of response was 24 weeks (range, 8+ to 33+ weeks), and the 6-month PFS rate was 24% (Muro et al 2015). Additional studies with immunotherapy agents are ongoing.

1.1.12. Transitional Cell Carcinoma of the Genitourinary Tract

Urothelial carcinomas, also referred to as TCCs, are the most common histological subtype in the United States. Transitional cell carcinoma may develop anywhere transitional epithelium is present, from the renal pelvis to the ureter, bladder, and proximal two-thirds of the urethra (NCCN 2015). In the United States, approximately 75,000 new cases and 16,000 deaths occur each year due to bladder cancer (Siegel et al 2015). Occupational and environmental carcinogens as well as tobacco use greatly increase risk of developing bladder cancer. In addition, several studies have suggested a relationship between TCC and HPV infection. A recent meta-analysis found that approximately 17% of bladder cancers are HPV-positive (Li et al 2011). The life expectancy for patients with metastatic urothelial cancer is poor, with a median OS of 12 to 18 months. Treatment selection for advanced disease is dependent on a number of factors, including the presence of medical comorbidities, cardiac disease, renal functional, performance status, and disease extent. There is no standard second-line therapy for patients who have progressed on first-line therapy for metastatic disease. First-line therapy for a robust elderly patient often includes gemcitabine plus cisplatin or dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin. Alternatively, carboplatin, taxane-based regimens, or single-agent chemotherapy may be considered as well (NCCN 2015). Second-line chemotherapy data are highly variable, and treatment choices in this setting largely depend on the patient's first-line treatment.

More recently clinical activity has been observed with PD-1 and PD-L1 targeted agents. In the Phase 2 study IMvigor210, subjects who progressed after treatment with a platinum-based chemotherapy were administered the anti–PD-L1 agent atezolizumab. The ORR was 15%

(p = 0.0058) for all subjects on study, 18% (p = 0.0004) for subjects with PD-L1 expression ≥ 1%, and 27% (p = 0.0001) in subjects with PD-L1 expression ≥ 5%. Median duration of response at the time of analysis had not yet been reached; however, 92% (43 of 47) of responses were ongoing at 24 weeks (Rosenberg et al 2015). In a separate Phase 1b study, 33 subjects with PD-L1+ urothelial tract tumors of mostly transitional cell histology were administered monotherapy pembrolizumab. The ORR by central review was 24.1%, with 10.3% of subjects achieving CRs. Duration of response was 16 to 40+ weeks (median not reached), with 6 of the 7 responders ongoing at the time of analysis. The median PFS was 8.6 weeks and the median OS in all subjects was 9.3 months (6-month OS rate, 58%; Plimack et al 2014). Several additional studies are ongoing to further evaluate the activity of PD-1 and PD-L1 agents in TCC of the GU tract.

1.1.13. Preclinical and Clinical Study Data

Refer to the current Investigator's Brochures for both durvalumab (mIB) and epacadostat (iIB) for additional preclinical and clinical study data.

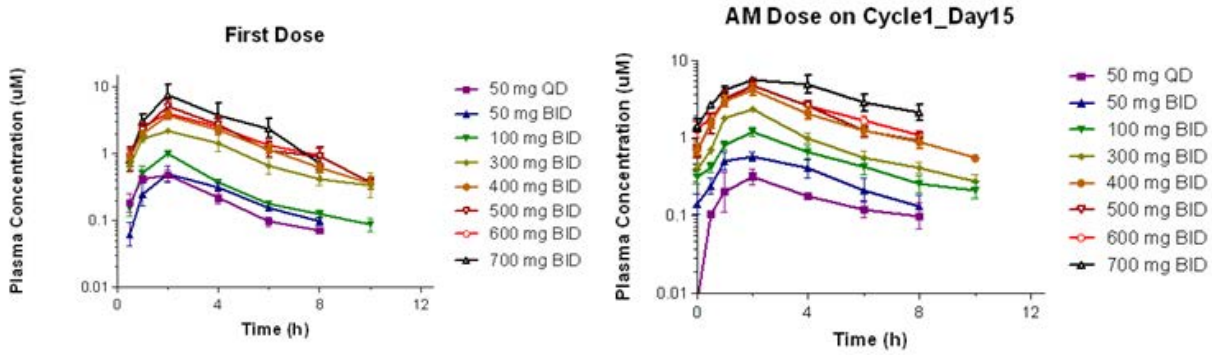
1.1.13.1. Summary of Epacadostat Pharmacokinetics in Humans

As of 29 OCT 2015, a total of 253 subjects were enrolled and received at least 1 dose of epacadostat in Incyte-sponsored studies, and 47 subjects were enrolled and received at least 1 dose of epacadostat in investigator-sponsored studies.

In Study INCB 24360-101, the multiple-dose PK of epacadostat was evaluated in subjects with refractory solid tumors at doses of 50 mg QD to 700 mg BID. Pharmacokinetic observations include the following and are summarized in Figure 1.

- After oral dose administration in the fasted state, the peak plasma concentration of epacadostat was typically attained at 2 hours postdose. Epacadostat was eliminated with a geometric mean terminal disposition half-life of 2.9 hours.
- Systemic accumulation after BID administration increased the mean epacadostat C_{max} and AUC_{0-t} by 16% and 33%, respectively, suggesting an "effective" half-life of 4 to 6 hours.
- Increases in epacadostat C_{max} and AUC_{0-t} were less than proportional to dose. The slightly lower than dose-proportional relationship was most likely because of the limited rate and/or extent of intestinal absorption for this compound at higher doses.
- A high-fat meal delayed epacadostat median T_{max} by 4 hours but did not cause a clinically significant change in epacadostat plasma exposures. Therefore, epacadostat may be administered without regard to food.
- Moderate intersubject variability was observed for epacadostat plasma exposure at the steady state after administration in the fasted state.
- The highest steady-state mean unbound 0- to 24-hour AUC (2.2 µM·h) observed in this study (700 mg BID dose group) was well below the NOAEL unbound AUC_{0-24h} of 7.9 µM·h observed in the 28-day GLP toxicology study.

Figure 1: Epacadostat Plasma Concentrations (Mean ± SE) in Cancer Patients Receiving Multiple Doses of Epacadostat in the Fasted State



1.1.13.2. Summary of Epacadostat Pharmacodynamics in Humans

Tryptophan and kynurenine levels were measured in plasma and in stimulated whole blood samples from Studies INCB 24360-101, INCB 24360-201, and INCB 24360-210 as pharmacodynamic measures of the inhibition of IDO1 activity by epacadostat. Whole blood samples were stimulated ex vivo with LPS and interferon-γ in order to increase the levels of IDO1 expression before measurement of tryptophan to kynurenine levels 24 hours later. In addition, systemic changes in plasma markers of inflammation and lymphocyte subsets were monitored.

Pharmacodynamic observations include the following:

- Epacadostat administration effectively inhibits IDO1 enzyme activity, which is upregulated in many cancers and correlated with poor prognosis.
- Inhibition of IDO1 is dose-dependent, and at doses at or above 300 mg BID, epacadostat effectively achieves maximal inhibition of IDO1 activity at trough, as assessed using changes in kynurenine levels.
- Epacadostat inhibits IDO1 in all subjects, irrespective of cancer type.
- The elevated kynurenine levels at baseline that are observed in cancer subjects are reduced at first measure after onset of treatment with epacadostat. The elevated kynurenine levels are reduced back to the range noted in normal healthy individuals in most subjects.
- The pharmacodynamic effects of epacadostat are consistent with the PK.
- No significant changes in peripheral blood immune cell subsets or immune plasma proteins have been noted, suggesting that IDO1 inhibition does not elicit global changes in the peripheral immune system.

Figure 2 summarizes the changes in plasma kynurenine levels observed in Study INCB 24360-101. The levels of IDO1 inhibition are quantified in Table 1.

Figure 2: IDO1 Inhibition as a Function of Kynurenine Plasma Concentrations Attributable to IDO1 (Mean ± SEM) at the Steady State (on Cycle 1 Day 15) in Study INCB 24360-101

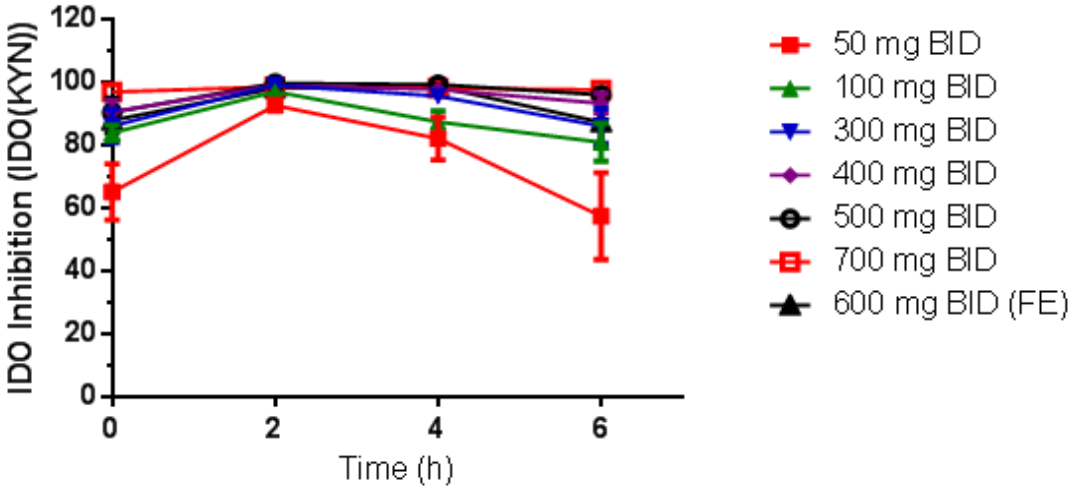


Table 1: IDO1 Inhibition at Steady State in Study INCB 24360-101

Study/Cohort	Dose	No. of Subjects	Mean ± SD		
			Inhibition Max (%)	Average Inhibition (0-6 h; %)	Inhibition Trough (%)
101/1	50 mg QD	3	74 ± 18	47 ± 18	6 ± 10
101/2	50 mg BID	4	94 ± 3	79 ± 12	65 ± 18
101/3	100 mg BID	5	97 ± 1	89 ± 6	84 ± 6
101/4	300 mg BID	4	99 ± 1	94 ± 4	86 ± 11
101/5	400 mg BID	7	100 ± 1	96 ± 3	91 ± 10
101/6	500 mg BID	5	100 ± 1	94 ± 7	91 ± 9
101/7	700 mg BID	4	99 ± 1	98 ± 1	97 ± 1
101/8	600 mg BID	7	100 ± 4	94 ± 6	88 ± 11

Preliminary data from Studies INCB 24360-201 and INCB 24360-210 demonstrated no differences in pharmacodynamic effects based on comparison with subjects in Study INCB 24360-101, as assessed using changes in kynurenine levels (see Table 2).

Table 2: IDO1 Inhibition at the Steady State in Studies INCB 24360-201 and INCB 24360-210

Study/Cohort	Dose	No. of Subjects	Mean ± SD		
			Inhibition Max (%)	Average Inhibition (0-6 h; %)	Inhibition Trough (%)
201/1	300 mg BID	2	99 ± 1	93 ± 1	92 ± 6
201/2	25 mg BID	4	86 ± 8	66 ± 15	40 ± 29
201/3	50 mg BID	7	93 ± 7	81 ± 15	64 ± 31
210/1	600 mg BID	3	99 ± 0	97 ± 2	94 ± 3

These results demonstrate that epacadostat is pharmacologically active in blocking IDO1 enzyme activity when administered to subjects with malignant disease. [redacted]

1.1.13.3. Summary of Durvalumab Pharmacokinetics in Humans

As of the data cutoff date of 12 JUL 2015, a total of 1883 subjects have been enrolled and treated with durvalumab in 30 ongoing clinical studies: of the 1883 subjects, 1279 received durvalumab monotherapy, 440 received durvalumab in combination with tremelimumab or other anticancer agents, 14 received other agents, and 150 have been treated with blinded investigational product. No studies have been completed or terminated prematurely due to toxicity.

1.1.13.3.1. Pharmacokinetics and Product Metabolism

Durvalumab monotherapy exhibited nonlinear (dose-dependent) PK. The area under the concentration-time curve from 0 to 14 days (AUC_{0-14}) increased in a greater than dose-proportional manner over the dose range of 0.1 to 15 mg/kg and approached linearity at ≥ 3 mg/kg, [redacted] Exposures after multiple doses demonstrated accumulation consistent with PK parameters estimated from the first dose. Pharmacokinetic simulations indicate that after administration of MEDI4736 10 mg/kg every 2 weeks, > 90% of subjects are expected to maintain PK exposure ≥ 40 µg/mL throughout the dosing interval.

As of 09 FEB 2015, 8 of 388 subjects (1 subject each in 0.1, 1, 3, and 15 mg/kg cohorts, and 4 subjects in 10 mg/kg cohort) were ADA-positive, with an impact on PK/pharmacodynamics in 1 subject in the 3 mg/kg cohort.

After administration of durvalumab in combination with tremelimumab, the observed PK exposures of both durvalumab and tremelimumab were consistent with respective monotherapy data, indicating no PK interaction between the 2 agents.

As of 20 FEB 2015, ADA data were available from 60 subjects for durvalumab and 53 subjects for tremelimumab. Four of 60 subjects were ADA-positive for anti-MEDI4736 antibodies after treatment. One of 53 subjects was ADA-positive for anti-tremelimumab antibodies after treatment. There was no clear relationship between ADA and the dose of either MEDI4736 or tremelimumab, and no obvious association between ADA and safety or efficacy.

Durvalumab has also been combined with other anticancer agents, including gefitinib, dabrafenib, and trametinib. To date, no PK interaction has been observed between durvalumab and these agents (refer to the mIB).

1.2. Study Rationale

The goal of cancer immunotherapy is to initiate or reinitiate a self-sustaining cycle of cancer immunity, enabling it to amplify and propagate. Cancer immunotherapies must overcome the negative feedback mechanisms inherent in most cancers. The current approach will attempt to further amplify an immune response by targeting multiple nonredundant immune checkpoints. Expression of IDO1 represents an early checkpoint that results in a diminished immune response and tolerance to tumor antigen. In preclinical models, inhibition of IDO1 was shown to

synergize with blockade of PD-1/PD-L1 in delaying tumor growth and increasing OS (Holmgaard et al 2013). Many recent clinical results suggest that a common rate-limiting step is the expression of PD-L1 as a distal immune modulator expressed in 20% to 50% of human cancer (Hiraoka et al 2010, Herbst et al 2013), including but not limited to the ones selected for investigation in this study: advanced or metastatic NSCLC, melanoma, pancreatic cancer (Phase 1 only), SCCHN, TNBC, gastric or GE junction cancer, and TCC of the GU tract. Expression of IDO and PD-1/L1 have been found to be increased in NSCLC as the disease progresses, and expression of these markers in tumor cells has been associated with shorter subject survival (Iversen et al 2014). Anti–PD-L1 and anti–PD-1 monotherapy response rates of approximately 20% have been reported in refractory NSCLC (Garon et al 2015, Brahmer et al 2013) with a survival median of approximately 12 months. In subjects with PD-L1 expression in at least 50% of tumor cells, the reported response rate was 45.2% with a median PFS of 6.3 months. At the time of analysis, OS had not yet been reached (Garon et al 2015).

In APR 2018, the ECHO-301/KEYNOTE-252 study, a Phase 3 trial evaluating the anti–PD-1 antibody pembrolizumab in combination with epacadostat vs pembrolizumab with placebo as first line treatment in subjects with unresectable or metastatic melanoma, underwent a preplanned eDMC review. This eDMC review concluded that the co-primary endpoint of improvement in progression-free survival was not met (HR = 1.00; 95% CI 0.83 to 1.21) and that the co-primary 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.

1.3. Potential Risks and Benefits of the Treatment Regimen

1.3.1. Risks From Epacadostat

In 28-day toxicology studies, C_{max} values have exceeded the 50% inhibitory concentration for the IDO1 enzyme in cells (7 nM) by up to 370-fold in the absence of any toxicity, so the risk of unintended pharmacological activity is expected to be low. In the Phase 1 clinical study in subjects with refractory solid tumors (INCB 24360-101), epacadostat was well tolerated with a single SAE of radiation pneumonitis (also considered a DLT) in a subject with mediastinal metastasis of endometrial cancer, 1 report of asymptomatic and reversible hypopituitarism despite continued dosing of epacadostat, and 1 event of Grade 3 fatigue determined by the investigator to be related to study drug and considered a DLT. Preliminary data from study INCB 24360-201 (evaluating the combination of epacadostat and ipilimumab) suggest that epacadostat doses ≤ 50 mg BID were well tolerated with ipilimumab. In the 50 mg BID continuous cohort, 4 DLTs (Grade 3 diarrhea, Grade 3 ALT/AST elevation, Grade 3 colitis, and Grade 3 pneumonitis) in 18 subjects were reported. Immune-related AEs were reversible with appropriate management. The initial evaluation of epacadostat 300 mg BID in combination with ipilimumab was terminated due to the occurrence of Grade 3 or 4 ALT/AST elevation in 5 of 7 subjects treated at this dose. These AEs were reversible in all subjects upon discontinuation of study therapy and institution of corticosteroids based on an established protocol for the management of immune toxicities related to ipilimumab therapy. Treatment-emergent AEs were reported in 100% of subjects administered 25 mg BID, 50 mg BID, 50 mg intermittent, 75 mg

total daily dose, and 300 mg BID of epacadostat in combination with ipilimumab. Treatment-emergent AEs occurring in ≥ 20% of patients overall included fatigue (n = 29 [69%]), constipation and nausea (n = 13 [31%] each), decreased appetite and headache (n = 11 [26%] each), and vomiting (n = 10 [24%]) (Gibney et al 2015).

A potential concern 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). Preclinical data suggest that SS is unlikely after treatment with either epacadostat alone or with combination with MAOIs such as linezolid (Zhang et al 2016). As of 27 FEB 2017, 2 subjects across the epacadostat program (958 subjects treated) have reported non-serious SS or symptoms of SS, and both were mild in their severity and resolved.

1.3.2. Risks From Durvalumab

Risks associated with durvalumab monotherapy and in combination are provided below. Additional safety information can be found in the durvalumab Investigator Brochure (mIB).

1.3.2.1. Possible Risks Based on Mechanism of Action

Durvalumab, an anti–PD-L1 antibody, binds with high affinity and specificity to PD-L1 and blocks its binding to PD-1 and CD80, thus promoting antitumor immunity and tumor cell killing. Potential risks based on the mechanism of action of durvalumab and related molecules include immune-mediated reactions such as enterocolitis, pneumonitis, dermatitis, hepatotoxicity, endocrinopathy, and neuropathy.

A hypothetical risk exists for agents that activate the immune system by delivering agonistic signals through activating receptors, such as CD28 (Suntharalingam et al 2006). Such agents have an increased potential to trigger systemic, nonspecific activation of T cells since they can exert their effects in the absence of any antigen-specific T-cell receptor signals. In contrast, agents that act via antagonism of an inhibitory pathway modulate an existing antigen-specific T-cell receptor signal and have a limited potential to drive systemic, nonspecific activation of T cells. This is exemplified clinically by molecules targeting CTLA-4 and PD-1, which are not associated with acute, severe adverse effects, such as cytokine storm (Brahmer et al 2010, Berger et al 2008, Wolchok et al 2010). Like these molecules, durvalumab antagonizes an inhibitory receptor (PD-L1). As such, in the absence of an antigen-specific T-cell receptor signal, inhibition of function of PD-L1 is not anticipated to elicit any response. This expectation is supported by published data showing no effect for anti–PD-L1 antibodies in the absence of a T-cell receptor stimulus (Dong et al 2002). To assess directly the potential of durvalumab to induce a release of cytokines, cytokine release assays were conducted in human whole blood. Durvalumab did not induce release of any cytokine from any donor at any concentration tested. These results support that, consistent with its mechanism of action as a PD-L1 antagonist, durvalumab is not expected to induce acute cytokine release in humans. Nevertheless, the durvalumab first-time-in-human study design took into account the unlikely possibility of a cytokine release event by having a low starting dose, extensive monitoring, and cytokine sampling. To further mitigate the risk to subjects, vital signs will be monitored every 15 minutes

throughout the infusion, at the end of the infusion, and 30 and 60 minutes postinfusion. In addition, subjects will be observed for 3 hours following the first infusion of durvalumab. Thus, the target occupancy will be well controlled with ample opportunity for observation, cessation of treatment, or intervention, if necessary.

1.3.2.2. Possible Risks Based on Clinical Data

As of 12 JUL 2015, > 1800 subjects have been treated across the ongoing durvalumab (MEDI4736) studies, including sponsored studies and collaborative studies. The majority of subjects have been treated with monotherapy durvalumab (n = 1279); however, 440 subjects have received MEDI4736 in combination with tremelimumab or other anticancer agents, 14 received other agents (1 gefitinib, 13 MEDI6383), and 150 subjects were blinded (mIB).

The safety profile of durvalumab as monotherapy and combined with other anticancer agents was consistent with the pharmacology of the target and other agents in the immune checkpoint inhibitor class. No tumor types appeared to be associated with unique AEs. Immune-related AEs, which are important risks of immune checkpoint inhibitors, have been observed with durvalumab and include colitis, pneumonitis, hepatitis/hepatotoxicity, neuropathy/neuromuscular toxicity, endocrinopathy, dermatitis, and nephritis.

1.3.2.2.1. Risks of Durvalumab Monotherapy

Risks with durvalumab monotherapy include diarrhea, colitis, pneumonitis/interstitial lung disease, endocrinopathies (eg, hypo- and hyperthyroidism, Type I DM, diabetes insipidus, hypophysitis, and adrenal insufficiency), hepatitis/hepatotoxicity/increases in transaminases, neurotoxicities, nephritis/increases in creatinine, pancreatitis, rash/pruritus/dermatitis, infusion-related reactions, anaphylaxis, hypersensitivity or allergic reactions, myocarditis, and immune complex disease.

Further information on the identified and potential risks can be found in the current version of the durvalumab IB (mIB).

In monotherapy clinical studies, very commonly reported (≥ 10% of subjects) AEs of all grades are fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back pain, pyrexia, abdominal pain, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Approximately 8% of subjects experienced an AE that resulted in permanent discontinuation of durvalumab, and approximately 5% of subjects experienced an SAE that was considered to be related to durvalumab by the study investigator.

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and, in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity (see Section 5.6.3).

A detailed summary of durvalumab monotherapy AE data can be found in the current version of the durvalumab IB (mIB).

1.3.2.3. Possible Risks Based on Nonclinical Data

Nonclinical studies have demonstrated that durvalumab partially suppressed the primary antibody response to a T-cell–dependent antigen (KLH). Secondary antibody responses to this antigen were normal. The relevance of this finding with respect to a human immune response is

theoretical; a reduction in humoral immunity may result in a reduced response to vaccination and increased risk of infection.

1.3.2.4. Possible Risks Common to Any Immunoglobulin

Durvalumab is being developed for the treatment of advanced solid tumors refractory to standard therapy or for which no standard therapy exists. As with the administration of any immunoglobulin, infusion reactions and acute IgE-mediated allergic reactions may occur, may be severe, and may result in death.

Administration of polyclonal immunoglobulin preparations and monoclonal antibodies has been associated with infusion reactions that occur during or shortly after dosing such as fever, chills, myalgia, nausea, vomiting, pruritus, rash, headache, flushing, sweating, tachycardia, dyspnea, bronchospasm, hypotension, dizziness or lightheadedness, and hemodynamic instability. These reactions are more common with higher doses, higher rates of infusion, and in subjects with a history of allergies.

Immunoglobulin E–mediated allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, and unresponsiveness. Acute severe allergic reactions (anaphylaxis) usually occur during infusion or within a few minutes or up to 24 hours after exposure. Subjects may experience paresthesia, hypotension, laryngeal edema, mental status changes, facial or pharyngeal angioedema, airway obstruction, bronchospasm, urticaria and pruritus, serum sickness, arthritis, allergic nephritis, glomerulonephritis, temporal arteritis, and death.

Clinical studies with durvalumab will closely monitor study subjects during and after infusion. Severe hypersensitivity reactions should be managed according to standard clinical practice, and medical equipment and staff trained to treat acute anaphylactic reactions must be immediately available at all sites that perform monoclonal antibody infusions.

1.3.2.5. Possible Risks Associated With Immune Reactivity

Although durvalumab is a human monoclonal antibody, there still is a chance that humans could develop ADAs. The occurrence of such ADAs could result in immune complex disease (with manifestations such as arthralgias, serum-sickness, and vasculitis) or altered durvalumab levels or activity. Subjects will be monitored clinically and for the presence of such antibodies.

1.3.2.6. Possible Risks Associated With Administration

Durvalumab is to be administered as an IV infusion. Possible risks associated with IV administration of durvalumab are infection, redness, swelling, pain, and induration at the administration site.

1.3.3. Risks for Combination (Epacadostat and Durvalumab)

The combination of epacadostat and durvalumab has the potential to precipitate more frequent, more severe, and/or new immune-related toxicities as compared with each individually. [redacted]

1.4. Justification for Treatment Regimen

The goal of the present study is to explore doses of epacadostat that may synergize or otherwise augment the efficacy observed with the PD-L1 inhibitor durvalumab in subjects with advanced cancer. The established regimen of durvalumab (3 mg/kg or 10 mg/kg once every 14 days) will be combined with doses of epacadostat that provide partial and more complete IDO1 inhibition based on observations from the Phase 1 study (INCB 24360-101). The initial dose selected for epacadostat in combination with durvalumab is 25 mg BID with escalation to 300 mg BID. This is based on the preliminary observation that the average kynurenine inhibition for epacadostat 25 mg BID and 300 mg BID are 66% and > 94%, respectively, and the safety of these doses, as well as doses up to 700 mg BID in the Phase 1 monotherapy study and in combination with ipilimumab in INCB 24360-201. Dose escalation of epacadostat will evaluate 25 mg BID, 50 mg BID, 75 mg BID, 100 mg BID, and 300 mg BID. This dose range will span a range of average inhibition of IDO1 from approximately 40% (at 25 mg BID dosing) to 60% (50 mg BID dosing) to 89% (100 mg BID dosing) and 94% (300 mg BID dosing), based on pharmacodynamic testing. Pharmacokinetic and pharmacodynamic observations from Studies INCB 24360-101 and INCB 24360-201 in cancer subjects support these doses, which provide a differential pharmacologic effect.

The 200 mg dose level of epacadostat will not be explored in combination with durvalumab based on PK and pharmacodynamic considerations. The results from Study INCB 24360-101 demonstrated that epacadostat displays mildly sublinear exposure-dose response, as shown in Figure 3 and Table 3. It is likely that there would be significant overlap in exposure at 200 mg compared to both 100 mg and 300 mg dose steps. Furthermore, inhibition of IDO1 is well described by an E_{max} model that is fundamentally nonlinear, especially beyond the inhibition > 80%. Any incremental increase in IDO1 inhibition begins to level off and would be insensitive to further increased epacadostat concentration. Our pharmacodynamic model estimates I_{ave} increases from 83% to 89% with dose stepping from 100 mg to 300 mg BID, which justifies not exploring the 200 mg intermediate dose in combination with durvalumab.

Figure 3: INCB24360-101 Dose Response

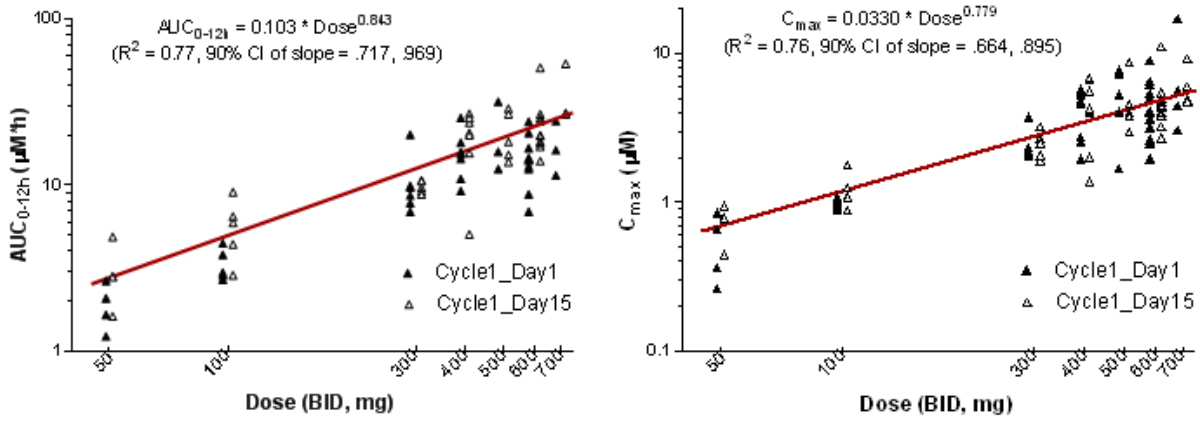


Table 3: Summary of Epacadostat Steady-State Pharmacokinetic Parameters in Study INCB 24360-101

Dose	No. of Subjects	C_{max} (µM)	T_{max} (h)	C_{min} (µM)	$t_{½}$ (h)	AUC_{0-t} (µM·h)	$AUC_{0-\tau}$ (µM·h)[a]	CL/F (L/h)
50 mg QD	3	0.396 ± 0.172 0.365	2.0 (1.0- 4.0)	0.00 ± 0.00 NC	2.4 ± 0.26 2.4	1.39 ± 0.256 1.37	1.58 ± 0.31 1.56	73.8 ± 14.7 73.0
50 mg BID	4	0.742 ± 0.212 0.715	2.0 (1.0-3.9)	0.084 ± 0.063 NC	2.4 ± 0.56 2.3	2.74 ± 1.08 2.58	3.05 ± 1.36 2.83	43.3 ± 19.2 40.3
100 mg BID	5	1.23 ± 0.348 1.19	2.0 (1.0-2.2)	0.201 ± 0.111 0.171	3.3 ± 0.75 3.2	5.32 ± 2.16 4.97	5.77 ± 2.34 5.38	45.8 ± 20.9 42.4
300 mg BID	5	2.48 ± 0.515 2.44	2.0 (1.0-2.0)	0.287 ± 0.146 0.251	3.9 ± 2.1 3.5	8.92 ± 0.841 8.88	9.78 ± 0.86 9.75	70.4 ± 6.19 70.2
400 mg BID	8	4.39 ± 2.02 3.88	2.0 (1.0-6.0)	0.624 ± 0.339 0.523	2.7 ± 0.62 2.6	16.7 ± 6.79 15.0	19.6 ± 7.43 17.6	62.3 ± 52.3 51.8
500 mg BID	5	4.82 ± 2.26 4.48	2.0 (2.0-2.4)	0.604 ± 0.260 0.562	2.4 ± 0.37 2.4	18.2 ± 6.46 17.3	20.6 ± 6.82 19.7	60.5 ± 19.1 58.0
600 mg BID	12	4.82 ± 2.16 4.52	2.0 (1.0-2.1)	0.932 ± 0.704 0.731	3.3 ± 0.97 3.2	19.5 ± 8.4 18.3	22.9 ± 10.0 21.6	66.4 ± 18.6 63.5
700 mg BID	4	6.23 ± 2.09 6.00	3.0 (2.0-4.5)	1.32 ± 0.417 1.26	3.0 ± 1.2 2.9	30.8 ± 10.5 29.6	35.8 ± 15.5 33.9	49.5 ± 17.1 47.2
P-values from a 1-factor ANOVA (factor = dose) of log-transformed exposures after dose normalization								
Dose		0.0051					0.0961	

NC = not calculable.
Note: Values are mean ± SD and geometric mean, except T_{max} is reported as median (range).
[a] The $t_{½}$ and hence AUC_{0-12h} values could not be estimated for 4 subjects.

In general, as single agents, epacadostat and durvalumab have been well tolerated in this study population that has significant comorbidities.

It should be noted that the initial evaluation of epacadostat at 300 mg BID in combination with ipilimumab (Study INCB 24360-201) was terminated due to the occurrence of Grade 3 or 4 ALT/AST elevation in 5 of 7 subjects treated at this dose. These AEs were reversible in all subjects upon discontinuation of study therapy and institution of corticosteroids based on an established protocol for the management of immune toxicities related to ipilimumab therapy. The study was subsequently amended, and preliminary data suggest that doses of epacadostat up to 50 mg BID are well tolerated with ipilimumab. In the 25 mg cohort, 1 DLT of Grade 3 AST elevation was observed. Four DLTs (Grade 3 diarrhea, Grade 3 colitis, Grade 3 pneumonitis, and Grade 3 ALT/AST elevation) have been observed in the 50 mg BID continuous dosing cohort among 18 evaluable subjects, and 1 occurrence of Grade 3 colitis has been observed in the 50 mg BID intermittent dosing cohort (2 weeks on/1 week off) among 9 evaluable patients. In the 75 mg total daily dose cohort (50 mg every morning and 25 mg every evening), there was 1 DLT of Grade 3 rash among 7 evaluable subjects. The most common all-grade irAEs were rash (52.4%), pruritus (38.1%), diarrhea (33.3%), increased ALT and AST (21.4% and 16.7%), and hypothyroidism (11.9%). irAEs ≥ Grade 3 occurring in > 1 subject were AST elevation and colitis (n = 4 [9.5%] each) and ALT elevation (n = 3 [7.1%]). Other treatment-emergent AEs occurring in ≥ 20% of subjects overall included fatigue (n = 29 [69%]); constipation and nausea (n = 13 [31%] each); decreased appetite and headache (n = 11 [26%] each); and vomiting (n = 10 [24%]; Gibney et al 2015). Adverse events reported in this study were consistent with what has been reported previously in subjects treated with ipilimumab monotherapy (iIB). Complete inhibition of the IDO1 target is not required for maximally effective activity in preclinical models. As monotherapy, maximally effective doses in nonclinical models result in exposures that are comparable to doses of 25 to 50 mg BID in humans.

1.5. Rationale for Endpoints

1.5.1. Efficacy Endpoints

The primary efficacy objective of this study is to evaluate activity of study treatment using ORR as per investigator assessed response using modified RECIST v1.1 (mRECIST v1.1). Modified RECIST v1.1 will also be used by the local site to determine eligibility and make treatment decisions. Imaging will be collected and held for possible future central imaging vendor assessment.

Immunotherapeutic agents such as durvalumab work to enhance antitumor immune responses and these response patterns may lead to a clinical benefit (eg, CR, PR, SD) after an initial increase in tumor burden that may be classified as PD by standard RECIST criteria (Wolchok et al 2009). Standard RECIST criteria may not provide an adequate response assessment of immunotherapeutic agents such as durvalumab. Therefore, RECIST v1.1 will be used with the following modification (and defined as mRECIST v1.1).

Progressive disease should be confirmed a minimum of 4 weeks after the initial radiologic indication of PD. If the confirmation scan shows a decrease in the tumor burden, study treatment may be continued or resumed. If PD is confirmed the subject will be discontinued from study

treatment. Clinically stable subjects have the option of continuing study treatment per the investigator's discretion while waiting for radiologic confirmation of progression.

Clinically stable for this purpose is defined by the following criteria:

- Absence of signs and symptoms indicating disease progression.
- No decline in ECOG performance status.
- 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 deemed clinically unstable are not required to have repeat imaging for confirmation of PD. Additional information regarding mRECIST v1.1 is provided in Section 7.4.

2. STUDY OBJECTIVES AND PURPOSE

2.1. Primary Objectives

- Phase 1: To evaluate the safety and tolerability, and define the MTD or a PAD of epacadostat administered in combination with durvalumab in subjects with select advanced solid tumors.
- Phase 2: To evaluate the efficacy of epacadostat administered in combination with durvalumab in subjects with select advanced solid tumors by assessing the ORR per mRECIST v1.1 at the MTD or PAD.

2.2. Secondary Objectives

- Phase 1: To evaluate the efficacy of epacadostat administered in combination with durvalumab in subjects with select advanced solid tumors by assessing the ORR per mRECIST v1.1.
- Phase 2: To evaluate the safety and tolerability of the MTD or PAD of epacadostat administered in combination with durvalumab in subjects with select advanced solid tumors.
- Phases 1 and 2: To evaluate the efficacy of epacadostat administered in combination with durvalumab in subjects with select advanced solid tumors by assessing duration of response and PFS.
- Phases 1 and 2: To evaluate the PK of epacadostat and durvalumab when administered in combination.
- Phases 1 and 2: To determine the immunogenicity of durvalumab when administered with epacadostat.

[redacted]

3. SUBJECT ELIGIBILITY

3.1. Study Population

Subjects with histologically or cytologically confirmed advanced melanoma, NSCLC, pancreatic cancer (Phase 1 only), SCCHN, TNBC, gastric or GE junction cancer, and TCC of the GU tract will be enrolled.

3.2. Subject Inclusion Criteria

The following criteria are required for inclusion in the study:

1. Male or female subjects, age 18 years or older.
2. Ability to comprehend and willingness to sign an ICF.
3. Histologically or cytologically confirmed diagnosis of melanoma, NSCLC, pancreatic cancer (Phase 1 only), SCCHN, TNBC, gastric or GE junction cancer, or TCC of the GU tract that is locally advanced (not amenable to curative therapy such as surgical resection) or metastatic.
4. Must have failed at least 1 prior treatment regimen for locally advanced or metastatic disease or be intolerant to treatment or refuse standard treatment. Investigational agents used in combination with standard therapies are allowed. Adjuvant, neoadjuvant, or chemoradiation regimens given within 6 months of screening would be counted as having received 1 prior systemic regimen and would not require an additional systemic regimen for advanced or metastatic disease.
5. For subjects with metastatic melanoma:
    a. Must have known V600E activating BRAF mutation status or consent to BRAF V600E mutation testing during screening. Testing should be performed in a CLIA certified laboratory. BRAF mutation status determined as part of a panel of genetic tests performed in gene expression analysis will also satisfy the inclusion criterion for BRAF mutation testing.
    b. May be treatment-naive or have received prior treatment with an anti–CTLA-4 or anti–PD-1 targeted agent. ***Note:*** *In Phase 1, subjects who are BRAF mutation positive must have received prior treatment with a BRAF inhibitor with or without a MEK inhibitor.*
    c. Ocular melanoma will be excluded.
6. For subjects with NSCLC:
    a. Subjects who have tumors with driver mutations (eg, EGFR mutation positive or anaplastic lymphoma kinase fusion oncogene positive) must have received treatment with a targeted therapy and have progressed or be intolerant, if a targeted agent is available for the specific driver mutation.
    b. Subjects may have received prior treatment with an anti–PD-1 targeted agent.

7. For subjects with pancreatic cancer (Phase 1 only):
    a. Subjects in Phase 1 must have an exocrine pancreatic neoplasm.
    Note: *Exocrine pancreatic neoplasms include all tumors related to the pancreatic ductal and ancinar cells and their stem cells.*
8. For subjects with SCCHN:
    a. Histology of squamous cell carcinoma.
    b. Carcinoma of the nasopharynx and salivary gland will be excluded.
    c. Prior systemic regimens must include a platinum-based therapy. Investigational agents used in combination with standard therapies are allowed. Subjects who relapse within 6 months of adjuvant therapy, including a platinum-containing regimen, may enroll.
9. For subjects with TNBC:
    a. Histologically or cytologically confirmed breast adenocarcinoma that is unresectable or metastatic.
    b. Subjects with breast cancer history of different phenotypes (ie, ER/PgR/HER2 positive) must have pathologic confirmation of triple-negative disease from the most current biopsy.
    c. Pathologically confirmed as triple negative, source documented, defined as both of the following:
        i) ER and PgR negative: < 1% of tumor cell nuclei is immunoreactive in the presence of evidence that the sample can express ER or PgR (positive intrinsic controls).
        ii) HER2 negative as per ASCO/CAP HER2 test guidelines.
        Note: *HER2 test result should be reported as negative if a single test or all tests performed in a tumor specimen show the following:*
            - *IHC 1+ as defined by incomplete membrane staining that is faint/barely perceptible and within > 10% of the invasive tumor cells.*
            - *IHC result is 0 as defined by no staining observed or membrane staining that is incomplete and is faint/barely perceptible and within ≤ 10% of the invasive tumor cells.*
            - *In situ hybridization (ISH) assay is negative based on a single probe average HER2 copy number < 4.0 signals/cell or dual probe HER2/CEP17 ratio < 2.0 with an average HER2 copy number < 4.0 signals/cell.*
            - *If results are equivocal, reflex testing (same specimen using the alternative test or new specimen, if available) should be performed using an alternative assay (IHC or ISH).*
10. For subjects with TCC of the GU tract:
    a. Histologically or cytologically confirmed TCC of the bladder, ureter, or renal pelvis or mixed histology bladder cancer.
    b. Metastatic or locally advanced and not amenable to curative therapy with disease progression on or after platinum-based chemotherapy or alternative therapy if platinum-based therapy is not appropriate.

11. For subjects with gastric or GE junction cancer:
    a. Histologically or cytologically confirmed diagnosis of gastric or GE junction adenocarcinoma.
    b. Progression on or after therapy containing platinum/fluoropyrimidine.
    c. Documentation of HER2/neu status.
12. Presence of measurable disease per RECIST v1.1 guidelines.
13. Life expectancy > 12 weeks.
14. ECOG performance status 0 to 1.
15. Fresh baseline tumor biopsies (fresh baseline biopsy is defined as a biopsy specimen taken within 28 days prior to Cycle 1 Day 1) are required at baseline as specified in Section 7.6.3.2, except if inaccessible with medical monitor approval. Archival tissue should also be submitted if available.

    Note: *If a fresh baseline biopsy is inaccessible, an archival specimen should be submitted.*
16. Female subjects of childbearing potential (defined as women who have not undergone surgical sterilization with a hysterectomy and/or bilateral oophorectomy, and are not postmenopausal, defined as ≥ 12 months of amenorrhea) must have a negative serum pregnancy test at screening. All female subjects of childbearing potential (and male subjects) must agree to take appropriate precautions to avoid pregnancy (or fathering children) (with at least 99% certainty) from screening through the 90-day safety follow-up visit. Permitted methods that are at least 99% effective in preventing pregnancy (Appendix A) should be communicated to the subject and their understanding confirmed.

    Note: *Male subjects should refrain from sperm donation from screening through 90 days after the last dose of study drug.*

3.3. Subject Exclusion Criteria

If met, any of the following criteria will lead to exclusion 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 treatment initiation.
    a. ANC < 1.5×10^9/L.
    b. Platelets < 75×10^9/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 creatinine clearance (glomerular filtration rate can also be used in place of creatinine or CrCl) < 50 mL/min for subjects with creatinine levels > 1.5 × institutional ULN.
    e. AST or ALT > 2.5 × institutional ULN OR > 5 × ULN for subjects with liver metastases.

f. Total bilirubin > 1.5 × ULN OR direct bilirubin > institutional ULN for subjects with total bilirubin levels > 1.5 × ULN.
   - If there is no institutional normal range available for the direct bilirubin, the direct bilirubin should be < 40% of the total bilirubin.
   - In no case can total bilirubin exceed 3.0 × ULN.

g. INR or PT > 1.5 × ULN (unless subject is receiving anticoagulant therapy, then subject may be included as long as PT or INR is within therapeutic range of intended use of anticoagulants).

h. aPTT > 1.5 × ULN (unless subject is receiving anticoagulant therapy, then subject may be included as long as aPTT is within therapeutic range of intended use of anticoagulants).

2. Current pregnancy or breastfeeding.

3. Participation in any other study in which receipt of an investigational study drug occurred within 28 days or 5 half-lives (whichever is longer) prior to the first dose. For investigational agents with long half-lives (eg, 5 days), enrollment prior to the fifth half-life requires medical monitor approval.

4. Receipt of prior immune checkpoint inhibitors (eg, anti-CTLA-4, anti–PD-1, anti–PD-L1, and any other antibody or drug specifically targeting T-cell costimulation) 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: *The exception to this exclusion criterion would be subjects who have received a prior anti–CTLA-4 or PD-1 pathway targeted agent for indications in which an anti–CTLA-4 or PD-1 pathway targeted agent has been approved (eg, melanoma). In this case, the subject would be eligible to participate in the study.*

5. Receipt of an immunologically based treatment for any reason, including chronic use of systemic steroid at doses ≥ 10 mg/day prednisone equivalent within 14 days prior to the first dose of study treatment. Use of inhaled or topical steroids or systemic corticosteroids < 10 mg is permitted.

6. Receipt of any anticancer medication in the 21 days prior to receiving their first dose of study medication or any unresolved toxicity > Grade 1 from previous anticancer therapy, except for stable chronic toxicities not expected to resolve, such as peripheral neurotoxicity. Prior treatment with nitrosureas (eg, carmustine or lomustine) require a 6-week washout prior to the first dose of study treatment.

7. Major surgical procedure (as defined by the investigator, with the exception of local surgery of isolated lesions for palliative intent) within 28 days of starting study treatment OR inadequate recovery from toxicity and/or complications from major surgery before starting study treatment.

8. 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.

9. Untreated CNS metastases or carcinomatous meningitis, or CNS metastases that have progressed (eg, evidence of new or enlarging CNS metastasis or new neurological symptoms attributable to CNS metastases). Subjects with treated and clinically stable CNS metastases (defined as 2 brain images at least 4 weeks apart, both of which were obtained after treatment to the brain metastases) and who are off all corticosteroids for at least 2 weeks are eligible.

   Any active or inactive autoimmune process or inflammatory disorder (including rheumatoid arthritis, moderate or severe psoriasis, multiple sclerosis, sarcoidosis syndrome, diverticulitis [with the exception of diverticulosis], inflammatory bowel disease, systemic lupus erythematosus, Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, hypophysitis, uveitis, etc]) or receipt of systemic therapy for an autoimmune or inflammatory disease.

   Note: *Exceptions include subjects with vitiligo, hypothyroidism stable on hormone replacement, controlled asthma, Graves' disease, or Hashimoto's disease, celiac disease controlled by diet alone, or with medical monitor approval. Subjects without active disease in the last 5 years may be included but only after consultation with medical monitor.*

10. Evidence of interstitial lung disease or active, noninfectious pneumonitis.
11. Prior radiotherapy within 2 weeks of therapy. Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation to non-CNS disease with medical monitor approval.
12. Active infection requiring systemic therapy.
13. History of organ transplant that requires use of immunosuppressives.
14. Presence of a gastrointestinal condition that may affect drug absorption.
15. Known history of human immunodeficiency virus infection or known history of or is positive for hepatitis B (eg, HBsAg reactive or HBV DNA detected) or hepatitis C (HCV antibody positive and/or HCV RNA qualitative is detected).

    Note: *Hepatitis C antibody positive subjects who received and completed treatment for hepatitis C that was intended to eradicate the virus may participate if hepatitis C RNA levels are undetectable.*

16. Receipt of MAOIs within the 21 days prior to the first dose of study treatment.
17. History of SS after receiving 1 or more serotonergic drugs.
18. Any condition that would jeopardize the safety of the subject or compliance with the Protocol.
19. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab.

20. History or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful. Screening QTc interval > 480 msec is excluded (corrected by Fridericia or Bazett's formula). In the event that a single QTc is > 480 msec, the subject may be enrolled if the average QTc for the 3 ECGs is ≤ 480 msec. For subjects with an intraventricular conduction delay (QRS interval ≥ 120 msec), the JTc interval may be used in place of the QTc with sponsor approval. The JTc must be < 340 msec if JTc is used in place of the QTc. Subjects with left bundle branch block are excluded.
21. Clinically significant cardiac disease, including unstable angina, acute myocardial infarction within 6 months from Day 1 of study drug administration, New York Heart Association Class III or IV congestive heart failure, and arrhythmia requiring therapy.

    Note: *A subject with an arrhythmia may enroll if the subject is on anti-arrhythmic medication and is in sinus rhythm on the screening ECG.*
22. Any prior ≥ Grade 3 irAE while receiving immunotherapy, including anti–PD-1, anti–PD-L1, or anti–CTLA-4 treatment, or any unresolved irAE > Grade 1. Must not have experienced a toxicity that led to permanent discontinuation of prior immunotherapy. Subjects with endocrine AEs ≤ Grade 2 are permitted to enroll if they are stably maintained on appropriate replacement therapy and are asymptomatic. Subjects with prior anti–PD-1, anti–PD-L1, or anti–CTLA-4 therapy must not have required the use of additional immunosuppression other than corticosteroids for the management of an AE, not have experienced recurrence of an AE if rechallenged, and not currently require maintenance doses of > 10 mg prednisone or equivalent per day.

    Note: *Previous immune-related ocular or neurologic toxicity of any grade is excluded.*
23. Known allergy or reaction to any component of either study drug formulation.
24. Subjects who require ongoing thoracentesis or paracentesis for palliation must be discussed with the medical monitor to determine eligibility.
25. History of primary immunodeficiency.
26. History of leptomeningeal carcinomatosis.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is a Phase 1/2 open-label study of epacadostat administered in combination with durvalumab in subjects with advanced melanoma, NSCLC, pancreatic cancer (Phase 1 only), SCCHN, TNBC, gastric or GE junction cancer, or TCC of the GU tract. The dose-escalation part of the study (Phase 1) uses a 3 + 3 design to identify the MTD or PAD of epacadostat in combination with durvalumab. Phase 2 will further explore the safety and efficacy of the MTD or PAD of epacadostat in combination with durvalumab determined in Phase 1.

The study will consist of 3 periods:

Screening: Up to 28 days.

Treatment Period: The treatment period will continue every 14 days for up to 12 months as long as subjects are receiving benefit from treatment and have not met any criteria for study withdrawal as defined in Section 5.7.1. Once subjects complete 12 months of study treatment or permanently discontinue study treatment for any other reason, the EOT visit should be conducted, and they should enter the follow-up period of the study.

Follow-Up Period: The safety follow-up visits will occur at 42 days (±7 days) and 90 days (± 7 days) after the EOT visit or the last dose of study treatment if the EOT visit is not completed.

4.1.1. Phase 1 Dose Escalation

Phase 1 is the dose-escalation phase, which will include up to 6 cohorts of subjects treated with epacadostat at doses of 25 mg BID, 50 mg BID, 75 mg BID, 100 mg BID, and 300 mg BID in combination with durvalumab 3 mg/kg or 10 mg/kg given on Day 1 of each 14-day cycle. A minimum of 3 subjects will be enrolled and treated in each cohort, and all 3 subjects will be observed for a minimum of 42 days before the subsequent cohort begins enrollment.

Subjects must have received the cohort-specific dose of epacadostat for at least 75% of the doses (63 doses) and have received at least 3 doses of durvalumab during the 42-day DLT observation period, or have experienced a DLT to be evaluable for dose tolerability. Additional subjects will be enrolled in a cohort to achieve the minimum of 3 evaluable subjects if dropouts or dose interruptions/reductions occur that result in a subject being nonevaluable for DLTs.

The dose of epacadostat will be escalated if 0 of the first 3 evaluable subjects enrolled experience a DLT. If 1 of the first 3 evaluable subjects enrolled experience a DLT, the cohort will be expanded to include 3 additional evaluable subjects. If 2 or more of either 3 or 6 subjects enrolled experience a DLT, the prior dose level will be considered the MTD. If only 3 subjects were treated at this dose level, the dose will be confirmed as the MTD by evaluation of an additional 3 subjects before this dose is recommended for Phase 2 testing.

The cohorts and dose levels are shown in Table 4.

Table 4: Dosing Cohorts

Cohort	Maximum Daily Dose of Epacadostat	Dose of Durvalumab (Once Every 14 Days)
1	**25 mg BID orally**	**3 mg/kg IV**
2	25 mg BID orally	10 mg/kg IV
3	50 mg BID orally	10 mg/kg IV
4	75 mg BID orally	10 mg/kg IV
5	100 mg BID orally	10 mg/kg IV
6	300 mg BID orally[a]	10 mg/kg IV

[a] Intermediate dose levels may be explored based on emerging PK or pharmacodynamic data.

During the study, dose interruptions and/or dose decreases may be implemented based on toxicity as described in Section 5.6.

For the definition of DLT, see Section 5.5.1.

All subjects who received epacadostat and durvalumab in the dose-escalation phase and remain on study treatment will be observed for at least 42 days from the first dose prior to enrolling subjects in Phase 2 of the study.

4.1.2. Phase 2

Approximately 140 to 192 subjects with advanced melanoma, NSCLC, SCCHN, TNBC, gastric or GE junction cancer, and TCC of the GU tract will be enrolled at the MTD or PAD of epacadostat in combination with durvalumab. More than 1 PAD may be evaluated in Phase 2. The approximate number of subjects needed for the melanoma, TNBC, and gastric and GE junction cancer cohorts will be determined using the Simon 2-stage design: Stage 1 will be the initial number of subjects per tumor type, and the decision to proceed with Stage 2 will be determined by the response rate observed in Stage 1 (further number of subjects to be enrolled in each stage per tumor type is detailed in Table 5). If more than 1 PAD is evaluated, the cohort may or may not be repeated for the specified tumor type as indicated in Table 5. The sponsor may limit enrollment of a specific tumor type to Stage 1.

Table 5: Approximate Number of Subjects by Tumor Type and Stage of Study

	No. of Subjects Enrolled		
Tumor Type	**Stage 1**	**Stage 2 (If Study Proceeds to Stage 2)**	**Total (Stage 1 + 2)**
Melanoma	15	25	40
TNBC	13	16	29
Gastric and GE junction cancer	9	11	20

Under Amendment 6, enrollment of the NSCLC, SCCHN, and TCC of the GU tract cohorts will be completed as expansion cohorts at the 300 mg BID dose level. The sample size for each cohort will be increased to account for the heterogeneity of PD-1 pathway–treated and PD-1 pathway–naive subjects within the selected tumor types. The approximate number of subjects per tumor type is listed in Table 6, and the number of PD-1 pathway–treated subjects in each cohort will be limited to 10 in order to reduce the risk of any cohort having a significant imbalance between PD-1 pathway–treated and PD-1 pathway–naive subjects, thereby preserving the predicted levels of baseline efficacy observed with PD-1 pathway monotherapy. Subjects enrolled at the 100 mg BID dose level will be analyzed independently.

Table 6: Approximate Number of Subjects for Expansion Cohorts

Tumor Type	No. of Subjects Enrolled	
	100 mg BID[a] (n = 19)	300 mg BID[b] (n = 84)
NSCLC	8	28
SCCHN	7	28
TCC of the GU tract	4	28

[a] Subjects enrolled in the 100 mg BID dose level were enrolled before Amendment 5.
[b] All subjects in the 300 mg BID NSCLC, SCCHN, and TCC of the GU tract cohorts enrolled in Amendment 5 or earlier are included in the total sample size.

4.2. Study Endpoints

4.2.1. Primary Endpoints

- Phase 1: MTD or PAD. The MTD is defined by the highest dose cohort where no more than 1 of 6 subjects experience a DLT, or the highest Protocol-defined dose for each agent in the absence of exceeding the MTD. Alternatively, the PAD is defined as a tolerated dose of epacadostat (in combination with durvalumab) that produces substantial pharmacological target inhibition. Safety and tolerability will be assessed by monitoring the 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: Objective response rate determined by radiographic disease assessments per mRECIST v1.1 described in Sections 1.5.1 and 7.4.

4.2.2. Secondary Endpoints

- Phase 1: Objective response rate determined by radiographic disease assessments per mRECIST v1.1.
- Phase 2: Safety and tolerability of the combination as assessed by monitoring the 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.
- Phases 1 and 2: Durability of response determined by radiographic disease assessment defined as the time from earliest date of disease response until earliest date of disease progression
- Phases 1 and 2: PFS determined from the date of randomization until disease progression or death.
- Phases 1 and 2: The endpoints for assessment of PK of durvalumab and epacadostat include individual durvalumab and epacadostat concentrations and PK parameters.
- Phases 1 and 2: The endpoints for assessment of immunogenicity of durvalumab include the number and percentage of subjects who develop detectable ADAs.

4.3. Measures Taken to Avoid Bias

The measurement of most toxicities using the CTCAE v4.0 and assessment of tumor size using the mRECIST v1.1 criteria represent objective endpoints.

4.4. Number of Subjects

Up to 36 subjects will be enrolled in the Phase 1 dose-escalation portion of the study, followed by approximately 140 to 192 subjects in the Phase 2 portion of the study.

4.5. 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 or IEC in writing of the study's completion or early termination, and 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 or if required by regulatory decision. 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 OF SUBJECTS

5.1. Treatment Groups and Administration of Study Drug

Subjects in Phase 1 will receive doses according to cohort enrollment. Subjects in Phase 2 will receive the dose or doses selected by the sponsor upon review of Phase 1 data. Study treatment should begin as close as possible to the date of enrollment.

5.1.1. Epacadostat

All BID doses of epacadostat will be taken orally morning and evening, approximately 12 hours apart without regard to food. If the morning or evening dose is missed by more than 4 hours, that dose should be skipped and the next scheduled dose should be taken at the usual time. If the subject vomits, an additional dose should not be taken. Doses of epacadostat will be self-administered except the days scheduled to be given at the study clinic (see Section 7.6). Epacadostat should be taken just prior to beginning the infusion of durvalumab on days given in clinic. Epacadostat will be given daily in combination with durvalumab for up to 12 months. Intrasubject dose escalation of epacadostat is not permitted.

5.1.2. Durvalumab

The dose of durvalumab will be calculated based on the subject's weight in kilograms. Durvalumab will be administered in the clinic as an IV infusion of 3 mg/kg or 10 mg/kg once every 14 days for up to 12 months. Intrasubject dose escalation of durvalumab is not permitted except as defined in Section 5.6.1.

5.1.2.1. Durvalumab Treatment Administration

Durvalumab will be administered as an IV infusion over approximately 60 minutes (± 5 minutes). The IV line will be flushed with a volume of normal saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered (unless prohibited by institutional practice). No incompatibilities have been observed between durvalumab and polypropylene, polyethylene, polyolefin copolymers, or polyvinylchloride.

Since the compatibility of durvalumab with other IV medications and solutions, other than normal saline (0.9% [w/v] sodium chloride for injection), is not known, the durvalumab solution should not be infused through an IV line in which other solutions or medications are being administered. The date, start time, interruption, and completion time of durvalumab administration must be recorded in the source documents.

5.1.2.2. Monitoring of Durvalumab Administration

Subjects will be monitored during and after infusion with assessment of vital signs at the beginning of the infusion (± 5 minutes), every 15 minutes (± 5 minutes) during the infusion of durvalumab, at the end of infusion (± 5 minutes), and at **30 minutes** (± 5 minutes) and 60 minutes (± 5 minutes) postinfusion. Subjects will be monitored during a 3-hour (± 15 minutes) postinfusion period of observation after the first dose of durvalumab only. For subsequent doses, the 3-hour observation period will not be required unless a subject experiences

an infusion-related reaction. If the infusion takes longer than 60 minutes, then the vital signs assessments should follow the principles as described above.

In the event of ≤ Grade 2 infusion-related reaction, the infusion rate of durvalumab may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and reinitiated at 50% of the initial rate until completion of the infusion. In subjects experiencing ≤ Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (eg, diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is ≥ Grade 3 in severity, treatment with durvalumab will be discontinued. As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit subjects to an intensive care unit if necessary.

5.2. Treatment Compliance

Treatment compliance with all study-related medications should be emphasized to the subject by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Subjects will bring all unopened, empty, and unused bottles of epacadostat with them to each study visit. Investigative site staff will perform a count of returned tablets to assess compliance, and this information will be entered into the CRF. Bottles of study drug, including unopened, partially opened, or empty bottles cannot be destroyed or returned to the depot until a monitor reviews and verifies all tablet counts for compliance. Compliance with durvalumab will also be documented in the medical record and monitored by the sponsor or its designee.

5.3. Randomization and Blinding

This is not a randomized or blinded study.

5.4. Duration of Treatment and Subject Participation

Each subject enrolled in the study will continue receiving combination study treatment in continuous 14-day cycles for up to 12 months as long as subjects are receiving clinical benefit and have not met any criteria for study withdrawal. When a subject discontinues all study treatment, the treatment period will end, the EOT visit should be conducted, and the subject will enter the safety follow-up period (see Section 6.4).

Protocol Amendment 6 (28 JUN 2017) removed the option for subjects to receive epacadostat monotherapy once they completed 12 months of combination therapy with durvalumab. However, subjects already receiving epacadostat monotherapy prior to Amendment 6 were allowed to continue if they were receiving clinical benefit and their investigator felt it was in the best interest of the subject. These subjects will be allowed to continue epacadostat monotherapy for up to an additional 12 months, and their maximum overall study treatment duration should not exceed 24 months. Exceptions for these subjects to continue study treatment beyond 24 months will require medical monitor review and approval every 3 months.

Study participation is expected to average about 6 months.

5.5. Rationale for Dose Modification

The purpose of the dose-escalation portion of the study (Phase 1) is to establish a suitable dose of epacadostat in combination with durvalumab.

A 42-day DLT window, along with regular internal reviews of safety events, will be used for the dose-escalation phase of the study. While the rules for adjudicating DLTs in the context of dose escalation/cohort expansion are specified in Section 5.5.1, an AE not listed above, or an AE meeting the DLT criteria above but occurring outside of the DLT period, may be defined as a DLT after consultation between the sponsor and investigator, based on the emerging safety profile. The final recommended dose for the dose-expansion phase will be based on the review of the safety and tolerability data, including cumulative toxicity from available cohorts.

Independent of the determination of tolerability during Phase 1 of the study, subjects may require individual modification or interruption of epacadostat or durvalumab if necessitated by AEs, including irAEs. Dose adjustments are summarized in Section 5.6.

5.5.1. Definition of Dose-Limiting Toxicities

Dose-limiting toxicities will be evaluated during the dose-escalation phase. The period for evaluating DLTs will be from the time of first administration of study treatment until the planned administration of the fourth dose of durvalumab, 42 days from receiving the first doses of epacadostat and durvalumab. Subjects who do not remain on the study up to this time for reasons other than DLT will be replaced with another subject at the same dose level. Grading of DLTs will be according to the NCI CTCAE v4.0. A DLT will be defined as the occurrence of any treatment-related toxicity described in Table 7 occurring up to and including Study Day 42 (6-week observation period). Only toxicities with a clear alternative explanation (eg, due to disease progression, comorbid conditions, concomitant medications) or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms based on investigator determination can be deemed non-DLT. Grade 3 irAEs (excluding ocular, pneumonitis, or colitis) that improve to ≤ Grade 1 by appropriate care or corticosteroid therapy within 14 days after the initiation of supportive care or corticosteroid therapy will not count as DLTs. Subjects who may not have experienced a DLT but who experienced intolerable, lower grade persistent toxicity determined to be due to study drug or have experienced recurrent dose interruptions and/or reductions will be considered in the determination of the study drug doses to be used in Phase 2.

Table 7: Criteria for Defining Dose-Limiting Toxicities

Hematologic Toxicities: • Grade 4 thrombocytopenia related to either drug • ≥ Grade 3 neutropenia lasting > 5 days related to either drug • Grade 4 anemia related to either drug • Febrile neutropenia (ANC < 1.0×10^9/L and fever > 101°F/38.3°C) related to either drug • Thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, disseminated intravascular coagulation, idiopathic thrombocytopenic purpura, ≥ Grade 3 hemolysis
Nonhematologic Toxicities: • Any drug-related/immune-related[a] Grade 4 toxicity • Any Grade 3 or 4 AST, ALT, or total bilirubin elevation • Any other drug-related/immune-related[a] Grade 3 toxicity, EXCLUDING: – Grade 3 nausea/vomiting controlled by medical intervention within 72 hours – Grade 3 immune-related AE[a] (other than ocular events, colitis, and pneumonitis) that improves to Grade ≤ 1 or baseline within 14 days after the initiation of supportive care or corticosteroid therapy – Grade 3 endocrinopathy that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject is asymptomatic or minimally or transiently symptomatic based on Investigator assessment – Grade 3 fatigue lasting ≤ 7 days from onset – Grade 3 rash in the absence of desquamation, with no mucosal involvement, that does not require systemic steroids, that does not interfere with activities of daily living and resolves to Grade 1 by the next dose of durvalumab or 14 days, whichever is longer – Any grade vitiligo or alopecia • Grade 2 or higher episcleritis, uveitis, or iritis • Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 3 days of initiation of maximal supportive care
General: • Greater than 2-week delay in starting Cycle 4 because of a treatment-related toxicity even if the toxicity does not meet DLT criteria defined above. • If subjects are unable to receive 75% of epacadostat or 3 doses of durvalumab during the DLT observation period because of drug-related toxicity, even if the toxicity does not meet DLT criteria defined above. • While the rules for adjudicating DLTs in the context of dose escalation are specified above, an AE not listed above may be defined as a DLT after a consultation with the sponsor and investigators, based on the emerging safety profile.

[a] Immune-related AEs are defined as AEs of an immune nature (ie, inflammatory) in the absence of a clear alternative etiology. In the absence of a clinically significant abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT.

5.5.2. Procedures for Cohort Review and Dose Escalation in Phase 1

Telephone conferences will be scheduled by the sponsor with Phase 1 investigators in order to review cohort-specific data, overall safety data from prior cohorts (if applicable), and to agree on dose escalation. For additional safety oversight, this group will review and adjudicate individual high-grade AEs as potentially dose-limiting and for guiding the study team on decisions regarding dose escalation and cohort expansion. The same method will be employed for reviewing data in Phase 1 to determine the recommended dose for Phase 2.

5.5.2.1. Follow-Up for Dose-Limiting Toxicities

Subjects whose treatment is discontinued due to a DLT must be followed until resolution or stabilization of the DLT event, whichever comes first.

5.6. Dose Adjustment of Study Drug

5.6.1. Planned Dose Increases

Cohort dose escalation is described in Section 4.1.1.

Intrasubject dose escalations of epacadostat are not permitted.

Intrasubject dose escalation of durvalumab to 10 mg/kg every 2 weeks will be allowed only for subjects who were enrolled into the study at a dose of durvalumab 3 mg/kg every 2 weeks, provided that the following criteria are met:

- The Protocol inclusion criteria are met.
- The subject has not experienced related or possibly related toxicity ≥ Grade 2.
- The next dose level of epacadostat 25 mg BID and durvalumab 10 mg/kg has been determined to be safe based on DLT rules (eg, no DLTs during the DLT observation period).
- The subject is willing to submit to the PK [redacted] sampling schedule and durvalumab infusion observation as in Cycle 1.
- In the opinion of the investigator, the subject does not have any concurrent condition or circumstance that would complicate the dose escalation or PK sampling, or pose increased risk to the subject.
- The intrasubject dose escalation has been approved by the sponsor.

Note that if a subject dose escalates and experiences toxicity, guidance for dose interruption is provided in Sections 5.6.2 and 5.6.3. In cases of persistent toxicity, dose de-escalation may be considered if approved by the medical monitor.

5.6.2. Criteria and Procedures for Interruption or Dose Reduction

In some circumstances, it may be necessary to temporarily interrupt treatment as a result of adverse experiences that may have an unclear relationship to study drug.

Table 8 summarizes the dosing actions for epacadostat and durvalumab that must be implemented with the indicated related AEs. Additional information related to dose changes and AE management for irAEs can be found in Section 5.6.3.

In general, treatment with both study drugs should be withheld for ≥ Grade 3 irAEs or non-irAEs and may be withheld for ≥ Grade 2 irAEs. Additional details for irAEs are provided in Section 5.6.3.

If a criterion for dose reduction of epacadostat is met, refer to Table 9 to determine the appropriate dose for the subject. There will be no dose reductions of durvalumab allowed for the management of toxicities of individual subjects (exception noted in Section 5.6.1). Doses of

durvalumab may be delayed for toxicity management. In general, study treatment should be discontinued for toxicities that do not resolve to Grade 1 or less within 4 weeks of onset. Exceptions to this must be discussed with the medical monitor.

Note: There may be some circumstances where, due to toxicity attributed to epacadostat, a subject may not tolerate the combination therapy but may benefit from monotherapy with durvalumab. These cases must be discussed and approved by the medical monitor before the subject may receive durvalumab monotherapy on study.

Any interruptions of > 4 weeks or for LFT abnormalities must be discussed with the medical monitor prior to resuming treatment.

Except in cases of emergency, it is recommended that the investigator consult with the medical monitor (or other representative of the sponsor) before temporarily interrupting therapy for reasons other than Protocol-mandated medication hold. Additionally, the investigator must notify the sponsor's medical monitor and study project manager via email before restarting study drug that was interrupted for > 4 weeks due to an AE.

Table 8: Dose Modification Guidelines of Epacadostat and Durvalumab for Non–Immune-Related Adverse Events

Adverse Event	CTCAE v4.0 Grade	Action With Respect to Epacadostat	Action With Respect to Durvalumab
Non-irAE (first occurrence)	3	Hold study treatment until resolution to ≤ Grade 1 or baseline.[a] For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume study treatment administration. Otherwise, discontinue study treatment.	Hold study treatment until resolution to ≤ Grade 1 or baseline.[a] For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume study treatment administration. Otherwise, discontinue study treatment.
Non-irAE (second occurrence)	3	Hold study treatment until resolution to ≤ Grade 1 or baseline.[a] For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume study treatment administration. Otherwise, discontinue study treatment.	Hold study treatment until resolution to ≤ Grade 1 or baseline.[a] For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume study treatment administration. Otherwise, discontinue study treatment.
Non-irAE (third occurrence)	3	Discontinue epacadostat.	Hold study treatment until resolution to ≤ Grade 1 or baseline.[a] For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume study treatment administration. Otherwise, discontinue study treatment.

Table 8: Dose Modification Guidelines of Epacadostat and Durvalumab for Non–Immune-Related Adverse Events (Continued)

Adverse Event	CTCAE v4.0 Grade	Action With Respect to Epacadostat	Action With Respect to Durvalumab
Non-irAE	4	Discontinue epacadostat.	Discontinue durvalumab.
Infusion-related reactions	1 or 2	Not applicable.	The infusion rate of durvalumab may be decreased by 50% or temporarily interrupted until resolution of the event. For Grade 2 infusion-related reactions, subsequent infusions may be given at 50% of the initial infusion rate. • Acetaminophen and/or antihistamines may be administered per institutional standards at the discretion of the investigator. • Consider premedication prior to subsequent doses. • Steroids should not be used for routine premedication of ≤ Grade 2 infusion reactions.
Infusion-related reactions	≥ 3	Discontinue epacadostat.	Discontinue durvalumab. Manage severe infusion-related reactions per institutional standards (eg, intramuscular epinephrine followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

[a] If event is a laboratory AE without associated clinically significant signs or symptoms, as determined by the principal investigator, the subject may continue study treatment administration with approval from the medical monitor as long as steroid treatment has not been planned or initiated. Laboratory testing should be repeated within 72 hours. If the AE does not resolve to ≤ Grade 1 in 7 days, the subject should then interrupt study treatment until event has resolved to ≤ Grade 1 and restart at the next lower dose level.

Table 9: Dose Reductions for Epacadostat

Current Dose	Dose Reduction
25 mg BID	Discontinue epacadostat
50 mg BID	25 mg BID
75 mg BID	50 mg BID
100 mg BID	75 mg BID
300 mg BID	100 mg BID

5.6.3. Criteria for Subjects Exhibiting Immune-Related Adverse Events

This section is meant to apply to suspected irAEs from epacadostat, durvalumab, or the combination. Immune-related AEs may be predicted based on the nature of the durvalumab or epacadostat compounds, their mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes prior to labeling an AE as an irAE. Subjects who develop a ≥ Grade 2 irAE should be discussed immediately with the medical monitor.

Recommendations for management of specific immune-mediated AEs such as pneumonitis (see Section 5.6.3.1), enterocolitis (see Section 5.6.3.2), hepatitis (see Section 5.6.3.3), dermatitis (see Section 5.6.3.4), immune-mediated neuropathies (see Section 5.6.3.5), immune-mediated endocrinopathies (see Section 5.6.3.6), immune-mediated nephritis or renal dysfunction (see Section 5.6.3.7), and ocular manifestations (see Section 5.6.3.8) are detailed in the sections below.

General recommendations to managing irAEs not detailed elsewhere in this section are detailed in Section 5.6.3.12.

5.6.3.1. Procedures and Guidelines for Pneumonitis

Subjects with symptomatic pneumonitis should immediately stop receiving durvalumab and epacadostat and have an evaluation. Subjects should be monitored for signs and symptoms of pneumonitis or interstitial lung disease. The evaluation may include imaging (high resolution CT scan), bronchoscopy, and pulmonary function tests such as monitoring of oxygenation via pulse oximetry (resting and exertion) and laboratory work-up to rule out other causes such as infection. If the subject is determined to have study drug–associated pneumonitis, the suggested treatment plan is detailed in Table 10.

Table 10: Recommended Approach for Handling Noninfectious Pneumonitis

Toxicity Grade	Withhold/Discontinue Durvalumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 1 (asymptomatic)	No action. **Note:** Consider holding study treatment as clinically appropriate during diagnostic work-up for other etiologies.	Not applicable.	**For Grade 1 (radiographic changes only):** • Monitor and closely follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. • Consider pulmonary and infectious disease consult.
Grade 2	Withhold epacadostat and durvalumab. **Note:** Permanently discontinue study treatment if upon rechallenge subject develops pneumonitis ≥ Grade 2.	Hold treatment until resolution to ≤ Grade 1 or baseline. • If toxicity improves to ≤ Grade 1 or baseline, then the decision to reinitiate study treatment will be based on treating physician's clinical judgment and after completion of steroid taper. • If toxicity worsens, treat as Grade 3 or Grade 4.	**For Grade 2 (mild to moderate new symptoms):** • Monitor symptoms daily and consider hospitalization. • Promptly start systemic steroids (eg, prednisone 1-2 mg/kg per day PO or IV equivalent). • Reimaging as clinically indicated. • If no improvement within 3-5 days, additional work-up should be considered, and prompt treatment with IV methylprednisolone 2-4 mg/kg per day should be started. • If still no improvement within 3-5 days despite IV methylprednisone at 2-4 mg/kg per day, promptly start immunosuppressive therapy such as tumor necrosis factor inhibitors (eg, infliximab 5 mg/kg every 2 weeks). Caution: Important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungal or anti-PCP treatment (refer to current NCCN Guidelines for treatment of cancer-related infections [Category 2B recommendation]). • Consider pulmonary and infectious disease consult. • Consider discussing with medical monitor as necessary.

Table 10: Recommended Approach for Handling Noninfectious Pneumonitis (Continued)

Toxicity Grade	Withhold/Discontinue Durvalumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 3 and Grade 4	Discontinue epacadostat and durvalumab.	Not applicable.	**For Grade 3 or Grade 4 (severe or new symptoms, new/worsening hypoxia, life threatening):** • Promptly initiate empiric IV methylprednisolone 1-4 mg/kg per day or equivalent. • Obtain pulmonary and infectious disease consult. • Hospitalize the subject. • Supportive care (oxygen, etc). • If no improvement within 3-5 days, additional work-up should be considered and prompt treatment with additional immunosuppressive therapy such as tumor necrosis factor inhibitors (eg, infliximab at 5 mg/kg every 2 weeks) started. Caution: Rule out sepsis and refer to infliximab label for general guidance before using infliximab. • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PCP treatment (refer to current NCCN Guidelines for treatment of cancer-related infections [Category 2B recommendation]).

PCP = pneumocystis pneumonia.

5.6.3.2. Procedures and Guidance 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 sepsis, peritoneal signs, and ileus). In symptomatic subjects, rule out infectious etiologies and consider endoscopic evaluation for persistent or severe symptoms.

Subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, infections including testing for clostridium difficile toxin, etc). Steroids should be considered in the absence of clear alternative etiology, even for low grade events, in order to prevent potential progression to higher grade event. Use analgesics carefully; they can mask symptoms of perforation and peritonitis. The recommended approach for handling enterocolitis is detailed in Table 11.

Table 11: Recommended Approach for Handling Enterocolitis

Toxicity Grade	Withhold/Discontinue Durvalumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 1	No action.	Not applicable.	• Closely monitor for worsening symptoms. • Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide. Use of probiotics as per treating physician's clinical judgment.
Grade 2	Withhold durvalumab and epacadostat.	Hold treatment until resolution to ≤ Grade 1 or baseline. • If toxicity improves to ≤ Grade 1, then study treatment can be resumed after completion of steroid taper. Epacadostat will be reduced by 1 dose level, and durvalumab will resume at the same dose/schedule. • If toxicity worsens, treat as Grade 3 or Grade 4.	• Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide and/or budesonide. • Promptly start prednisone 1-2 mg/kg per day PO or IV equivalent. • If event is not responsive within 3-5 days or worsens despite prednisone 1-2 mg/kg per day PO or IV equivalent, GI consult should be obtained for consideration of further work-up such as imaging and/or colonoscopy to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2-4 mg/kg per day started. • If still no improvement within 3-5 days despite 2-4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeks. Caution: Important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. • Consult with medical monitor if no resolution to ≤ Grade 1 in 3-4 days. • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN Guidelines for treatment of cancer-related infections [Category 2B recommendation]).

Table 11: Recommended Approach for Handling Enterocolitis (Continued)

Toxicity Grade	Withhold/Discontinue Durvalumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 3 and Grade 4	Discontinue epacadostat and durvalumab.	Not applicable.	• Treatment with systemic corticosteroids (IV administration) should be initiated promptly at a dose of 2-4 mg/kg per day of prednisone or equivalent. • Monitor stool frequency and volume and maintain hydration. • Urgent GI consult and imaging and/or colonoscopy as appropriate. • If still no improvement within 3-5 days of IV methylprednisolone 2-4 mg/kg per day or equivalent, promptly start further immunosuppressives (eg, infliximab at 5 mg/kg once every 2 weeks). Caution: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN Guidelines for treatment of cancer-related infections [Category 2B recommendation]).

5.6.3.3. Procedures and Guidance for Hepatitis

Monitor LFTs (hepatic transaminase, alkaline phosphatase, and bilirubin levels) and assess subjects for signs and symptoms of hepatotoxicity on Day 1 of each cycle before dosing of durvalumab. In subjects with hepatotoxicity, rule out infectious or malignant causes and increase frequency of LFT monitoring to twice per week until resolution. Recommendations for management of hepatitis are shown in Table 12.

Table 12: Recommended Approach for Handling Hepatitis

Toxicity Grade	Withhold/Discontinue Epacadostat and Durvalumab	Guidance for Restarting Study Treatment	Supportive Care
Grade 1	No dose modifications. If it worsens, then treat as Grade 2 event.	Not applicable.	Increase frequency of LFT monitoring to twice per week until LFTs return to baseline.
Grade 2 elevation in AST/ALT or total bilirubin	Withhold epacadostat and durvalumab.	Hold treatment until resolution to ≤ Grade 1 or baseline. • If improves to ≤ Grade 1 or baseline, resume study treatment after completion of steroid taper. Epacadostat will be reduced by 1 dose level, and durvalumab will resume at the same dose/schedule. • If toxicity worsens, then treat as Grade 3 or Grade 4.	• Regular and frequent checking of liver chemistries (eg, every 1-2 days) until improving or resolved. • Rule out viral and other etiologies. • If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1-2 mg/kg per day PO or IV equivalent. • If still no improvement within 3-5 days despite prednisone 1-2 mg/kg per day PO or IV equivalent, consider additional work-up and start prompt treatment with IV methylprednisolone 2-4 mg/kg per day. • If still no improvement within 3-5 days despite 1-4 mg/kg per day methylprednisolone IV or equivalent, promptly start immunosuppressives (mycophenolate mofetil). Discuss with medical monitor if mycophenolate mofetil is not available. **Infliximab should NOT be used**. • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN Guidelines for treatment of cancer-related infections [Category 2B recommendation]).

Table 12: Recommended Approach for Handling Hepatitis (Continued)

Toxicity Grade	Withhold/Discontinue Epacadostat and Durvalumab	Guidance for Restarting Study Treatment	Supportive Care
Grade 3 elevation in AST/ALT of > 5 × ULN but < 8 × ULN OR Grade 3 elevation in total bilirubin of ≤ 5 × ULN	Withhold epacadostat and durvalumab.	Hold treatment until resolution to ≤ Grade 1 or baseline. • Resume study treatment if elevations downgrade ≤ Grade 1 or baseline within 14 days; epacadostat will be reduced by 1 dose level, and durvalumab will resume at the same dose/schedule. • If AE does not resolve to ≤ Grade 1 or baseline within 14 days: Discontinue study treatment (exceptions may be made by the medical monitor on a case by case basis). • Permanently discontinue study treatment for any case meeting Hy's law criteria (AST and/or ALT > 3 × ULN + bilirubin > 2 × ULN without initial findings of cholestasis (ie, elevated alkaline P04) and in the absence of any alternative cause.	• Promptly initiate empiric IV methylprednisolone 1-4 mg/kg per day or equivalent • If still no improvement within 3-5 days despite IV methylprednisolone 1-4 mg/kg per day or equivalent, promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with medical monitor if mycophenolate is not available. **Infliximab should NOT be used.** • Hepatology consult, abdominal work-up, and imaging, as appropriate. • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN Guidelines for treatment of cancer-related infections [Category 2B recommendation]).
Elevation in AST/ALT of > 8 × ULN OR Elevation of total bilirubin of > 5 × ULN	Discontinue epacadostat and durvalumab.	Not applicable.	

5.6.3.4. 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 immune-mediated dermatitis are shown in Table 13. If there is any bullous formation, the medical monitor should be contacted and the study drug should be discontinued.

Table 13: Recommended Approach for Handling Dermatitis

Toxicity Grade	Withhold/Discontinue Epacadostat and Durvalumab	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, including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream). Administer topical or systemic corticosteroids if there is no improvement of symptoms within 1 week.
Grade 2	May withhold epacadostat and durvalumab per investigator discretion.	If persistent (> 1-2 weeks), hold treatment until resolution to ≤ Grade 1 or baseline. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to ≤ Grade 1 or baseline, then resume drug/study regimen after completion of steroid taper.	• Obtain dermatology consult. • Consider symptomatic treatment including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream). • Consider moderate-strength topical steroid. • If no improvement of rash/skin lesions occurs within 3-5 days or worsens despite symptomatic treatment and/or use of moderate-strength topical steroid, discuss with medical monitor and promptly start systemic steroids, such as prednisone 1-2 mg/kg per day PO or IV equivalent. • Consider skin biopsy if persistent for > 1-2 weeks or recurs.
Grade 3	Withhold epacadostat and durvalumab. *Note: Permanently discontinue epacadostat and durvalumab in subjects with Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration or necrotic, bullous, or hemorrhagic manifestations.*	Hold treatment until resolution to ≤ Grade 1 or baseline. • If AE resolves within 4 weeks: Restart study treatment at same dose/schedule. • If AE does not resolve within 4 weeks: Approval to restart study treatment by medical monitor required; epacadostat will be reduced by 1 dose level, and durvalumab will resume at the same dose/schedule.	For Grade 3 or 4: • Consult dermatology. • Promptly initiate empiric IV methylprednisolone 1-4 mg/kg per day or equivalent. • Consider hospitalization. • Monitor extent of rash. • Consider skin biopsy (preferably > 1) as clinically feasible. • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN Guidelines for treatment of cancer-related infections [Category 2B recommendation]). • Discuss with medical monitor.
Grade 4	Discontinue epacadostat and durvalumab.	Not applicable.	

5.6.3.5. Procedures for Immune-Mediated Neuropathies

Subjects should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes, or medications). Monitor subjects for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, behavior changes, headache, nausea, vertigo, or paresthesia. Consider appropriate diagnostic testing (eg, electromyogram and nerve conduction investigations). Perform symptomatic treatment with neurological consult as appropriate. Recommendations for the management of immune-mediated neuropathies are shown in Table 14.

For any grade immune-mediated peripheral neuromotor syndromes, such as Guillain-Barré syndrome and myasthenia gravis, the following precautions should be followed:

- The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain subjects may unpredictably experience acute decompensations that can result in substantial morbidity or, in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability.
- Subjects should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes, and medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult.
- Neurophysiologic diagnostic testing (eg, electromyogram, nerve conduction investigations, and "repetitive stimulation," if myasthenia is suspected) is routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation.
- It is important to consider that the use of steroids as the primary treatment of Guillain-Barré syndrome is not typically considered effective. Subjects requiring treatment should be started with IVIG, followed by plasmapheresis if not responsive to IVIG.

Table 14: Recommended Approach for Handling Neuropathies

Toxicity Grade	Withhold/Discontinue Epacadostat and Durvalumab	Guidance for Restarting Study Treatment	Supportive Care
Immune-mediated neurotoxicity (to include but not limited to limbic encephalitis, autonomic neuropathy, excluding myasthenia gravis and Guillain-Barré syndrome)			
Grade 1	No action.	Not applicable.	Provide symptomatic treatment.
Grade 2	May withhold epacadostat and durvalumab per investigator discretion.	• For acute motor neuropathies or neurotoxicity, hold study treatment until resolution to ≤ Grade 1. • For sensory neuropathy/ neuropathic pain, consider holding study treatment until resolution to ≤ Grade 1. – If toxicity worsens, then treat as Grade 3 or Grade 4. – Study treatment can be resumed once event improves to ≤ Grade 1 or baseline and after completion of steroid taper. Epacadostat will be reduced by 1 dose level, and durvalumab will resume at the same dose/schedule.	• Consider systemic corticosteroids in addition to appropriate symptomatic treatment. • If no improvement within 3-5 days despite prednisone 1-2 mg/kg per day PO or IV equivalent, consider additional work-up and promptly treat with additional immunosuppressive therapy (eg, IVIG).
Grade 3 and Grade 4	Discontinue epacadostat and durvalumab.	Not applicable.	• Discuss with medical monitor and consider hospitalization. • Obtain neurology consult. • Consider prompt initiation of systemic corticosteroids (IV administration should be strongly considered) at a dose of 1-2 mg/kg per day prednisone or equivalent. • Institute medical intervention as appropriate for management of severe neuropathy. • If no improvement within 3-5 days despite IV corticosteroids, consider additional work-up and promptly treat with additional immunosuppressants (eg, IVIG). • Once stable, gradually taper steroids over ≥ 28 days.
Immune-mediated peripheral neuromotor syndromes (eg, Guillain-Barré syndrome and myasthenia gravis)			
Grade 1	No action.	• Not applicable.	• Provide symptomatic treatment. • Discuss with the study physician. • Care should be taken to monitor subjects for sentinel symptoms of a potential decompensation as described above. • Obtain a neurology consult, unless the symptoms are very minor and stable.

Table 14: Recommended Approach for Handling Neuropathies (Continued)

Toxicity Grade	Withhold/Discontinue Epacadostat and Durvalumab	Guidance for Restarting Study Treatment	Supportive Care
Grade 2	Withhold epacadostat and durvalumab.	• Hold study treatment until resolution to ≤ Grade 1. • Permanently discontinue study treatment if it does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	• Discuss with the study physician. • Care should be taken to monitor subjects for sentinel symptoms of a potential decompensation as described below. • Obtain a neurology consult. • Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin, duloxetine). **Myasthenia Gravis:** • Steroids may be successfully used to treat myasthenia gravis. Important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. • Subjects unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each subject. • If myasthenia gravis–like neurotoxicity is present, consider starting acetylcholine esterase inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. **Guillain-Barré Syndrome:** • Important to consider that the use of steroids as the primary treatment is not typically considered effective. Subjects requiring treatment should be started with IVIG, followed by plasmapheresis if not responsive to IVIG.

Table 14: Recommended Approach for Handling Neuropathies (Continued)

Toxicity Grade	Withhold/Discontinue Epacadostat and Durvalumab	Guidance for Restarting Study Treatment	Supportive Care

Grade 3 or Grade 4	Withhold epacadostat and durvalumab (Grade 3). Discontinue epacadostat and durvalumab (Grade 4).	• Hold study treatment until resolution to ≤ Grade 1.
		• Permanently discontinue study treatment if Grade 3 irAE does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.
			• For severe or life-threatening (Grade 3 or 4) events:
			  • Discuss with study physician.
			  • Recommend hospitalization.
			  • Monitor symptoms and obtain neurological consult.
			Myasthenia Gravis:
			• Steroids may be successfully used. They should typically be administered in a monitored setting under supervision of a consulting neurologist.
			• Subjects unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG.
			• If myasthenia gravis–like neurotoxicity is present, consider starting acetylcholine esterase inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis.
			• **Guillain-Barré Syndrome:**
			• Important to consider that the use of steroids as the primary treatment is not typically considered effective. Subjects requiring treatment should be started with IVIG, followed by plasmapheresis if not responsive to IVIG.

IVIG = intravenous immunoglobulin.

5.6.3.6. 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 nonspecific symptoms that 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. Consult an endocrinologist.

Monitor subjects' thyroid function tests and other relevant clinical chemistries at the start of treatment, every 6 cycles, and as clinically indicated based on symptoms. In a limited number of subjects, hypophysitis was diagnosed by imaging studies through enlargement of the pituitary gland. If a subject experiences an AE that is thought to be possibly of an autoimmune nature (eg, thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.

Treatment may be withheld for ≥ Grade 2 events and treatment may be restarted after the initiation of appropriate hormone-replacement therapy. Recommendations are shown in Table 15.

Table 15: Recommended Approach for Handling Endocrinopathies

Toxicity Grade	Withhold/Discontinue Epacadostat and Durvalumab	Guidance for Restarting Study Treatment	Supportive Care
Grade 1	No action.	Not applicable.	• Provide symptomatic treatment. • Monitor patient with appropriate endocrine function tests. • If TSH < 0.5 × LLN, or TSH > 2 × ULN or consistently out of range in 2 subsequent measurements, include FT4 at subsequent cycles as clinically indicated and consider endocrinology consult (includes those with asymptomatic TSH elevation). • For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency).

Table 15: Recommended Approach for Handling Endocrinopathies (Continued)

Toxicity Grade	Withhold/Discontinue Epacadostat and Durvalumab	Guidance for Restarting Study Treatment	Supportive Care
Grade 2	For endocrinopathy other than hypothyroidism, withhold epacadostat and durvalumab.	If study treatment is held, resume study treatment at same dose/schedule until subject is clinically stable. • If toxicity worsens, then treat as Grade 3 or Grade 4. • Study treatment can be resumed once the event stabilizes and after completion of steroid taper. • Subjects with endocrinopathies who may require prolonged or continued steroid replacement can be re-treated with study treatment on the following conditions: 1) the event stabilizes and is controlled, 2) the subject is clinically stable as per investigator or treating physician's clinical judgement, and 3) doses of prednisone are at ≤ 10 mg/day or equivalent.	• Consult endocrinologist to guide evaluation of endocrine function, and as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. • Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids. • Isolated Type 1 DM may be treated with appropriate diabetic therapy, without study drug interruption, and without corticosteroids. • For subjects with abnormal endocrine work-up, except for those with isolated hypothyroidism, consider short-term, high-dose corticosteroids (eg, methylprednisolone 1-2 mg/kg per day or IV equivalent) and initiate appropriate hormone replacement therapy. • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN Guidelines for treatment of cancer-related infections [Category 2B recommendation]). • For subjects with normal endocrine work-up (labs or MRI), repeat labs/MRI as clinically indicated.

Table 15: Recommended Approach for Handling Endocrinopathies (Continued)

Toxicity Grade	Withhold/Discontinue Epacadostat and Durvalumab	Guidance for Restarting Study Treatment	Supportive Care
Grade 3 and Grade 4	For endocrinopathy other than hypothyroidism, withhold epacadostat and durvalumab until endocrinopathy symptom(s) are controlled.	• Study treatment can be resumed once event stabilizes and after completion of steroid taper.	• Consult endocrinologist to guide evaluation of endocrine function, and as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. • Discuss with medical monitor. • Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids. • Isolated Type 1 DM may be treated with appropriate diabetic therapy, without study drug interruption, and without corticosteroids. • For all patients with abnormal endocrine work-up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1-2 mg/kg per day or equivalent. • For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity. • Once improving, gradually taper immunosuppressive steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN Guidelines for treatment of cancer- related infections [Category 2B recommendation])

FT4 = free thyroxine; LLN = lower limit of normal; MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

5.6.3.7. Procedures for Immune-Mediated Nephritis or Renal Dysfunction

Subjects should be monitored for signs and symptoms that may be related to changes in renal function (eg, routine urinalysis, elevated serum blood urea nitrogen and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria). Consult with a nephrologist. Subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, infections). Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2) in order to prevent potential progression to higher grade event. Recommendations are shown in Table 16.

Table 16: Recommended Approach for Handling Nephritis or Renal Dysfunction

Toxicity Grade	Withhold/Discontinue Epacadostat and Durvalumab	Guidance for Restarting Study Treatment	Supportive Care
Grade 1	No action.	Not applicable.	For Grade 1 elevated creatinine: • Monitor serum creatinine weekly and any accompanying symptom – If creatinine returns to baseline, resume its regular monitoring per study Protocol. – If it worsens, depending on the severity, treat as Grade 2 or Grade 3 or Grade 4. • Consider symptomatic treatment, including hydration, electrolyte replacement, diuretics, etc.
Grade 2	Withhold epacadostat and durvalumab.	Resume study treatment at same dose/schedule when nephritis is controlled. Hold study treatment until resolution to ≤ Grade 1 or baseline. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to ≤ Grade 1 or baseline, then resume study treatment after completion of steroid taper. Study treatment can be resumed at the next scheduled dose once event stabilizes to ≤ Grade 1 and 5-7 days have passed after completion of steroid taper.	For Grade 2 elevated creatinine: • Consider symptomatic treatment, including hydration, electrolyte replacement, diuretics, etc. • Carefully monitor serum creatinine as clinically warranted. • Consult nephrologist and consider renal biopsy if clinically indicated. • If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1-2 mg/kg per day PO or IV equivalent. • If event is not responsive within 3-5 days or worsens despite prednisone 1-2 mg/kg per day PO or IV equivalent, additional work-up should be considered and prompt treatment with IV methylprednisolone 2-4 mg/kg per day started. • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN Guidelines for treatment of cancer-related infections [Category 2B recommendation]). • When event returns to baseline, resume study treatment and routine serum creatinine monitoring per study Protocol.

Table 16: Recommended Approach for Handling Nephritis or Renal Dysfunction (Continued)

Toxicity Grade	Withhold/Discontinue Epacadostat and Durvalumab	Guidance for Restarting Study Treatment	Supportive Care
Grade 3 or Grade 4	Discontinue epacadostat and durvalumab.	Not applicable.	• Carefully monitor serum creatinine on daily basis. • Consult nephrologist and consider renal biopsy if clinically indicated. • Promptly start prednisone 1-2 mg/kg per day PO or IV equivalent. • If event is not responsive within 3-5 days or worsens despite prednisone 1-2 mg/kg per day PO or IV equivalent, additional work-up should be considered, and prompt treatment with IV methylprednisolone 2-4 mg/kg per day started. • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN Guidelines for treatment of cancer-related infections [Category 2B recommendation]).

5.6.3.8. Procedures and Guidelines for Lipase or Amylase Elevations

Subjects should be carefully monitored for signs and symptoms of pancreatitis, including upper abdominal pain, abdominal pain that radiates to the back, abdominal pain that feels worse after eating, fever, rapid pulse, nausea, vomiting, and tenderness when touching the abdomen. If any symptoms occur, dosing should be held, and, if severe, abdominal imaging should be considered and treatment should be permanently discontinued. Recommendations for the management of lipase or amylase elevations are provided in Table 17.

Table 17: Recommended Approach to Handling Lipase or Amylase Elevations

Toxicity Grade	Withhold/Discontinue Epacadostat and Durvalumab	Guidance for Restarting Study Treatment	Supportive Care
Grade 1	No action.	Not applicable.	Not applicable.
Grade 2	Subjects with intolerable or persistent Grade 2 toxicity may hold study treatment per investigator discretion.	If held, study treatment may resume when toxicity resolves to ≤ Grade 1.	Not applicable.
Grade 3	• If asymptomatic, may continue study treatment with medical monitor approval. • Permanently discontinue study treatment if clinical signs and symptoms of pancreatitis develop (eg, abdominal pain, nausea, vomiting). • If toxicity does not resolve to ≤ Grade 1 within 12 weeks of last dose after interruption, study treatment must be permanently discontinued unless approved by the medical monitor.	If held, study treatment may resume when toxicity resolves to ≤ Grade 1.	Not applicable unless symptomatic; then treat with systemic corticosteroids at a dose of 1-2 mg/kg per day prednisone or equivalent.
Grade 4	• Withhold epacadostat and durvalumab. • If lipase/amylase elevation is asymptomatic and abdominal imaging suggests no pathology, study treatment may continue with medical monitor approval. • Permanently discontinue if clinical signs and symptoms of pancreatitis develop (eg, abdominal pain, nausea, vomiting). • If toxicity does not resolve to ≤ Grade 1 within 12 weeks of last dose after interruption, study treatment must be permanently discontinued unless approved by the medical monitor.	If held, study treatment may resume when toxicity resolves to ≤ Grade 1.	May consider treatment with systemic corticosteroids at a dose of 1-2 mg/kg per day prednisone or equivalent.

5.6.3.9. Procedures for Ocular Manifestations

An ophthalmology consult should be considered. Administer corticosteroid eye drops to subjects who develop uveitis, iritis, or episcleritis. Permanently discontinue epacadostat and durvalumab for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy. The use of systemic immunosuppressive therapy may be appropriate for worsening ocular disease.

5.6.3.10. Procedures and Guidelines for Myocarditis

Table 18 provides recommendations for the management of suspected and confirmed myocarditis.

Table 18: Recommended Approach to Handling Myocarditis

Toxicity Grade	Withhold/Discontinue Epacadostat and Durvalumab	Guidance for Restarting Study Treatment	Supportive Care
Any	Discontinue study treatment permanently if biopsy-proven immune-mediated myocarditis.	Not applicable.	• The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. • Consider, as necessary, discussing with the medical monitor. • Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (eg, pulmonary embolism, congestive heart failure, malignant pericardial effusion). • A cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. • Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, ECHO, monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. • Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or infections).
Grade 1	No dose modifications required unless clinical suspicion is high, in which case hold study treatment during diagnostic work-up for other etiologies.	If study treatment is held, resume after complete resolution to Grade 0.	• Monitor and closely follow up in 2-4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. • Consider using steroids if clinical suspicion is high.

Table 18: Recommended Approach to Handling Myocarditis (Continued)

Toxicity Grade	Withhold/Discontinue Epacadostat and Durvalumab	Guidance for Restarting Study Treatment	Supportive Care
Grade 2 or greater	• **Grade 2**: Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently discontinue study drug/study regimen. • **Grade 3-4**: Permanently discontinue study treatment	• **Grade 2 only**: – If toxicity rapidly improves to Grade 0, then the decision to reinitiate study treatment after steroid taper will be up to investigator's clinical judgment. – If toxicity does not rapidly improve, permanently discontinue study treatment	• Monitor symptoms daily, hospitalize. • Promptly start IV methylprednisolone 2-4 mg/kg per day or equivalent after cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. • Supportive care (eg, oxygen). • If no improvement within 3-5 days despite IV methylprednisolone at 2-4 mg/kg per day, promptly start immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. • Once the patient is improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN Guidelines for treatment of cancer-related infections [Category 2B recommendation])

5.6.3.11. Procedures and Guidelines for Myositis/Polymyositis

Table 19 provides recommendations for the management of myositis/polymyositis.

Table 19: Recommended Approach to Handling Myositis/Polymyositis

Toxicity Grade	Withhold/Discontinue Epacadostat and Durvalumab	Guidance for Restarting Study Treatment	Supportive Care
Any	Refer to guidance for specific grades below.	Not applicable.	• Monitor patients for signs and symptoms of myositis/polymyositis (poly/myositis). Typically, muscle weakness/pain occurs in proximal muscles, including upper arms, thighs, shoulders, hips, neck, and back but rarely affects the extremities, including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. • Consider, as necessary, discussing with the medical monitor, • If poly/myositis is suspected, a neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. – Myocarditis may co-occur with poly/myositis; refer to guidance under Section 5.6.3.10. – Given breathing complications, refer to guidance under Section 5.6.3.1. – Given possibility of an existent (but previously unknown) autoimmune disorder, consider rheumatology consultation. • Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (ie, consider whether a rheumatologist consultation is indicated and could guide the need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, an MRI of the muscles, and/or a muscle biopsy. Consider barium swallow for evaluation of dysphagia or dysphonia. • Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or infections).

Table 19: Recommended Approach to Handling Myositis/Polymyositis (Continued)

Toxicity Grade	Withhold/Discontinue Epacadostat and Durvalumab	Guidance for Restarting Study Treatment	Supportive Care
Grade 1	No dose modifications	Not applicable.	• Monitor and closely follow up in 2-4 days for clinical symptoms and initiate evaluation as clinically indicated. • Consider a neurology consult. • Consider, as necessary, discussing with the medical monitor.
Grade 2	Hold study treatment	• Restart study treatment when resolved to ≤ Grade 1. • Permanently discontinue study treatment if it does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency.	• Monitor symptoms daily and consider hospitalization. • Obtain a neurology consult, and initiate evaluation. • Consider, as necessary, discussing with the medical monitor. • If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2-4 mg/kg per day systemic steroids along with receiving input from the neurology consultant. • If clinical course is not rapidly progressive, start systemic steroids (eg, prednisone 1-2 mg/kg per day PO or IV equivalent); if no improvement within 3-5 days, continue additional work-up and start treatment with IV methylprednisolone 2-4 mg/kg per day. • If after start of IV methylprednisolone at 2-4 mg/kg per day there is no improvement within 3-5 days, consider start of immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. • Once the patient is improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN Guidelines for treatment of cancer-related infections [Category 2B recommendation]).

Table 19: Recommended Approach to Handling Myositis/Polymyositis (Continued)

Toxicity Grade	Withhold/Discontinue Epacadostat and Durvalumab	Guidance for Restarting Study Treatment	Supportive Care
Grade 3 or Grade 4	• **Grade 3**: Hold study treatment • **Grade 4**: Permanently discontinue study treatment	• **Grade 3 only**: – Restart study treatment when resolved to ≤ Grade 1. – Permanently discontinue study treatment if it does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency.	• Monitor symptoms closely; recommend hospitalization. • Obtain a neurology consult, and complete full evaluation. • Consider, as necessary, discussing with the medical monitor. • Promptly start IV methylprednisolone 2-4 mg/kg per day systemic steroids along with receiving input from the neurology consultant. • If after start of IV methylprednisolone at 2-4 mg/kg per day there is no improvement within 3-5 days, consider start of immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. • Consider whether patient may require IVIG, plasmapheresis. • Once the patient is improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN Guidelines for treatment of cancer-related infections [Category 2B recommendation]).

5.6.3.12. Procedures for Immune-Related Adverse Events Not Specifically Described Above

Table 20 provides information on the diagnosis and treatment of potential irAEs.

Table 20: General Guidance for Diagnosis and Treatment of Immune-Related Adverse Events (Not Described in Previous Sections)

Subject evaluation to identify any alternative etiology
In the absence of a clear alternative etiology, all events of inflammatory nature should be considered to be immune-related
Symptomatic and topical therapy should be considered for low-grade events
Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event
More potent immunosuppressives should be considered for events not responding to systemic steroids

In general, both study drugs should be permanently discontinued for clinically significant or severe irAEs or for events where the steroid course cannot be tapered below 10 mg/day prednisone equivalent to manage symptoms. Following an irAE where treatment was withheld, study treatment may resume when the following conditions are met: steroid taper has reached ≤ 10 mg/day prednisone or equivalent, symptoms have improved to ≤ Grade 1 within 4 weeks of

onset (or longer with medical monitor approval), and, as appropriate, physiologic replacement of hormones has been instituted. Additional treatment regarding modifications to study drug administration for irAEs is detailed in Table 21.

Table 21: Recommended Approach for Handling Immune-Related Adverse Events (Not Described in Previous Sections)

Toxicity Grade	Withhold/Discontinue Epacadostat and Durvalumab	Guidance for Restarting Study Treatment
Grade 1	No action.	Not applicable.
Grade 2	Withhold epacadostat and durvalumab. If toxicity worsens, treat as Grade 3 or Grade 4. Subjects with endocrinopathies who may require prolonged or continued steroid replacement can be re-treated with study treatment on the following conditions: 1) the event stabilizes and is controlled, 2) the subject is clinically stable as per investigator or treating physician's clinical judgement, and 3) doses of prednisone are at ≥ 10 mg/day or equivalent. Consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality (eg, myocarditis, or other similar events even if they are not currently noted in the guidelines) when they do not rapidly improve to < Grade 1 upon treatment with systemic steroids and following full taper.	Resume study treatment at same dose/schedule when AE resolves to ≤ Grade 1 or baseline.
Grade 3	Discontinue epacadostat and durvalumab (exceptions to this approach allowing study treatment to continue after resolution of the AE may be granted only with medical monitor approval).	Not applicable (unless approved by the medical monitor).
Grade 4	Discontinue epacadostat and durvalumab. Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (ie, hyperthyroidism, hypothyroidism, Type 1 DM).	Not applicable (unless approved by the medical monitor).

5.6.4. Procedures for Subjects Exhibiting Serotonin Syndrome

As noted in Section 1.3.1, there is a rare chance that epacadostat could 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 (see Section 5.10.2). Selective serotonin reuptake inhibitors and SNRIs are permitted during 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 22) 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 22, including tremor, hyperreflexia, and spontaneous ocular or inducible clonus together with agitation, fever, diaphoresis, or muscle rigidity:

- Immediately interrupt study 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, durvalumab administration may be resumed once all signs and symptoms have resolved unless other AE management guidelines apply for the specific event (eg, immune-mediated neurotoxicities).
- If the subject chooses to remain in the study, restart dosing with epacadostat after the SSRI or SNRI has been discontinued, no sooner than 5 half-lives have elapsed for the specific SSRI or SNRI in question, and after resolution of signs/symptoms of SS. The SSRI or SNRI dosing MAY NOT be restarted.
- If the subject chooses to discontinue the study, or must restart treatment with SSRI or SNRI, subject should be scheduled for a follow-up visit. SSRI or SNRI treatment may be initiated 2 weeks after resolution of signs and symptoms of SS.
- If a subject has experienced moderate or severe unconfounded SS in the opinion of the investigator, without concomitant SSRI or SNRI usage or serotonergic concomitant medications, epacadostat treatment should be permanently discontinued. Durvalumab administration may be resumed with medical monitor approval once all signs and symptoms have resolved.

Table 22: Signs 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.

5.7. Withdrawal of Subjects From Study Treatment

5.7.1. Withdrawal Criteria

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

- The subject completes 12 months of study treatment with epacadostat and durvalumab, or had completed 12 months of combination treatment (prior to Amendment 6 [28 JUN 2017]), and has taken epacadostat monotherapy for an additional 12 months (for a total of 24 months of study treatment).
  - Note: A subject may be granted an exception by the medical monitor to continue on epacadostat monotherapy beyond 24 months of overall treatment duration if they are clinically stable or clinically improved. Approvals to remain on epacadostat monotherapy will require continuing review every 3 months.
- In the investigator's medical judgment, further participation would be injurious to the subject's health or well-being.
- The subject becomes pregnant.
- Consent is withdrawn by subject or legal representative (such as legal guardian).
- The subject has experienced an unacceptable toxicity as described in Section 5.6 or a toxicity that does not recover in 4 weeks. Investigators who wish to continue treatment after a treatment delay of 4 weeks should consult with the sponsor's medical monitor for approval.
- Confirmed radiographic progression of disease per modified RECIST v1.1.
  See Section 7.4 for details on subjects with unconfirmed radiographic progression.
  An exception to continue on treatment with confirmed radiographic progression may be granted to clinically stable subjects. See Section 7.4 for additional details.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority or IRB or IEC.
- ≥ Grade 3 infusion reaction.
- Initiation of alternative anticancer therapy including another investigational agent.

A subject **may** be withdrawn from the study treatment as follows:

- If subject attains a CR (see Section 7.4.3), and the decision is made to discontinue durvalumab.
- If, during the course of the study, a subject is found not to have met eligibility criteria, the medical monitor, in collaboration with the investigator, will determine whether the subject should be withdrawn from study treatment. See Section 11.3, Protocol Adherence.
- If a subject is noncompliant with study procedures or study drug administration in the opinion of the investigator, the sponsor should be consulted for instruction on handling the subject.

5.7.2. Withdrawal Procedures

Discontinuation of study treatment does not constitute study withdrawal or completion. The subject will proceed to the safety follow-up period when both study drugs are permanently discontinued. In the event that any subject discontinues study drug and subsequently withdraws from the study before completion, regardless of reason, reasonable efforts should be made to have the subject return for the EOT procedures to be completed as described in Section 6.3.

If the subject discontinues study treatment and actively withdraws consent for collection of safety follow-up data, then no additional data collection should occur; however, subjects will have the option of withdrawing consent for study treatment but continuing in the follow-up period of the study for safety assessments. The date the subject was withdrawn from the study and the specific reason for withdrawal will be recorded in the CRF.

If a subject is withdrawn from 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 CRF.
- The EOT visit should be performed.
- Subjects must be followed for safety until the time of the safety follow-up visits or until study drug–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer.

5.8. Study Completion

5.8.1. Study Completion Criteria

Subjects will be considered completing the study if they met 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).
- Subject completes the 90-day safety follow-up period.
- 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 the subject is otherwise entitled. Every reasonable effort should be made to determine the reason a subject withdraws prematurely, and this information should be recorded in the CRF.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority or IRB or IEC.

5.9. Beginning and End of the Study

The study begins when the first subject signs the informed consent. The end of the study may be designated as the timepoint when all subjects have discontinued the study drug and have completed applicable safety follow-up assessments.

If there are ≤ 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 Protocol. The remaining subjects are considered to be on study until a study completion criterion is met and/or written notification is provided to the sponsor.

In addition, the investigator will be expected to monitor for and report any SAEs, as detailed in Section 8.3 (Serious Adverse Events). The subject is considered on study until such time that he or she meets any of the discontinuation criteria and written notification is given to the sponsor.

5.10. Concomitant Medications and Measures

All concomitant medications and treatments must be recorded in the CRF. Any prior medication received up to 28 days prior to enrollment will be recorded in the CRF. Concomitant treatments/procedures that are required to manage a subject's medical condition during the study will also be recorded in the CRF. Concomitant medications administered as treatment prophylaxis (eg, for the management of infusion reactions) should also be recorded in the CRF.

5.10.1. Restricted Medications and Measures

- Systemic steroids may be used at doses ≤ 10 mg/day prednisone or equivalent with medical monitor approval.
- Use of coumarin-based anticoagulants (eg, warfarin) is discouraged. Low-dose warfarin (1 mg) is acceptable; however, doses that increase the INR are discouraged and will require a dose modification. If an alternative to coumarin-based anticoagulants cannot be used, investigators should follow the guidelines in Table 23 and either closely monitor or closely monitor and reduce the subject's dose of coumarin-based anticoagulant upon initiating therapy with epacadostat.

Table 23: Warfarin Dose Modification

	Epacadostat Dose		
Stable Baseline INR	**≤ 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%	Reduce warfarin by ~33% and monitor INR

- Use of the anticonvulsant carbamazepine (a UGT1A9 inducer) is discouraged. Because there is a potential interaction that could result in lower epacadostat exposures, an alternative to carbamazepine should be used if possible.

5.10.2. Prohibited Medications and Measures

Subjects are prohibited from receiving the following therapies during the screening and treatment periods of this study unless otherwise noted below:

- Any investigational medication other than the study drugs.
- Use of any anticancer medications including chemotherapy or biologic therapy other than the study medications.
- Use of any immunological-based treatment for any reason is prohibited. (NOTE: Inhaled or topical steroids are allowed, and systemic steroids at doses ≥ 10 mg/day prednisone or equivalent and immune suppressants are allowed with medical monitor approval for treatment of immune-related toxicities.) Temporary courses of corticosteroids for treatment of underlying or concurrent illness may be permitted upon discussion with the medical monitor.
- Radiation therapy.
  - Note: Local treatment of isolated lesions for palliative intent is acceptable (eg, by local surgery or radiotherapy).
- Use of any MAOI or drug associated with significant MAO inhibitory activity is prohibited from 21 days before Day 1 through 2 weeks after the final dose of epacadostat has been taken (see Appendix C).
- Use of any UGT1A9 inhibitor (see Appendix D).
  - Note: Administration of epacadostat on the morning of a procedure where propofol may be administered is permitted; however, the evening dose after the procedure should be held, and subjects may resume regular dosing the following day.
- Administration of live attenuated vaccines is prohibited from 30 days prior to the first dose of study treatment through 30 days after the final dose of durvalumab. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette–Guérin, typhoid vaccine, and intranasal influenza vaccines.
- Administration of inactivated vaccines (including the injectable influenza vaccine) is prohibited during the DLT observation period (ie, 42 days after Cycle 1 Day 1).

6. STUDY ASSESSMENTS

All study assessments will be performed as indicated in the schedule of assessments (see Table 24) and laboratory assessments (see Table 25). The required analytes for each laboratory test are shown in Table 26. The order of assessments is suggested by the order of mention within the schedule of assessments.

Table 24: Schedule of Assessments

Visit (Range)	Screening	Treatment Cycles					EOT	Follow-Up	
		C1D1	C1D8	C2D1	Day 1 All Subsequent Cycles	Every 12 Weeks	Discontinuation	Safety Follow-Up Visit 1	Safety Follow-Up Visit 2
	Days -28 to -1	±3 Days	±3 Days	±3 Days	±3 Days	±5 Days	+ 7 Days After Last Dose	42 Days After EOT ±7 Days	90 Days After EOT ±7 Days
Administrative procedures									
Informed consent	X								
Inclusion/exclusion criteria	X	X							
Medical and cancer history	X								
Smoking history	X								
Prior/concomitant medications review	X	X		X	X				
Administer epacadostat at clinic		X	X[a]	X					
Administer durvalumab		X		X	X				
Poststudy anticancer therapy status								X	X
Survival status									
Clinical procedures and assessments									
Comprehensive physical exam	X						X	X	X
Targeted physical exam		X		X	X				
Vital signs and weight (height at screening only)	X	X		X	X		X		
Postinfusion observation[b]		X							
12-lead ECG	X	X[c]		X[c]			X	X	X
Adverse event assessment[d]	X	X		X	X		X	X	X
Laboratory assessments	X	X[e]	X[f]	X	X[e]	X	X	X	X
Chest radiograph	X								
Tumor tissue collection[g]	X	X[h]							
Tumor imaging	X					X[i]	X[j]		

C1D1 = Cycle 1 Day 1; C1D8 = Cycle 1 Day 8; C2D1 = Cycle 2 Day 1.

[a] **Phase 1 Subjects Only:** Administer epacadostat in clinic on C1D8 when PK assessment is performed.

[b] Patients will be observed in clinic for 3 hours after the first infusion of durvalumab is administered.

[c] ECGs should be performed on Cycle 1 Day 1 and Cycle 2 Day 1 before epacadostat and durvalumab administration and 1 and 2 hours after administration of epacadostat. See Table 27 for details regarding specific timing of ECGs.

[d] Subjects need to be followed for AEs for 90 days after the last dose of durvalumab or epacadostat (whichever comes later).

[e] If LFTs are abnormal, then LFT monitoring should increase to twice per week until resolved to baseline.

[f] **Phase 1 Subjects Only:** Pharmacokinetic samples are collected at Cycle 1 Day 8.

[g] If subject agrees to such in the ICF, any leftover tissue will be stored for future biomedical research.

[h] Optional and can be obtained anytime for safety or with confirmed response or progression. If a subject consents to an on-treatment biopsy, the sample must be collected at peak exposure after the morning epacadostat dose (approximately 2-3 hours after dosing) and a peripheral whole blood sample should be collected at the same time as the biopsy. Additionally, one of the subject's target lesions may be used to collect this sample if it is the most accessible for biopsy (see Section 7.6.3.2.1).

[i] Imaging will be performed every 12 weeks scheduled from C1D1.

[j] If a scan was obtained within 4 weeks before the date of discontinuation, then a scan at treatment discontinuation isn't mandatory. In subjects who discontinue study therapy without confirmed disease progression, a radiologic evaluation should be repeated at the time of treatment discontinuation (ie, date of discontinuation ± 4 week window).

Table 25: Laboratory Assessments

Visit (Range)	Screening	Treatment Cycles					EOT	Follow-Up	
		C1D1	C1D8	C2D1	Day 1 All Subsequent Cycles	Every 12 Weeks[a]	Discontinuation	Safety Follow-Up Visit 1	Safety Follow-Up Visit 2
	Days -28 to -1	±3 Days	±3 Days	±3 Days	±3 Days	±5 Days	+ 7 Days After Last Dose	42 Days After EOT ±7 Days	90 Days After EOT ±7 Days
Safety and eligibility[b]									
Chemistry panel	X[c]			X	X		X	X	X
Liver chemistry tests[d]	X[c]			X	X[d]		X	X	X
Hematology with differential	X[c]			X	X		X	X	X
Coagulation panel (PT, INR, aPTT)[e]	X[c]								
Endocrine function testing	X[c]					X	X		
Urinalysis	X					X	X		
Serum pregnancy or urine[f]	X[c]								
Hepatitis B and C	X								
Pharmacokinetics									
Blood sample for epacadostat PK		X[g]	X[g]	X[g]					
Blood sample for durvalumab PK		X[h]		X[h]					
Immunogenicity									
Immunogenicity assessment		X			X[i]		X		X
[redacted]									
[redacted]									
[redacted]									
[redacted]									

C1D1 = Cycle 1 Day 1; C1D8 = Cycle 1 Day 8; C2D1 = Cycle 2 Day 1.

[a] Pharmacokinetic sample for durvalumab will be drawn at Cycle 5 and every 4 cycles (8 weeks) thereafter (Phase 1 only).

[b] All safety laboratory tests will be performed locally.

[c] Screening laboratory tests must be performed within 7 days of Cycle 1 Day 1. If performed more than 7 days before Cycle 1 Day, the tests must be repeated and eligibility confirmed before study drug administration on Cycle 1 Day 1.

[d] Liver chemistry tests should be performed at screening and then at Day 1 of each subsequent cycle. If analytes are abnormal, then monitoring should increase to twice per week until resolved to baseline.

[e] Subjects on anticoagulation treatment should have parameters monitored throughout the study as clinically indicated. See Section 5.10.1 and Table 23 for use of coumarin-based anticoagulant guidelines.

[f] For women of childbearing potential, a serum pregnancy test is required at screening. Pregnancy tests (serum or urine) should be repeated if required by local regulations.

[g] See Section 7.6.1.1 for detailed timing and information for epacadostat PK sample collection. **Only subjects in Phase 1 should have epacadostat PK samples collected at C1D8.**

[h] Pharmacokinetic samples for durvalumab for subjects in Phase 1 of the study should occur at Cycle 1 Day 1, Cycle 2 Day 1, Cycle 5 Day 1, Cycle 9 Day 1, Cycle 13 Day 1, every 4 cycles (8 weeks) thereafter, EOT, and safety follow-up visit 2. For subjects in Phase 2 of the study, PK sampling should occur only at Cycles 1 and 2. See Table 30 for details regarding timing of PK for durvalumab.

[i] For subjects in Phase 1 of the study, immunogenicity sampling should occur at Cycles 5, 13, and 25. For subjects in Phase 2 of the study, immunogenicity and soluble PD-L1 sampling should occur at Cycles 7, 13, and 25.

[redacted]

Table 26: Laboratory Tests: Required Analytes

Comprehensive Chemistry Panel	Hematology	Other
Albumin Alkaline phosphatase ALT AST Amylase Bicarbonate Blood urea nitrogen Calcium Chloride Creatinine Glucose Iron Lactate dehydrogenase Lipase Phosphorus Potassium Sodium Total bilirubin Direct bilirubin (if total bilirubin is elevated above ULN) Total protein Uric acid	Complete blood count including: Hemoglobin Hematocrit Platelet count Red blood cell count White blood cell count Differential count including: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils	**Serology:** Hepatitis B surface antigen Hepatitis B core antibody HBV-DNA HCV-RNA Hepatitis C virus antibody **Pregnancy test:** 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. **Urinalysis with microscopic examination:** Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein Urobilinogen **Coagulation:** PT aPTT INR
Endocrine Monitoring	**Standard LFT Monitoring**	[redacted]
Adrenocorticotropic hormone Serum cortisol (9 AM)[a] Luteinizing hormone[b] Prolactin Thyroid stimulating hormone Free tyroxine (T4) Total triiodothyronine (T3) Serum testosterone (9 AM)[c]	Alkaline phosphatase ALT AST Total bilirubin	[redacted]

[a] Serum cortisol ideally should be drawn close to 9 AM but can be done any time before noon.
[b] Not needed in subjects receiving testosterone therapy.
[c] Not needed in women, surgically castrated men, or men taking luteinizing hormone-releasing hormone agonist therapy. Ideally should be drawn before 9 AM, but can be done any time before noon.

6.1. Screening Period

The screening period is up to 28 days and is the interval between the signing of the ICF and the day the subject receives the first dose of study treatment (Cycle 1 Day 1). Informed consent must be obtained before performing any study-specific procedures. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during this phase.

Results from the screening visit evaluations will be reviewed to confirm subject eligibility before randomization or the administration of study drug. Tests with results that fail eligibility requirements may be repeated once during the screening period if the investigator believes the

results to be in error. 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 (eg, following recovery from an infection).

6.2. Treatment Period

The treatment period with the combination therapy will continue every 14 days for up to 12 months. Once subjects complete 12 months of study treatment or permanently discontinue study treatment for any other reason, the EOT visit should be conducted, and they should enter the follow-up period of the study. Subjects enrolled prior to Protocol Amendment 6 (28 JUN 2017) who were on epacadostat monotherapy and allowed to continue taking it will be allowed to continue epacadostat monotherapy for up to an additional 12 months. The overall treatment duration for these subjects should not exceed 24 months. Exceptions to continue on epacadostat monotherapy will require medical monitor review and approval every 3 months.

6.3. End of Treatment

If a decision is made that the subject will permanently discontinue study drug, 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 should be entered in the EOT page in the CRF. The EOT visit should be performed within 7 days of the last dose of either epacadostat or durvalumab (whichever comes later). The subject should be encouraged to return for the safety follow-up visits.

6.4. Follow-Up Period

6.4.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the last scheduled safety follow-up visit, which should occur 90 days after the EOT visit (or after the last dose of study drug if the EOT visit was not performed). Safety follow-up visit 1 will be performed 42 days (± 7 days) after the EOT visit or the last dose of study treatment (if the EOT visit was not performed). Safety follow-up visit 2 will be performed 90 days (± 7 days) after the EOT visit or last dose of study treatment (if the EOT visit was not performed). Adverse events and SAEs must be reported up until at least 90 days after the last dose of study treatment or until study drug-related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the subject return for the safety follow-up visits and report any AEs that may occur during this phase.

If a subject initiates a new anticancer therapy within 90 days after the last dose of study treatment, reasonable efforts should be made to conduct the next scheduled safety follow-up (42-day or 90-day) visit before the first dose of the new therapy.

6.5. Unscheduled Visits

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

6.6. Early Termination

Not applicable.

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. The granting of informed consent for study participation must be documented in writing using an ICF that contains all of the 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; a copy of the signed ICF must be provided to the study subject. 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. Demography and History

7.2.1. Demographics and 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 concurrent illnesses assessed using the NCI CTCAE v4.0 (NCI 2010). Documentation of disease history, including details of malignancy (date of diagnosis, primary tumor histology, prior systemic anticancer therapies, surgeries, radiation therapy, and stage of cancer) will also be collected at screening.

7.2.2. Prior and Concomitant Medications

Prior and ongoing medications will be reviewed to determine study eligibility. All prior treatments for the subject's advanced cancer will be recorded in the CRF.

The medication record will be maintained after enrollment as documentation of 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.

7.3. Safety Assessments

7.3.1. 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 CRFs 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.

7.3.2. Comprehensive Physical Examination

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.

The comprehensive physical examination will include 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 neurological examination.

7.3.3. Targeted Physical Examination

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

7.3.4. Vital Signs

Vital sign measurements (blood pressure, pulse, respiratory rate, body temperature) will be taken with the subject in the recumbent, semirecumbent, or sitting position after 5 minutes of rest for the baseline measurements. Weight will be measured at each visit where vital signs are assessed, and height will be measured at screening only.

Vital sign measurements will also be performed at the following times in regard to infusion of durvalumab:

- At the beginning of the infusion (at 0 minutes ± 5 minutes).
- Every 15 minutes during the infusion (at 15, 30, and 45 minutes; all ± 5 minutes).
- At the end of the infusion (at 60 minutes ± 5 minutes).
- 30 and 60 minutes after the infusion (ie, 90 and 120 minutes from the start of the infusion; ± 5 minutes).
- Followed by a 3-hour period of observation (± 15 minutes) after the first infusion.

7.3.5. Twelve-Lead Electrocardiograms

All 12-lead ECGs will be performed with the subject in a recumbent position after 5 minutes of rest for the baseline ECG. Electrocardiograms will be obtained as outlined in Table 27 (unless emerging PK data suggest alternate timing). Electrocardiograms should be performed before the PK blood draw when collected at the same visit.

Table 27: Schedule and Timing of ECG Assessments

Study Visit	Timing of ECG Relative to Epacadostat Administration	ECG Frequency
Screening	NA	Singlet[a]
Cycle 1 Day 1	Predose[b,c] 1 hour postdose (± 10 min)[b] 2 hours postdose (± 30 min)[b]	Singlet
Cycle 2 Day 1	Predose[b,c] 1 hour postdose (± 10 min)[b] 2 hours postdose (± 30 min)[b]	Singlet
EOT	Any time during visit[b]	Singlet
Safety Follow-Up 1	Any time during visit	Singlet
Safety Follow-Up 2	Any time during visit	Singlet

[a] At screening, in the event that a single QTc is > 480 msec, the subject may be enrolled if the average QTc for the 3 ECGs is < 480 msec. For subjects with an intraventricular conduction delay (eg, right bundle branch block), JTc < 340 msec is acceptable; however, subjects with a left bundle branch block would be excluded.
[b] ECGs must be performed before PK draws.
[c] ECGs should be performed before durvalumab and epacadostat administration.

The 12-lead ECGs will be interpreted by the investigator at the site and will be used for immediate subject management. The decision to include or exclude a subject or withdraw a subject from the study based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the sponsor's medical monitor, as appropriate.

7.3.6. Laboratory Assessments

A laboratory local to the study site may perform all clinical laboratory assessments for safety (including comprehensive chemistry, hematology assessments, and urinalysis). A central laboratory will perform PK, immunogenicity, [redacted] assessments.

7.3.6.1. Chemistry

A comprehensive chemistry panel will be performed as indicated in Table 25; required analytes for this panel are listed in Table 26.

7.3.6.1.1. Liver Chemistry Monitoring

If analytes are found to be abnormal (Grade 1 or higher), frequency of monitoring should be increased to twice weekly until they have resolved to baseline or corticosteroid treatment has begun, at which time monitoring will be performed according to institutional standards or approximately weekly, whichever is shorter. Liver chemistry monitoring for persistent low-grade abnormalities does not need to be monitored twice weekly indefinitely. Appropriate liver chemistry monitoring intervals should be discussed with the medical monitor for these circumstances. Required analytes for liver chemistry monitoring are listed in Table 26.

7.3.6.2. Hematology

Hematology assessments will be performed as indicated in Table 25. Required analytes for this panel are listed in Table 26.

7.3.6.3. Coagulation Panel

A coagulation panel including PT and INR will be measured at screening. Subjects who are taking anticoagulant therapy should be monitored per local institutional guidelines. See Section 5.10.1 for use of coumarin-based anticoagulant guidelines and warfarin dose modification.

7.3.6.4. Endocrine Function Testing

Endocrine function testing will be performed as indicated in Table 25; required analytes for this panel are listed in Table 26.

7.3.6.5. Serology

Serology will be performed at screening to rule out hepatitis infection; required analytes are shown in Table 26.

7.3.6.6. Pregnancy Testing

A serum pregnancy test will be required for all female subjects of childbearing potential during screening. Subsequent pregnancy tests (either serum or urine) may be conducted as medically necessary or as required per local guidelines.

7.3.6.7. Urinalysis

Urinalysis will be analyzed as indicated in Table 25; required analytes for this panel are listed in Table 26.

7.3.7. Chest Radiograph

A chest radiograph is required at screening. Subsequent chest radiographs will be conducted only as clinically indicated.

7.4. Efficacy Assessments

7.4.1. Initial Tumor Imaging

Initial tumor imaging must be performed within 28 days before the first dose of study treatment. The site study team must review prestudy images to confirm the subject has measurable disease per RECIST v1.1. Images of the chest and abdomen are required for all subjects. In addition, neck imaging is also required for subjects with SCCHN. Imaging of the pelvis is only required for subjects with TCC of the GU tract but is strongly encouraged for all subjects. 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 central nervous system.

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 study treatment. The preferred method of disease assessment is CT with contrast. If CT with contrast is contraindicated, CT without contrast is preferred over MRI. The same imaging technique should be used in a subject throughout the study.

7.4.2. Tumor Imaging During the Study

Tumor assessments will be based on RECIST v1.1 guidelines (Eisenhauer et al 2009) with modifications for all subjects and will be performed every 12 weeks from the first dose of study treatment (see Table 24). This assessment schedule also applies to those subjects who continue to receive study treatment beyond confirmed PD (see Section 7.4.3.3.4). Scheduled disease assessments should always be calculated from the first dose of study treatment. Imaging should not be delayed for delays in cycle starts. For those subjects who discontinue study treatment as a result of confirmed PD, disease evaluation will be performed at the EOT visit if clinically appropriate (ie, in the absence of rapidly deteriorating clinical status). Additional disease assessments may be performed as clinically indicated. Images of the chest and abdomen are required for all subjects, and neck imaging is also required for subjects with SCCHN. Imaging of the pelvis is only required for subjects with TCC of the GU tract but is strongly encouraged for all subjects.

7.4.3. RECIST v1.1

Tumor lesions that are located in a previously irradiated area, or in an area subjected to other locoregional therapy, should not be selected as target lesions. Additionally, tumor lesions that will be biopsied should not be selected as target lesions.

7.4.3.1. Tumor Assessments

- Physical examination:
  - Lesions detected by physical examination will only be considered measurable if superficial, eg, skin nodules and palpable lymph nodes. Documentation by color photography including ruler is recommended for estimating the size of skin lesions.
- CT scan with contrast of the chest, abdomen, and pelvis (plus head and neck if applicable):
  - CT scans should be performed with contiguous cuts in slice thickness of 5 mm or less. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm.
- MRI scans:
  - MRI of the abdomen and pelvis (plus head and neck if applicable) is acceptable for measurement of lesions provided that the same anatomical plane is used for serial assessments. If possible, the same imaging device should be used for serial evaluations. In case of MRI, measurements will be preferably performed in the axial (transverse) plane on contrast-enhanced T1 weighted images. However, there are no specific sequence recommendations.

7.4.3.2. Measurability of Tumor Lesions

Tumor lesions will be categorized as follows:

- **Measurable Lesions:** Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm).
  - 10 mm caliper measurement by clinical examination (when superficial).
  - Malignant lymph nodes are considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).
- **Nonmeasurable Lesions:** Nonmeasurable lesions are defined as all other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis). Lesions considered truly nonmeasurable include the following: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.
- **Target Lesions:** All lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.
- **Nontarget Lesions:** It is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

7.4.3.3. Response Criteria

7.4.3.3.1. Evaluation of Target Lesions

- **Complete Response:** Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm (the sum may not be "0" if there are target nodes).
- **Partial Response:** At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease:** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: The appearance of 1 or more new lesions is also considered progression.)
- **Stable Disease:** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

7.4.3.3.2. Evaluation of Nontarget Lesions

- **Complete Response:** Disappearance of all nontarget lesions [redacted] All lymph nodes must be nonpathological in size (< 10 mm short axis).
- **Non–Complete Response/Non–Progressive Disease:** Persistence of 1 or more nontarget lesion(s) [redacted]
- **Progressive Disease:** Unequivocal progression of existing nontarget lesions will be defined as the overall level of substantial worsening in nontarget disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. In the absence of measurable disease, change in nonmeasurable disease comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from "trace" to "large," an increase in lymphangitic disease from localized to widespread.

7.4.3.3.3. Appearance of New Lesions

The appearance of new lesions is considered PD according to RECIST v1.1 guidelines. Considering the unique response kinetics that have been observed with immunotherapy, new lesions may not represent true disease progression. In the absence of rapid clinical deterioration, subjects may continue to receive study treatment if investigators consider that subjects continue to benefit from treatment.

7.4.3.3.4. Evaluation of Overall Response With Modifications

Confirmation of PD should be assessed by a repeat, consecutive assessment no less than 4 weeks from the date of first documentation. Treatment with study treatment will continue between the initial assessment of PD and confirmation for PD if they are considered clinically stable as defined by the following criteria:

- Absence of signs and symptoms indicating disease progression.
- No decline in ECOG performance status.
- Absence of rapid progression of disease.
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention.

In addition, subjects may continue to receive study treatment beyond confirmed PD in the absence of clinical deterioration and if investigators consider that subjects continue to receive benefit from treatment after consultation with the medical monitor. For example, subjects who are clinically stable with no further tumor increase after the initial scan demonstrating PD may be allowed to continue study treatment. In the absence of clinical deterioration, such modifications to the RECIST criteria may discourage the early discontinuation of study treatment and provide a more complete evaluation of its antitumor activity than would be seen with

conventional response criteria. Table 28 provides overall responses for all possible combinations of tumor responses in target and nontarget lesions with or without the appearance of new lesions.

Table 28: Evaluation of Overall Response

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
Complete response	Complete response (or no nontarget lesion)	No	Complete response
Complete response	Not evaluable[a]	No	Partial response
Complete response	Non–complete response / non–progressive disease	No	Partial response
Partial response	Non–progressive disease and not evaluable[a] (or no nontarget lesion)	No	Partial response
Stable disease	Non-progressive disease and not evaluable[a] (or no non-target lesion)	No	Stable disease
Not all evaluated	Non–progressive disease	No	Not evaluable
No target lesion[b]	Not all evaluated	No	Not evaluable
No target lesion[b]	Non–complete response / non–progressive disease	No	Non–complete response / non–progressive disease
Progressive disease	Any	Yes/No	Progressive disease
Any	Progressive disease	Yes/No	Progressive disease
Any	Any	Yes	Progressive disease
No target lesion[b]	Unequivocal progressive disease	Yes/No	Progressive disease
No target lesion[b]	Any	Yes	Progressive disease

[a] Not evaluable is defined as either when no or only a subset of lesion measurements are made at an assessment.
[b] Defined as no target lesion at baseline.

7.5. Performance and Quality of Life Assessments

Not applicable.

7.6. Pharmacokinetic, Immunogenicity, [redacted] Assessments

Instructions for sample preparation and shipping will be provided in the Laboratory Manual. Sample collection visits are outlined in Table 25.

7.6.1. Pharmacokinetics

7.6.1.1. Pharmacokinetic Assessment for Epacadostat

Subject will withhold morning dose of drug during PK days. The time of last dose of study medication and prior meal will be recorded in the CRF. Pharmacokinetic samples will be obtained at the visits indicated in Table 25 and Table 29. After the predose PK sample is drawn (predose is defined as within 24 hours before dosing of durvalumab and before dosing epacadostat), subjects will take epacadostat and then begin infusion of durvalumab. The exact

date and time of the PK blood draws will be recorded in the CRF along with the date and time of the last dose of study drug and last meal preceding the blood draw. Sample collection times for epacadostat are shown in Table 29.

Table 29: Sample Collection Windows for Pharmacokinetic Assessments for Epacadostat

Study Visit	Timing of Sample Relative to Epacadostat Administration						
Cycle 1 Day 1[a]	Predose[b]	0.5 h ± 10 min	1 h ± 10 min	2 h ± 30 min	4 h ± 30 min	6 h ± 60 min	OPTIONAL 8 to 10 h ± 60 min
Cycle 1 Day 8[c]	Predose[b]	0.5 h ± 10 min	1 h ± 10 min	2 h ± 30 min	4 h ± 30 min	6 h ± 60 min	OPTIONAL 8 to 10 h ± 60 min
Cycle 2 Day 1[a]	Predose[b]	0.5 h ± 10 min	1 h ± 10 min	2 h ± 30 min	4 h ± 30 min	6 h ± 60 min	OPTIONAL 8 to 10 h ± 60 min

[a] ECGs are also required. See Table 27 for timing of ECGs relative to PK sampling. ECGs should be performed before a PK draw.
[b] Predose samples should be collected before durvalumab infusions as well.
[c] **Only subjects in Phase 1 should have epacadostat PK performed on Cycle 1 Day 8**.

7.6.1.2. Pharmacokinetic Assessment for Durvalumab

Subjects will withhold morning dose of epacadostat on Cycle 1 Day 1 and Cycle 2 Day 1 before PK sample collection. Pharmacokinetic samples will be obtained in Phase 1 and Phase 2 of the study at the visits indicated in Table 30. After the predose PK sample is drawn, subjects will take epacadostat and then begin infusion of durvalumab. The exact date and time of the PK blood draws will be recorded in the CRF along with the date and time of the last dose of study drug and last meal preceding the blood draw.

Measurement of durvalumab concentrations in serum will be performed using validated immunoassays. Only subjects who receive at least 1 dose of durvalumab and provide at least 1 post-treatment sample will be evaluated. Individual durvalumab will be tabulated by dose cohort along with descriptive statistics. The following PK parameters after the first and steady-state dose will be estimated (as data allow): C_{max}, C_{min}, t_{max}, and AUC. Accumulation to steady state will be assessed as the ratio of $C_{max,ss}$:C_{max} and $C_{min,ss}$:C_{min}. All PK parameters will be estimated by noncompartmental analysis. Descriptive statistics of noncompartmental PK parameters will be provided.

Table 30: Sample Collection Windows for Pharmacokinetic Assessments for Durvalumab (Phase 1 and Phase 2)

Phase 1		
Study Visit	**Timing of Sample Relative to Durvalumab Administration**	
Cycle 1 Day 1[a]	Predose	End of durvalumab infusion (± 10 min)
Cycle 2 Day 1	Predose	N/A
Cycle 5 Day 1		
Cycle 9 Day 1		
Cycle 13 Day 1	Predose	End of durvalumab infusion (± 10 min)
Every 4 cycles after Cycle 13	Predose	N/A
EOT	Anytime	
Safety Follow-Up Visit 2		
Phase 2		
Cycle 1 Day 1[a]	Predose	End of durvalumab infusion (± 10 min)
Cycle 2 Day 1[a]	Predose	N/A

[a] Withhold the morning dose of epacadostat.

7.6.2. Immunogenicity for Durvalumab

Validated assays will be used for the determination of ADAs to durvalumab in human serum.

Only subjects who receive at least 1 dose of durvalumab and provide at least 1 post-treatment sample will be evaluated. Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of subjects who develop detectable anti-durvalumab antibodies. Samples confirmed positive may also be evaluated for neutralizing antibody activity.

[redacted]

7.6.3.2. Analysis of Tumor Samples

Fresh tumor biopsies (defined as a biopsy specimen taken within 28 days prior to the first dose of study treatment) will be required (except as indicated in the inclusion criteria) at baseline. A biopsy specimen from a sample taken since completion of the most recent prior systemic treatment may be acceptable in lieu of a fresh biopsy with medical monitor approval. Archival tissue should also be submitted if available. If a fresh baseline biopsy is inaccessible, an archival specimen should be submitted.

Biopsies should be performed on lesions that have not been exposed to prior radiation. Exceptions to this requirement for SCCHN subjects may be granted on an individual basis by the medical monitor. Tumor lesions used for biopsy should not be lesions used as RECIST target lesions, unless there are no other lesions suitable for biopsy. If a RECIST target lesion is used for biopsy, the lesion must be ≥ 2 cm in the longest diameter. Details and methods for obtaining, processing, and shipping the fresh tumor biopsy samples will be provided in the Study or Laboratory Manual for the study.

[redacted]

Biopsy samples may be used to investigate specific protein expression that can be measured using IHC, flow cytometry, mass spectroscopy, or other similar techniques. Biopsy samples may also be used to investigate molecular signatures. DNA and/or RNA may be extracted from these samples to do somatic mutation analysis and gene expression analysis. Genes to be assayed may include, but not be limited by those with known driver mutations in solid tumors. Potential somatic mutations in tumor samples may be confirmed by assessing the specific sequence change in a normal sample obtained by peripheral blood. Biopsy samples may also be assessed for chromosomal alterations that have been shown to be present in solid tumors. These samples will be analyzed by the sponsor or designee.

Note: The Ventana PD-L1 IHC assay will be used to determine the PD-L1 IHC status in this study. The Ventana IHC analysis will be performed at a Ventana-approved College of American Pathologists/Clinical Laboratory Improvement Act laboratory. To meet the requirement of the FDA approval of a companion diagnostic, sections of the tumor will be retained at Ventana for potential additional studies, as requested by the FDA, to support the test approval.

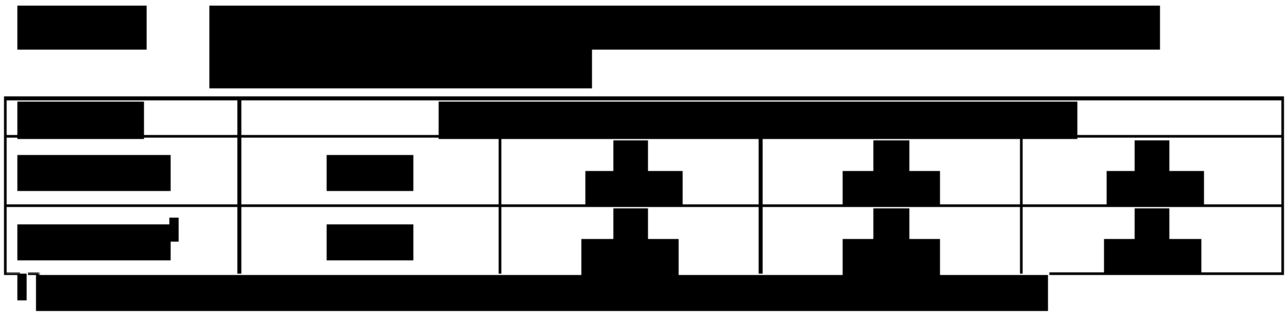
7.6.3.2.1. Optional On-Treatment Tumor Samples

Optional tumor biopsy specimens on study may also be obtained anytime in subjects with accessible tumors to assess intratumoral changes that might be associated with safety, response, or resistance to treatment.

If a subject consents to an on-treatment biopsy, the sample must be collected at peak exposure after the morning epacadostat dose (approximately 2-3 hours after dosing) and a peripheral whole blood sample should be collected at the same time as the biopsy and sent to Incyte or its designee in accordance with the Laboratory Manual.

Additionally, one of the subject's target lesions may be used to collect this sample if it is the most accessible for biopsy.

[redacted]



7.7. Other Study Procedures

7.7.1. Dispensing of Study Drug

7.7.1.1. Dispensing of Epacadostat

An initial bulk supply of epacadostat will be provided to investigative sites prior to enrollment of the first subject. Thereafter, the site staff will contact the sponsor for resupply of epacadostat. When dispensing to subjects, the investigator or designee will remove the appropriate quantity of epacadostat from their stock, dispense the medication, and enter the amount dispensed into the CRF and drug accountability log. Full details will be provided in the Study Manual.

7.7.1.2. Dispensing of Durvalumab

An initial bulk supply of durvalumab will be provided to investigative sites prior to enrollment of the first subject. Thereafter, the site will contact the sponsor for resupply of durvalumab. The investigator or designee will calculate the number of durvalumab vials needed, pull the appropriate number of vials to prepare the infusion solution, and enter the vials used into the CRF and drug accountability log. Full details will be provided in the Study Manual.

7.7.2. Administration of Study Drug

7.7.2.1. Administration of and Compliance With Epacadostat

Subjects will take their dose of epacadostat morning and evening, approximately 12 hours apart without regard to food. Subjects will self-administer epacadostat except on Cycle 1 Day 1, Cycle 1 Day 8 (Phase 1 only), and Cycle 2 Day 1, when the morning dose will be given at the study site clinic.

Epacadostat 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 investigators and their staff should evaluate compliance at each visit and take appropriate steps to optimize compliance.

7.7.2.2. Administration of and Compliance With Durvalumab

Administration of durvalumab will be witnessed by the investigator and/or study staff. The total volume of study treatment infused will be compared to the total volume prepared to determine compliance with each dose administered.

The instructions for preparing and administering durvalumab are described in a separate pharmacy manual.

7.7.3. Distribution of Subject Reminder Cards and Diaries

Subjects will be provided with reminder cards at each visit. The subject reminder cards will indicate the date/time of the next visit, and will also remind the subject when they should not take their morning dose of study drug and when they should arrive for the visit after an overnight fast of at least 8 hours or since midnight. On Day 1 only, subjects will also be given 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 and Reporting

For the purposes of this Protocol, an AE is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur 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).

Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events page of the CRF. Conditions that were already present at the time of informed consent should be recorded on the Medical History page of the CRF. Adverse event monitoring should be continued for at least 90 days after the last dose of study treatment. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

Adverse events will be assessed according to the CTCAE version 4.0. The CTCAE severity Grade 5 (death) will not be used in this study; rather, information about deaths will be collected as an outcome of the event. 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. As far as possible, each AE should be evaluated to determine:

- The severity grade (CTCAE Grade 1 to 4).
- Reasonable possibility that the AE is related to the study treatment: unrelated (no) or related (yes).

  NOTE: Since this is a combination study of epacadostat with durvalumab, the relationship to study drug can be assessed for epacadostat alone, durvalumab alone, the combination of epacadostat with durvalumab, or not related to either epacadostat or durvalumab.

- Start and end dates, unless unresolved at final examination.
- Action taken with respect to study drug (eg, none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable).
- Outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- Whether it is serious, as per 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 a concomitant medication or nondrug therapy is given, this action should be recorded on the AE and Prior/Concomitant medications pages of the CRF.

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 it, and the outcome.

Disease progression should not be regarded or reported as an AE itself, unless it is associated with a separate AE.

8.2. Laboratory Test Abnormalities

8.2.1. Definitions and Reporting

Laboratory abnormalities that constitute an AE in their own right (are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug), should be recorded on the AE page of the CRF. 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 (severe) AE, as per CTCAE, does not automatically indicate an SAE unless it meets the definition of serious, as defined in Section 8.3.1, and/or per the investigator's discretion. A dose interruption or adjustment for the laboratory abnormality may be required (see Section 5.6) and should not contribute to the designation of a laboratory test abnormality as an SAE.

8.2.2. Potential Drug-Induced Liver Injury (or Hy's Law)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event (also known as Hy's Law). All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 8.3.2 for reporting details).

Potential drug induced liver injury is defined as:

1. AT (ALT or AST) elevation > 3 times ULN
   AND
2. Total bilirubin > 2 times ULN, without initial findings of cholestatis (elevated serum alkaline phosphatase),
   AND
3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

8.3. Serious Adverse Events

8.3.1. Definitions

A SAE is defined as an event that meets 1 of the following criteria:

- Is fatal or life-threatening (ie, immediate risk of dying).
- Results in persistent or significant disability or incapacity.
- Constitutes a congenital anomaly or birth defect.
- Is clinically meaningful (ie, defined as an event that jeopardizes the subject or requires potential medical or surgical intervention to prevent 1 of the outcomes listed above). Considered meaningful by the investigator as an important medical event that may not result in death, be life-threatening, or require hospitalization, but may be considered a SAE when, based upon appropriate medical judgment, it may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is a result of:
  - Routine treatment or monitoring of the studied indication not associated with any deterioration in condition. Elective or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF.
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.
  - Social reasons and respite care, in the absence of any deterioration in the subject's general condition.
  - Any SAEs that are expected due to the condition being treated, including if the SAE is a primary outcome measure, or where there has been a clear agreement with regulators not to consider these as SAEs, provided the information is collected elsewhere.

8.3.2. Reporting

To ensure subject safety, every SAE, regardless of suspected causality, occurring after the subject has signed the ICF and up to the last study visit, or up to 90 days after the last dose of study treatment, must be reported to the sponsor (or designee) within 24 hours of learning of its occurrence. Any SAEs experienced after this period should be reported to the sponsor (or designee) only if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as the follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event. Previously planned (before providing informed consent) surgeries should not be reported as SAEs unless the underlying medical condition worsens over the course of the study.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to each specific study drug (if there is more than 1), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the sponsor or its designee. The investigator must assess if there is a reasonable possibility that the SAE is related to the study treatment: unrelated (no) or related (yes).

Serious AEs related to unblinded comparator drugs or concomitant medications/drug delivery systems are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

The telephone and facsimile number of the sponsor's contact persons, specific to the study, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the CRF documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each recurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation, or if study drug was interrupted or discontinued.

If the SAE is not previously documented in the IBs for the study drugs (new occurrence) and is thought to be related to the sponsor's study drug, a sponsor's associate may urgently require further information from the investigator for reporting to health authorities.

The sponsor or its designee may need to issue an IN to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions 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.

8.3.2.1. Hepatic Function Abnormalities (Hepatotoxicity)

As defined in Section 8.2.2, Hy's law cases must be reported as SAEs. Additional information regarding hepatic function abnormalities is provided in Section 8.8.

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, the following procedures should occur:

- The investigator must notify the sponsor or its designee immediately.
- The study drug must be discontinued immediately.
- The subject must be withdrawn from the study.
- The EOT visit evaluations must be performed.
- The investigator must complete and submit the Pregnancy Initial and Follow-Up Report forms to the sponsor or its designee.
- A serum pregnancy test must be performed to confirm the urine pregnancy test result. (The serum test should be performed at the investigative site to ensure the test will be performed promptly and the result available immediately for review.)

If a negative serum test does not confirm the urine pregnancy test result, then:

- The investigator will use his or her expert judgment, based on an assessment of the potential benefit/risk to the subject, to determine if it is in the subject's best interest to resume study drug and continue participation in the study.

To ensure subject safety, each pregnancy in a subject during maternal or paternal exposures to study drug must be reported within 24 hours of learning of its occurrence. Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation. Follow-up to each pregnancy should be conducted 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 Study Pregnancy Form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the sponsor's study drug of any pregnancy outcome and follow-up to the first well-baby visit. **Any SAE experienced during pregnancy must be reported on the SAE Report Form and to the sponsor or its designee.**

8.6. Warnings and Precautions

No evidence available at the time of the approval of this study Protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided IBs. Additional safety information collected between IB updates will be communicated in the form of INs. Any important new safety information should be discussed with the subject during the study as needed. If new, significant risks are identified, they will be added to the ICF.

8.7. Data Monitoring Committee

There will be no formal external Data Monitoring Committee for this open-label study. Approximately weekly the sponsor will conduct telephone conferences with investigators in order to review cohort-specific data, overall safety data from prior cohorts (if applicable), and to agree on dose escalation, de-escalation, and cohort expansion decisions.

8.8. Adverse Events of Special Interest

Adverse events of special interest include irAEs that are seen with immunotherapy and any other observed autoimmune phenomenon. Guidance for the assessment, diagnosis, and management of irAEs is provided in Section 5.6.3. Immune-related AEs will be monitored carefully at each cycle and during the safety follow-up period.

Adverse events of special interest for durvalumab are events of scientific and medical interest specific to the further understanding of the durvalumab safety profile and require close monitoring and rapid communication by the investigator to the sponsor. Durvalumab AEs of special interest may be serious or nonserious. The rapid reporting of these AEs of special interest allows ongoing analysis of these events in order to characterize and understand them in association with the use of this investigational product. Durvalumab, an anti–PD-L1 antibody, binds with high affinity and specificity to PD-L1 and blocks its binding to PD-1 and CD80, thus promoting antitumor immunity and tumor cell killing. Potential risks based on this mechanism of action of durvalumab and related molecules include immune-mediated reactions such as enterocolitis, dermatitis, hepatotoxicity or hepatitis, endocrinopathy, neuropathy, and pneumonitis. The class including anti–PD-L1 drugs and other immune checkpoint antibodies such as anti–PD-1 or anti–CTLA-4, have a wide spectrum of immune-mediated reactions that have been considered inflammatory in nature and can affect any organs of the body.

8.8.1. Pneumonitis

Pneumonitis has been reported in association with use of anti–PD-L1/anti–PD-1 antibodies (Brahmer et al 2012). Initial work-up should include a high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is recommended. Guidelines for the management of subjects with immune-mediated events including pneumonitis are outlined in Section 5.6.3.1.

8.8.2. Hypersensitivity Reactions

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti–PD-L1 and anti–PD-1 therapy (Brahmer et al 2012). As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of monoclonal antibodies can be caused by various mechanisms, including acute anaphylactic (IgE-mediated) and anaphylactoid reactions against the monoclonal antibody, and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, urticaria, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting, and unresponsiveness.

Guidelines for management of subjects with hypersensitivity (including anaphylactic reaction) and infusion-related reactions are outlined in Section 5.1.2.2.

8.8.3. Hepatic Function Abnormalities (Hepatotoxicity)

Increased transaminases have been reported during treatment with anti–PD-L1 (Brahmer et al 2012). Inflammatory hepatitis has been reported in 3% to 9% of subjects treated with anti–CTLA-4 monoclonal antibodies (eg, ipilimumab). The clinical manifestations of ipilimumab-treated subjects included general weakness, fatigue, nausea and/or mild fever, and increased liver chemistry tests such as AST, ALT, alkaline phosphatase, and/or total bilirubin. Hepatic function abnormality is defined as any increase in ALT or AST to > 3 × ULN and concurrent increase in bilirubin to > 2 × ULN (ie, Hy's law cases). Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (eg, cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product. If the underlying diagnosis for the hepatic function abnormality is known (including progression of pre-existing disease such as primary or metastatic malignancy), the diagnosis should be recorded as an AE/SAE. If the underlying diagnosis for the hepatic function abnormality remains unknown, the term "hepatic function abnormal" should be used to report the AE/SAE. Hepatic function abnormality of unknown etiology, or which is considered attributable to investigational product, is required to be reported as "hepatic function abnormal" within 24 hours of knowledge of the event to the sponsor using the SAE Report Form, even if the event is considered to be nonserious.

The investigator will review the data with the medical monitor. The investigator should then use clinical judgment to establish the cause based on local standard of care and follow the subject by conducting testing as clinically indicated.

8.8.4. Serotonin Syndrome

As noted in Section 1.3.1, there is a theoretical chance that epacadostat could 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. Procedures listed in Section 5.6.4 will be implemented if subjects exhibit the signs/symptoms of SS, including tremor, hyperreflexia, and spontaneous ocular or inducible clonus together with agitation, fever, diaphoresis, or muscle rigidity.

8.9. 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.

The investigator or his/her designee is responsible for reporting a complete description of the product complaint and any associated AEs via email or other written communication to the Incyte contact.

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

Safety Evaluable: All subjects enrolled who take at least 1 dose of study drug.

Pharmacokinetic [redacted] Evaluable: Includes subjects who received at least 1 dose of study drug(s) and provided at least 1 postdose blood sample for PK [redacted] assessmen [redacted]. The study pharmacokineticist will review data listings of subject dosing and sample records to identify subjects to be excluded from the analysis.

Phase 1 Population: All subjects enrolled in the Phase 1 portion of the study taking at least 1 dose of study drug.

9.2. Selection of Sample Size

9.2.1. Cohort Size in Phase 1

The primary objective of the open-label Phase 1 portion of the study is to determine the MTD or PAD and DLT of epacadostat in combination with durvalumab. The total number of subjects will depend on the number of dose levels tested before the MTD or PAD is established. Up to 36 subjects (6 subjects per dose level for 6 dose levels) will be included based on the dose escalation. Dose escalation will follow the 3 + 3 design algorithm as defined in Section 4.1.1. Based on this algorithm, which enrolls 3 evaluable subjects in each cohort with a maximum of 6 subjects at any dose level, the probabilities of dose de-escalation from a given dose level for the various DLT rates are provided in Table 32.

Table 32: Probability of Dose De-Escalation for Various DLT Rates

True DLT Rate	Probability of Dose De-Escalation
20%	23.6%
30%	47.2%
40%	68.3%
50%	83.4%
60%	92.4%

For example, if the true DLT rate is 50% at a given dose level, there is a 17% chance that the dose would be escalated. Further, if the true DLT rate is 20%, there is a 76% chance that the dose would be escalated.

9.2.2. Sample Size for Phase 2

The sample size for the melanoma, TNBC, and gastric and GE junction cohorts will be guided by the Simon 2-stage design (Simon 1989). Let P_0 denote a clinically uninteresting response rate (eg, for melanoma $P_0 = 30\%$). In order to determine whether a target response rate (eg, 55%) is likely, an initial number of subjects (eg, 15) will be treated at first in a cohort (Stage 1). For example, in a group in which ≤ 5 subjects have responses, it will be concluded that the true response rate is unlikely to be greater than or equal to the target rate and no more subjects will be enrolled in that group in Stage 2. Otherwise, in the groups in which at least 6 responses among the Stage 1 subjects is observed, 25 additional subjects will be treated in Stage 2 to estimate the response rate. At the end of Stage 2, if ≤ 16 subjects have responded among a total of 40 subjects, the drug will be declared nonpromising. In other words, after the study is finished, if there is a sufficient number of responses in the 2 stages combined, the study compound is considered promising; otherwise it is considered nonpromising. The detail is displayed in Table 33 using a Type I error of 0.05 and power of 90% for estimation.

Table 33: Details of Simon 2-Stage Design (Melanoma, TNBC, and Gastric and Gastroesophageal Junction Cancer)

	Melanoma (P_0 = 30%, Target RR = 55%)	**TNBC (P_0 = 15%, Target RR = 40%)**	**Gastric and GE Junction (P_0 = 10%, Target RR = 40%)**
Drug is not promising if Stage 1 responder number ≤	5	2	1
Sample size for Stage 1	15	13	9
Drug is not promising if total responder number ≤	16	7	4
Sample size total	40	29	20

Under Amendment 6, enrollment of the NSCLC, SCCHN, and TCC of the GU tract cohorts will be completed as expansion cohorts at the 300 mg BID dose level. The sample size for each cohort will be increased to account for the heterogeneity of PD-1 pathway–treated and PD-1 pathway–naive subjects within the selected tumor types. The approximate number of subjects per tumor type is listed in Table 34, and the number of PD-1 pathway–treated subjects in each cohort will be limited to 10 in order to reduce the risk of any cohort having a significant imbalance between PD-1 pathway–treated and PD-1 pathway–naive subjects, thereby preserving the predicted levels of baseline efficacy observed with PD-1 pathway monotherapy. Subjects enrolled at the 100 mg BID will be analyzed independently. The sample size for each cohort expansion is based on a power of 90% to detect a target ORR of about 20% increase with a 1-sided alpha of 10% and 10% lost to follow-up.

Table 34: Sample Size Details (NSCLC, SCCHN, and TCC of the GU Tract)

	ORR		
Tumor Type	**H_0**	**H_a**	**Sample Size**
NSCLC	10%	30%	28
SCCHN	10%	30%	28
TCC of the GU Tract	10%	30%	28

9.3. Level of Significance

No formal efficacy hypotheses will be tested. All CIs will be 95%.

9.4. Statistical Analyses

9.4.1. Primary Analyses

Phase 1: The safety and tolerability of epacadostat in combination with durvalumab will be evaluated. See Section 9.4.3 for more details. Descriptive statistics (eg, mean, standard deviation, range) will be derived where appropriate. Subject enrollment, disposition, demographics, and medical history will be summarized at baseline. The rate of DLTs will be summarized for each cohort. Dose exposure and density will be calculated for each cohort. Safety and disease response data will be compared over time to assess change from baseline, during treatment, and follow-up. Pharmacokinetic [redacted] data will be analyzed with appropriate standard nonlinear analytic software.

Phases 1 and 2: The proportion of subjects with objective response by mRECIST v1.1 will be summarized. A subject is considered an objective responder as assessed by mRECIST v1.1 if he or she has an overall response of CR or PR at any postbaseline visit. The proportion of responders within each treatment group will be estimated with 95% CIs by treatment group. Confidence intervals will be calculated based on the exact method for binomial distributions.

9.4.2. Secondary Analyses

For objective responders, the duration of response is the time from the first overall response contributing to an objective response, to the first overall response of PD (by mRECIST v1.1) occurring after the first overall response contributing to the objective response. Median duration of response and time to disease progression will be estimated using the Kaplan-Meier method. Confidence intervals for median survival time will be calculated using the method of Brookmeyer and Crawley (1982), which is the default method within SAS v9.1.

Progression-free survival data will be analyzed by the Kaplan-Meier method, treating subjects with no observed death or progression censored at their last date known to be alive and progression-free.

9.4.3. Safety Analyses

The principal analysis will be based on the safety evaluable population, according to treatment assignment.

Adverse events will be coded by the MedDRA, and incidences will be tabulated by preferred term and system organ class for all events, related events, and events ≥ Grade 3. Severity of AEs will be based on the CTCAE scale as indicated in Section 8.1.1. Quantitative safety variables and their changes from baseline (laboratory, vital signs) will be summarized with descriptive statistics. Clinically significant abnormal values will be flagged and tabulated based on predefined criteria.

Exposure will be analyzed by describing dose intensity, which is defined as the dose received, divided by the dose planned, over a given time interval. This will be done by cycle as well as overall cycles received for durvalumab + epacadostat and durvalumab alone. For each cycle,

incidences of dose reductions and cycle delays will also be tabulated by reason for the reduction or delay. The percentage of subjects with any delay and/or reduction will also be calculated.

9.4.4. Clinical Laboratory Tests

The clinical laboratory data will be analyzed using summary statistics (eg, means and frequencies). In addition, distributions of key laboratory parameters (including hemoglobin, neutrophils, and platelets) will be plotted over time; these values will also be classified into CTCAE toxicity grades and tabulated. Descriptive statistics and mean change from baseline will be determined for vital signs at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities.

9.5. Data Monitoring Committee

Not applicable.

9.6. Interim Analysis

An interim safety analysis is planned for Phase 2 after 16 subjects have been enrolled and treated for 8 weeks, and then approximately every 3 months thereafter. If the following is reported during these reviews, enrollment of subjects would be suspended until the sponsor determined the appropriate course of action and notified IRBs and regulatory authorities:

- ≥ 40% of subjects have experienced an AE ≥ Grade 3 that was attributable to the investigational agents.

No formal interim analysis for futility or efficacy is planned for this study.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Investigational Product Description

10.1.1. Packaging, Labeling, and Preparation of Study Drug

10.1.1.1. Epacadostat

The study drug will be available as 25 mg and 100 mg tablets packaged in HDPE bottles.

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

10.1.1.2. Durvalumab

Durvalumab will be provided as a vialed liquid solution containing 500 mg (nominal) durvalumab. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine-HCl, 275 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, at pH 6.0. The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and use of investigational product in accordance with the Protocol and any applicable laws and regulations.

10.1.2. Storage and Stability of Study Drug

10.1.2.1. Epacadostat

Clinical supplies must be stored as described in the iIB.

10.1.2.2. Durvalumab

Unopened vials of durvalumab liquid Drug Product must be stored at 2°C to 8°C (36°F to 46°F).

10.2. Accountability, Handling, and Disposal of Study Drug

Responsibility for drug accountability at the study site rests with the investigator; however, the investigator may assign some of the drug accountability duties 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 will be expected to collect and retain all used, unused, and partially used containers of study drug until the end of the study. 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.

These records should include dates, quantities, batch or serial numbers (if available), and the unique code numbers (if available) assigned to the investigational product and study 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 correct study drug specified.

Completed accountability records will be archived by the site. At the completion 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 site destruction of investigational supply, prior written approval must be obtained from Incyte.

11. STUDY ADMINISTRATION

11.1. Data Management

11.1.1. Data Collection

The investigator will be provided with a CRF for each subject. Entries made in the CRF must be verifiable against source documents; any discrepancies should be explained and documented. The investigator will be responsible for reviewing all data and CRF entries and will sign and date the designated pages in each subject's CRF, verifying that the information is true and correct. The investigator is responsible for the review and approval of all responses.

11.1.2. Data Management

Data management will be performed from CRFs. All CRF data will be entered into a validated database. 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.

11.2. Study Monitoring

Qualified representatives of the sponsor or its designee, "study monitors," will monitor the study according to a predetermined monitoring plan. Monitoring visits provide the sponsor with the opportunity to:

- Evaluate the progress of the study.
- Verify the accuracy and completeness of CRFs.
- Assure that all Protocol requirements, applicable laws and/or regulations, and investigator's obligations are being fulfilled.
- Resolve any inconsistencies in the study records.

The investigator must allow the study monitors to periodically review, at mutually convenient times during the study and after the study has been completed, all CRFs and office, hospital, and laboratory records supporting the participation of each subject in the study. The CRFs and other documentation supporting the study must be kept up-to-date by the investigator and the research

staff at the investigative site. These study materials must be available for review by the study monitor, and/or other qualified representatives of the sponsor or its designee, at each monitoring visit.

The study monitor will review the various records of the study (CRFs, subject medical and laboratory records, and other pertinent data). The study monitor will verify the CRF data against original source documentation for accuracy and completeness. The study monitor will identify data discrepancies and collaborate with the investigator and research staff to resolve the discrepancies in a timely manner. Protocol deviations will also be identified and recorded on a "Protocol Deviation Log." The study monitor will follow an "Issue Escalation" plan in order to ensure that each issue identified during a monitoring visit is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements.

11.3. Protocol Adherence

The principal investigator must obtain IRB or IEC approval for the investigation. Initial IRB or IEC approval and all materials approved by the IRB or IEC for this study including the subject ICF and recruitment materials must be maintained by the investigator and made available for inspection.

Each investigator must adhere to the Protocol as described in this document and agree that changes to the Protocol, with the exception of medical emergencies, must be discussed and approved, firstly, by the sponsor or its designee and, secondly, by the IRB or IEC. Each investigator is responsible for enrolling subjects who have met the Protocol inclusion and exclusion criteria. The IRB or IEC that granted original approval, or the IRB or IEC currently responsible for overseeing the conduct of the study, must be notified of all changes in and deviations from the Protocol that may increase risk to the subject, and/or that may adversely affect the rights of the subject or validity of the investigation. The investigator must send a copy of the approval letter from the IRB or IEC to the sponsor or its designee and retain the original in the site study regulatory file.

Major eligibility deviations must be reported to the IRB or IEC in accordance with the IRB or IEC requirements. During the course of the study, the monitor must notify the sponsor or its designee of subjects found not to have met eligibility criteria. The medical monitor, in collaboration with the investigator, will determine if the subject should be withdrawn from the study.

11.4. Financial Disclosure

All clinical investigators participating in clinical studies subject to FDA Regulation Title 21 CFR Part 54 – Financial Disclosure by Clinical Investigators, are required before study initiation to submit a completed Clinical Investigator Financial Disclosure Request 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. These requirements apply to both US and foreign clinical investigators conducting covered clinical studies.

Any new investigators or subinvestigators added to the covered clinical study during its conduct must also submit a completed Clinical Investigator Financial Disclosure Request 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 obligation to report to the sponsor or its designee any changes to the financial information previously reported. The clinical investigators will also be reminded that they must report any changes in their financial information for a period of 1 year after completion of the covered clinical study.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. Sponsor Audits

At some point during the study, individuals from the sponsor's Quality Assurance department and/or their authorized representative may visit the investigator's site to conduct an audit of the study. The purpose of this visit will be to determine the investigator's adherence to the Protocol, applicable regulations, and the sponsor's procedures, in addition to assessing the accuracy of the study data. Before initiating this audit, the investigator will be contacted by the sponsor to arrange a convenient time for this visit. The investigator and staff are expected to cooperate with the auditors and allow access to all subject records supporting the CRFs and other study-related documents.

12.2. Inspection by Regulatory Authorities

At some point during the investigational product's development program, a regulatory authority may visit the investigator to conduct an inspection of the study and the site. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the CRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for purposes of conducting an inspection.

13. ETHICS

13.1. Ethical Conduct of the Study

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, GCPs as defined in Title 21 of the US CFR Parts 50, 54 56, 312, and Part 11, as well as ICH GCP consolidated guidelines (E6) and applicable regulatory requirements.

13.2. Written Informed Consent

Informed consent documentation that includes both information about the study and the ICF will be prepared and given to the subject. This document will contain all elements required by the ICH E6 Guideline for GCP and any additional elements required by local regulations. The document must be in a language understandable to the subject and must specify who informed the subject. Where required by local law, the person who informs the subject must be a physician.

The principal investigator at each center will ensure that the subject is given full and adequate verbal and written information about the nature, purpose, and the possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue study drug and withdraw from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated ICF must be obtained before conducting any study procedures. The principal investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject. The investigator should inform the subject's primary physician about the subject's participation in the study if the subject has a primary physician and if the subject agrees to the primary physician being informed.

Preparation of the ICF is the responsibility of the investigator and must include all elements required by the ICH GCP, and applicable regulatory requirements, and must adhere to the ethical principles that have their origin in the Declaration of Helsinki. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and approve all changes to site-specific ICFs. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to subject records. Before the beginning of the study, the IRB or IEC must provide the investigator with written approval/favorable opinion of the written ICF and any other information to be provided to the subjects.

13.3. Ethics Review

It is the responsibility of the investigator to assure that all aspects of the ethics review are conducted in accordance with the Declaration of Helsinki as described in the ICH E6: Guideline for GCP, and/or local laws, whichever provides the greatest level of protection for the study participants. The Protocol and any information supplied to the subject to obtain informed consent, including written ICFs, subject recruitment procedures (eg, advertisements), and written information to be provided to subjects (information leaflets), must be reviewed and approved by a qualified IRB/IEC before enrollment of participants in the study. Before initiation of the study,

the sponsor or its designee must receive documentation of the IRB or IEC approval, which specifically identifies the study/protocol, and a list of the committee members.

The principal investigator is responsible for informing the IRB or IEC of any amendment to the Protocol in accordance with local requirements. Protocol amendments and revisions to the ICF must be submitted to and approved by the IRB or IEC.

Investigators must submit progress reports to the IRB or IEC in accordance with the IRB or IEC requirements and local regulations. Annual re-approval of the study must be obtained. Copies of progress reports and annual re-approvals must be sent to the sponsor or its designee.

The principal investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The sponsor or its designee will provide this information to the principal investigator.

When the sponsor or its designee provides the investigator with a safety report, the investigator must promptly forward a copy to the IRB or IEC.

After completion or termination of the study, the investigator must submit a final report to the IRB or IEC and to the sponsor or its designee.

The investigator, as part of the records retention requirements for the study, must maintain documentation of all submissions, correspondence, and approvals to and from the IRB or IEC.

Each clinical investigator is responsible to conduct the study in accordance with the Protocol, all applicable laws, regulations, and GCP according to ICH guidelines.

13.4. Data Privacy

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.

14. DATA HANDLING AND RECORDKEEPING

14.1. Inspection of Records

The sponsor or its designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

The investigator must ensure that all records pertaining to the conduct of the clinical study (as listed above) are adequately maintained for a period of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal termination of clinical development of the investigational product.

14.2. Retention of Records

The principal investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved, 2 years following the termination of the test article for investigation. If it becomes necessary for the sponsor or the regulatory authority to review any documentation relating to the study, the investigator must permit access to such records.

The investigator must not destroy any records associated with the study without receiving approval from Incyte. 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.

Whenever possible, an original recording of an observation must be retained as the source document. However, a photocopy of a record is acceptable, provided it is legible and is a verified copy of the original document.

All CRF 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 CRF data and audit trail.

14.3. Confidentiality

Subject names will not be supplied to the sponsor or its designee if applicable. Only the subject number and subject's initials will be recorded in the CRF, 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.

15. 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. The signed agreement is retained by the sponsor or its designee.

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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] Vasectomized 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 vasectomized 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. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

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

Source: Oken et al 1982.

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

Monoamine Oxidase Inhibitors	**Drugs Associated With Significant Monoamine Oxidase Inhibitory Activity**
Hydrazine (example phenelzine)	Meperidine
Caroxazone	Linezolid
Echinopsidine	Methylene blue
Furazolidone	
Tranylcypromine	
Brofaromine	
Metralindole	
Minaprine	
Moclobemide	
Pirlindole	
Toloxatone	
Lazbemide	
Pargyline	
Rasagiline	
Selegiline	

APPENDIX D. PROHIBITED UGT1A9 INHIBITORS

Acitretin	Linoleic acid
Amitriptyline	Mefenamic acid
Andosterone	Mycophenolic acid
Cyclosporine	Niflumic acid
Dasatinib	Nilotinib
Diclofenac	Phenobarbital
Diflunisal	Phenylbutazone
Efavirenz	Phenytoin
Estradiol (17-beta-)	Probenecid
Flutamide	Propofol
Gefitinib	Quinidine
Gemfibrozil	Ritonavir
Glycyrrhetinic acid	Sorafenib
Glycyrrhizin	Sulfinpyrazone
Imatinib	Valproic acid
Imipramine	Verapamil
Ketoconazole	

APPENDIX E. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment (Version) 1:	29 SEP 2014
Amendment (Version) 2:	20 FEB 2015
Amendment (Version) 3:	10 JUL 2015
Amendment (Version) 4:	12 JAN 2016
Amendment (Version) 5:	25 MAY 2016
Amendment (Version) 6:	28 JUN 2017
Amendment (Version) 7:	21 SEP 2018

Amendment 7 (21 SEP 2018)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to reduce required study procedures and update guidelines on the management of legacy subjects who remained on epacadostat monotherapy.

This amendment includes the changes to INCB 24360-203 Protocol Amendment 6 (28 JUN 2017) summarized below.

1. **Synopsis; Section 5.4, Duration of Treatment and Subject Participation; Section 5.7.1, Withdrawal Criteria; Section 6.2, Treatment Period; Section 6.2.1, Restarting Treatment With Study Therapy After Treatment Withdrawal; Section 7.3.6, Laboratory Assessments; Section 7.3.7, Chest Radiograph; Section 7.4.2, Tumor Imaging During the Study; Appendix F, Re-Treatment**

   Description of change: The duration of epacadostat monotherapy treatment for any subject taking epacadostat monotherapy at the time of Amendment 6 and allowed to remain on the monotherapy regimen was capped at 12 months, thereby also capping overall treatment duration maximum for these subjects at 24 months. Exceptions will require medical monitor review and approval every 3 months. The option for subjects who completed 12 months of combination therapy with SD or better, to restart study therapy post-progression was removed.

   Rationale for change: The sponsor has decided to cap the duration of epacadostat monotherapy and remove the option to restart combination therapy post-progression based on emerging data, from the Phase 3 KEYNOTE-252/ECHO-301 study in advanced or metastatic melanoma.

2. **Section 1.2, Study Rationale**

   Description of change: Language regarding the results of the ECHO-301/KEYNOTE-252 study eDMC review was added.

   Rationale for change: To provide updated data regarding the rationale of epacadostat and anti–PD-(L)-1 combination therapy.

3. **Section 1.3.1, Risks from Epacadostat; Section 5.6.4, Procedures for Subjects Exhibiting Serotonin Syndrome; Section 5.10.2, Prohibited Medications and Measures; Appendix C, Publication on Serotonin Syndrome**

   Description of changes: Protocol text relevant to serotonin syndrome was updated. Prohibition of concomitant melatonin supplements was lifted. Appendix C was removed.

   Rationale for changes: To make language consistent with epacadostat program-wide standards.

4. **Synopsis; Section 4.1, Overall Study Design; Section 5.4, Duration of Treatment and Subject Participation; Section 5.6.3.6, Procedures for Immune-Mediated Endocrinopathies; Section 5.7.2, Withdrawal Procedures; Section 5.8.1, Study Completion Criteria; Section 5.9, Beginning and End of the Study; Section 6, Study Assessments (Table 22: Schedule of Assessments; Table 23: Laboratory Assessments); Section 6.3, End of Treatment; Section 6.4, Follow-Up Period; Section 7.4.2, Tumor Imaging During the Study; Section 7.4.3.3.4, Evaluation of Overall Response With Modifications; Section 7.5.1 Eastern Cooperative Oncology Group Performance Status; Section 7.6.1.2, Pharmacokinetic Assessment for Durvalumab (Table 28: Sample Collection Windows for Pharmacokinetic Assessments for Durvalumab [Phase 1 and Phase 2]);** [redacted]

   Description of change: Follow-up phases (disease and survival follow-up) beyond the 90-day safety follow-up visit have been removed from the protocol. The frequency of required endocrine function testing and disease imaging studies has changed from every 8 weeks (4 cycles) to every 12 weeks (6 cycles). Study completion criteria have been revised to include completion of the 90-day safety follow-up period. ECOG performance status, durvalumab pharmacokinetic sample collection beyond Cycle 2, soluble PD-1 concentration, [redacted], and whole blood correlative assessment have all been removed from the protocol. The language regarding collection of optional on-treatment biopsies was modified. The requirement to submit copies of tumor imaging data to a central vendor was removed. The requirement to confirm radiographic responses was removed.

   Rationale for change: The frequency and necessity of study procedures were modified based on emerging data from the Phase 3 KEYNOTE-252/ECHO-301 study in advanced or metastatic melanoma.

5. **Section 5.6.2, Criteria and Procedures for Interruption or Dose Reduction (Table 8: Dose Modification Guidelines of Epacadostat and Durvalumab for Non–Immune-Related Adverse Events); Section 5.6.3, Criteria for Subjects Exhibiting Immune-Related Adverse Events**

   Description of change: Protocol language and recommendations for managing on-study toxicities were updated.

   Rationale for change: To align with current durvalumab toxicity management guidelines.

6. **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 6 (28 JUN 2017)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to revise the design and composition of the NSCLC, SCCHN, and TCC of the GU tract Phase 2 expansion cohorts. Additional changes include removal of the optional epacadostat monotherapy treatment period of the study updating inclusion/exclusion criteria and including updated safety information for epacadostat and durvalumab.

This amendment includes the changes to INCB 24360-203 Protocol Amendment 5 (25 MAY 2016) summarized below.

1. **Synopsis; Section 4.1.2, Phase 2; Section 4.4, Number of Subjects; Section 9.2.2, Sample Size for Phase 2**

   Description of change: The Phase 2 expansion cohorts for the NSCLC, SCCHN, and TCC tumors were revised from a Simon 2-stage design to single expansion cohorts treated at the epacadostat 300 mg BID dose level. The approximate sample size for each cohort was increased, as was the approximate total number of subjects expected to be enrolled into the study and the estimated last subject completion date. The number of prior PD-1 pathway–treated subjects in each cohort was restricted to 10. Table 6 and Table 31 were added to depict the new expansion cohort composition and statistical basis for the sample size.

   Rationale for change: The design and composition of the NSCLC, SCCHN, and TCC cohorts were revised to allow for the full complement of Phase 2 subjects enrolled with these tumor types to be analyzed at the epacadostat 300 mg BID dose level. The sample size for these tumor types, and subsequently the estimated planned number of total subjects enrolled and estimated last subject completed date, were modified to account for the heterogeneity of PD-1 pathway–treated and PD-1 pathway–naive subjects within the respective tumor types. Restricting the number of prior PD-1 pathway–treated subjects within each cohort was instituted to preserve the predicted levels of baseline efficacy observed with PD-1 pathway monotherapy.

2. **Synopsis; Section 4.1, Overall Study Design; Section 5.1.1, Epacadostat; Section 5.4, Duration of Treatment and Subject Participation; Section 5.6.2, Criteria and Procedures for Interruption or Dose Reduction; Section 5.7, Withdrawal of Subjects from Study Treatment; Section 6, Study Assessments (Table 21: Schedule of Assessments); Section 6.2, Treatment Period; Section 6.2.1, Restarting Treatment With Study Therapy After Treatment Withdrawal; Section 6.4.2, Follow-Up; Section 7.3.6, Laboratory Assessments; Section 7.3.7, Chest Radiograph; Section 7.4.2, Tumor Imaging During the Study; Appendix F: Re-Treatment**

   Description of change: The epacadostat monotherapy treatment option was removed from the Protocol. Relevant sections were modified to allow for restarting combination therapy upon evidence of disease progression under certain conditions and to allow for subjects to be re-treated with durvalumab monotherapy upon evidence of disease progression if the combination therapy was not tolerated in the initial treatment period

due to a toxicity attributed to epacadostat, but they completed 12 months of durvalumab and had a status of stable disease or better when they discontinued treatment.

Rationale for change: Based on emerging data with regard to epacadostat monotherapy as well as monotherapy data from other agents targeting the IDO pathway, there is no clear evidence of antitumor activity with IDO inhibitors as monotherapy in the tumors being evaluated in this study. IDO1 is an interferon response gene and a resistance mechanism to PD-1 pathway targeting agents. Based on Phase 2 studies, augmenting activity of PD-1 pathway–targeting agents has been reported in tumor types where PD-1 pathway–targeting agents have been approved by regulatory authorities. Thus, responders who complete 12 months of treatment and discontinue study treatment may resume combination therapy.

3. **Synopsis; Section 3.3, Subject Exclusion Criteria**

   Description of changes:

   a. Exclusion criteria 1e and 1f were revised to remove alkaline phosphatase and update requirements for aspartate aminotransferase, alanine aminotransferase, and total bilirubin.
   b. Criterion 7 was revised to exclude subjects with major surgical procedure within 28 days of starting study treatment OR inadequate recovery from toxicity and/or complications from major surgery before starting study treatment.
   c. Criterion 9 was revised to include carcinomatous meningitis and define CNS metastases.
   d. Criterion 10 was revised to include additional autoimmune and inflammatory disorders and updated exceptions.
   e. Criterion 23 was revised to include additional requirements for subjects who have received prior immunotherapy.
   f. New criteria 26 and 27 added to exclude subjects with a history of primary immunodeficiency or leptomeningeal carcinomatosis.

   Rationale for changes: To make criteria consistent with current epacadostat and/or durvalumab development program standard protocol language.

4. **Synopsis; Section 1.3, Potential Risks and Benefits of the Treatment Regimen; Section 5.6.2, Criteria and Procedures for Interruption or Dose Reduction (Table 8); Section 5.6.3, Criteria for Subjects Exhibiting Immune-Related Adverse Events (including Tables 10-17 and 19) Section 5.6.4, Procedures for Subjects Exhibiting Serotonin Syndrome**

   Description of change: Safety language with regard to epacadostat and durvalumab, including updated guidelines for the management of certain immune-related adverse events, were revised or added.

   Rationale for change: To align the Protocol with the current safety-related information and strategies pertinent to the epacadostat and durvalumab clinical development programs.

5. **Section 6, Study Assessments (Table 22, Laboratory Assessments); Section 7.6.3.3.2, Whole Blood for Correlative Assessment**

   Description of change: The whole blood correlative assessment was deemed not required for subjects enrolled under Protocol Amendment 6 or beyond.

   Rationale for change: The samples were no longer needed.

6. **Appendix F, Re-Treatment (Table 32, Re-Treatment Schedule of Assessments)**

   Description of change: An optional tumor tissue collection was added.

   [redacted]

7. **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 5 (25 MAY 2016)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to provide additional guidance for subjects continuing on monotherapy epacadostat and provide guidance for subjects who restart treatment with combination therapy after durvalumab has been stopped.

This amendment includes the changes to the INCB 24360-203 Protocol Amendment 4 (12 JAN 2016) summarized below.

1. **Synopsis; Section 3.3, Subject Exclusion Criteria (Criterion #5); Section 5.6.3.9, Procedures for Immune-Related Adverse Events Not Specifically Described Above; Section 5.10, Concomitant Medications and Measures**

   Description of change: The threshold for systemic steroids was changed from ≥ 7.5 mg/day to ≥ 10 mg/day prednisone equivalent.

   Rationale for change: Several recent studies evaluating immune-related adverse events (irAEs) and the need for systemic immunosuppression indicate that low doses of systemic steroids for the management of irAEs do not impact survival or time to treatment failure. Although the threshold for the study was increased, a maximum dose of 10 mg/day prednisone equivalent is still considered a low dose.

2. **Section 1.1.6, Melanoma; Section 1.1.7, Non–Small Cell Lung Cancer; Section 1.1.9, Squamous Cell Carcinoma of the Head and Neck; Section 1.1.11, Gastric and Gastroesophageal Junction Cancer**

   Description of change: Updated background information on therapies approved for the treatment of melanoma, non-small cell lung cancer, squamous cell carcinoma of the head and neck, and gastric and gastroesophageal junction cancer.

   Rationale for change: To provide up-to-date information.

3. **Section 3.2, Subject Inclusion Criteria**

   Description of change: Inclusion criterion #16 was updated to note that male subjects should refrain from sperm donation from screening through 90 days after the last dose of study drug.

   Rationale for change: Male subjects were required to take appropriate precautions throughout the study not to father a child, which was inclusive of sperm donation. The language seeks to clarify the subject's responsibilities while participating in the study.

4. **Section 3.3, Subject Exclusion Criteria; Section 6, Study Assessments (Table 21)**

   Description of change: Exclusion criterion #16 and Table 21 were updated to specify that subjects with hepatitis B no longer are required to have Hepatitis B surface antigen antibody testing. Subjects with hepatitis C antibody positivity may also enroll if they have completed treatment for hepatitis C intended to eradicate to the virus and hepatitis C RNA levels are undetectable.

   Rationale for change: The availability of highly active treatments for HCV has transformed hepatitis C into a curable illness. Subjects who have undergone antiviral therapy and have an undetectable viral load are an important population to consider for immunotherapy studies. In the dose-escalation phase of the study, subjects underwent increased monitoring of liver chemistry tests weekly for the first 8 weeks on study. There were no cases of hepatitis reported, and no subjects experienced drug-induced liver injury while on study. A recent case study of 2 HCV+ subjects treated with pembrolizumab alone and pembrolizumab + ipilumumab demonstrated that no significant toxicities and no increases in viral load occurred during the course of immunotherapy treatment.[1] The safety expansion portion of this 1b study includes interim safety analyses approximately every 3 months and offers a unique opportunity to study this population in the clinical trial setting. For this reason, we plan to allow subjects with previously treated and controlled hepatitis C infections to participate in the safety expansion.

   With respect to hepatitis B, the Protocol excluded subjects with prior HBV exposure, regardless of whether they are immune or have chronic active disease. The Protocol is modified to allow subjects who by definition of the CDC Guidelines are immune to HBV, and those with chronic active HBV are still excluded (http://www.cdc.gov/hepatitis/hbv/hbvfaq.htm#general).

5. **Section 3.3, Subject Exclusion Criteria**

   Description of change: Exclusion criterion #22 was updated to note that a subject with an arrhythmia may enroll if the subject is on anti-arrhythmic medication and is in sinus rhythm on the screening ECG.

   Rationale for change: More than 250 subjects have been administered epacadostat monotherapy or epacadostat in combination with other immune-checkpoint inhibitors, and no clinically meaningful changes or cardiac trends have been noted.

[1] Davar D, Wilson M, Pruckner C, Kirkwood JM. PD-1 blockade in advanced melanoma in patients with hepatitis C and/or HIV. Case Rep Oncol Med 2015; Article ID 737389, 5 pages. http://dx.doi.org/10.1155/2015/737389.

6. **Section 4.1.2, Phase 2**

   Description of change: Revised to indicate that if more than 1 PAD is evaluated, the cohort *may or may not be* repeated for the specified tumor type.

   Rationale for change: A higher dose level may be explored based on PK/PD data from the Phase 1 portion of the study. If target inhibition at the 300 mg BID dose level is greater than the 100 mg BID dose level, subjects may be enrolled at the higher dose level. If the lower dose level does not meet the threshold for the number of responses required to expand the cohort, the cohort may be enrolled at the higher dose level.

7. **Section 5.6.2, Criteria and Procedures for Interruption or Dose Reduction**

   Description of change: In Table 7 (Dose Modification Guidelines of Epacadostat and Durvalumab for Non−Immune-Related Adverse Events), "Action with Respect to Durvalumab" was revised for infusion-related reactions: For Grade 1 or 2, the time limit of "up to 4 hours" for temporary interruption of durvalumab was deleted; for Grade ≥ 3, a note was added that severe infusion-related reactions should be managed per institutional standards (eg, IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

   Rationale for change: To provide additional guidance to investigators regarding the management of irAEs.

8. **Section 5.6.3, Criteria for Subjects Exhibiting Immune-Related Adverse Events**

   Description of change: Tables 9 through 15 (Recommended Approach for Handling Noninfectious Pneumonitis, Enterocolitis, Hepatitis, Dermatitis, Neuropathies, Endocrinopathies, and Nephritis or Renal Dysfunction, respectively) were updated, and precautions were added for any grade immune-mediated peripheral neuromotor syndromes, such as Guillain-Barré syndrome and myasthenia gravis.

   Rationale for change: To provide additional guidance to investigators regarding the management of irAEs.

9. **Section 5.9, Beginning and End of Study**

   Description of change: Revised to define end of study as when all subjects have discontinued the study drug and have completed applicable follow-up assessments, and to indicate that if ≤ 5 subjects are 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 on study until a discontinuation criterion is met and/or written notification is provided to the sponsor.

   Rationale for change: To clarify that the end of study will be declared when all subjects have been discontinued the study drug and completed all applicable follow-up visits.

10. **Section 5.10.1, Restricted Medications and Measures**

    Description of change: A bullet was added indicating that the use of the anticonvulsant carbamazepine is discouraged and an alternative should be used if possible.

    Rationale for change: The use of carbamazepine is discouraged because there is a potential interaction that could result in lower epacadostat exposures.

11. **Section 5.10.2, Prohibited Medications and Measures**

    Description of change: A note was added to the UGT1A9 inhibitor bullet indicating that administration of epacadostat on the morning of a procedure where propofol may be administered is permitted; however, the evening dose after the procedure should be held, and subjects may resume regular dosing the following day.

    Rationale for change: Propofol has a very short half-life and exposure to the drug for on study biopsy procedures will not affect epacadostat metabolism via UGT1A9. Propofol administration may be warranted for a procedure while on study; therefore, concomitant medication guidance was provided.

12. **Section 6, Study Assessments; [redacted]; [redacted]**

    Description of change: Table 20 (Laboratory Assessments) footnote "k" and Sections 7.6.3.2 and 7.6.3.3.2 were revised to indicate that the whole blood and plasma samples may be collected at the visit that most closely aligns with the scheduled date of the computed tomography scan.

    Rationale for change: To provide clarification to study sites that the blood and plasma may be collected on the day of the clinic visit when other required laboratory assessments are drawn.

13. **Section 6.2.1, Epacadostat Monotherapy After 12 Months of Combination Therapy; Section 6.2.2, Restarting Treatment With Combination Therapy After Durvalumab Has Been Stopped; Section 7.3.6, Laboratory Assessments; Appendix F, Monotherapy Epacadostat Treatment; Appendix G, Combination Re-Treatment**

    Description of change: Appendix F and Appendix G were added to provide the schedule of assessments and laboratory assessments for epacadostat monotherapy and re-treatment with combination therapy (Tables 30-33). In Section 6.2.1, the exception regarding durvalumab pharmacokinetic and immunogenicity samples (that they should be collected during the treatment period as well as when durvalumab is discontinued and 90 days after discontinuation) has been deleted.

    Rationale for change: Subjects are no longer required to visit clinic every 2 weeks while on monotherapy epacadostat; therefore, the visit structure was altered once subjects become eligible for monotherapy epacadostat or re-treatment with combination therapy.

14. **Section 7.6.1.1, Pharmacokinetic Assessment for Epacadostat**

    Description of change: In Table 24 (Sample Collection Windows for Pharmacokinetic Assessments for Epacadostat), the window for the 6-hour and optional 8- to 10-hour samples was changed to ± 60 minutes (instead of ± 30 minutes).

    Rationale for change: Visit windows were lengthened to allow greater flexibility.

15. **Section 9.6, Interim Analysis**

    Description of change: The interim analysis was modified to evaluate all ≥ Grade 3 adverse events attributable to the investigational agents in Phase 2 of the study.

    Rationale for change: The revised criteria for evaluation allows for efficient monitoring of safety in a larger sample size.

16. **Section 10.1.1.1, Epacadostat**

    Description of change: The packaging/labeling statement was revised to: All Incyte investigational product labels will be in the local language and will comply with the legal requirements of each country.

    Rationale for change: The study will now include ex-US centers; therefore, the language was updated for global compliance.

17. **Appendix A, Information Regarding Effectiveness of Contraceptive Methods**

    Description of change: Appendix A was updated with Clinical Trial Facilitation Group's recommendations related to contraception in clinical studies.

    Rationale for change: The study will now include ex-US centers; therefore, the language was updated for global compliance.

18. **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 4 (12 JAN 2016)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to modify the tumor types that will be evaluated in the Phase 2 portion of the study.

This amendment includes the changes to INCB 24360-203 Protocol Amendment 3 (10 JUL 2015) summarized below.

1. **Synopsis; Section 1, Introduction; Section 3, Subject Eligibility; Section 4.1, Overall Study Design; Section 4.4, Number of Subjects; Section 9.2.2, Sample Size for Phase 2**

   Description of change: The Protocol was updated to include subjects with TNBC, gastric or GE junction cancer, and TCC of the GU tract, and to indicate that subjects with pancreatic cancer will be included only in Phase 1 of the study. All sections pertaining to the study design and study rationale were updated accordingly. Background sections for TNBC, gastric and GE cancer, and TCC of the GU tract were added to the Introduction (Sections 1.1.10, 1.1.11, and 1.1.12). Inclusion criteria specific to subjects with these tumor types were added, and the number of subjects/sample size information for Phase 2 was updated.

   Rationale for change: Clinical activity with monotherapy PD-1 pathway inhibitors have been observed in TNBC, gastric and GE junction cancers, and TCC of the GU tract. [redacted]

2. **Synopsis; Section 4.1.1, Phase 1 Dose Escalation**

   Description of change: In Table 4 (Dosing Cohorts), a footnote was added to the 300 mg BID dose to indicate that intermediate dose levels may be explored based on emerging PK [redacted] data.

   Rationale for change: Based on emerging PK/[redacted] data, it may be necessary to explore a 200 mg BID dose level if there is a substantial difference in the average target inhibition observed at 300 mg BID compared with 100 mg BID dose level.

3. **Synopsis; Section 4.1.2, Phase 2**

   Description of change: Updated to indicate that more than 1 PAD may be evaluated in Phase 2.

   Rationale for change: If more than 1 PAD is identified in Phase 1, it may be necessary to obtain additional efficacy data in Phase 2.

4. **Synopsis; Section 3.2, Subject Inclusion Criteria**

   Description of change: Inclusion criterion #6 was updated to indicate that subjects with NSCLC may have received prior treatment with an anti–PD-1 targeted agent.

   Rationale for change: The PD-1 targeted agents nivolumab and pembrolizumab were recently approved for the treatment of subjects with metastatic NSCLC who have disease progression on or after platinum-containing chemotherapy. Therefore, subjects may have received prior therapy with either of these agents.

5. **Synopsis; Section 3.3, Subject Exclusion Criteria**

   Description of change: Exclusion criterion #21 was revised to indicate that subjects with a screening QTc interval > 480 msec (instead of > 470 msec) are excluded.

   Rationale for change: An analysis of QTc interval prolongation and the relationship between epacadostat plasma concentration and QTc intervals in Phase 1 and 2 epacadostat studies was conducted, and no clinically meaningful changes or trends were noted.

6. **Section 1.1.5, Combined Immune Checkpoint Inhibition; Section 1.1.6, Melanoma; Section 1.1.7, Non–Small Cell Lung Cancer, Section 1.1.13, Preclinical and Clinical Study Data; Section 1.3, Potential Risks and Benefits of the Treatment Regimen; Section 1.4, Justification for Treatment Regimen**

   Description of change: In Section 1.1.5, additional background information was added from a study of nivolumab in combination with ipilimumab versus ipilimumab alone, and updated data were added from the ongoing Phase 1/2 study of epacadostat in combination with ipilimumab. In Sections 1.1.6 and 1.1.7, information regarding recent approvals for the treatment of melanoma and NSCLC was added. Preclinical and clinical study data were updated in Section 1.1.13. Safety data were updated in Sections 1.3 and 1.4.

   Rationale for change: To provide up-to-date information.

7. **Section 1.3.1, Risks from Epacadostat; Section 6, Study Assessments, Section 7.3.4, Assessment of Serotonin Syndrome Symptoms**

   Description of change: Serotonin syndrome assessment was deleted from the schedule of assessments (Table 19) and corresponding sections.

   Rationale for change: Of the 253 subjects administered INCB24360 to date, no subjects have exhibited serotonin syndrome. Subjects and sites are informed of the signs and symptoms associated with serotonin syndrome; however, the separate serotonin syndrome assessment has been removed from the Protocol.

8. **Section 5.6.3.3, Procedures and Guidance for Hepatitis; Section 6, Study Assessments, Section 7.3.6.1.1, Liver Chemistry Monitoring**

   Description of change: The requirement to conduct liver chemistry tests weekly for the first 8 weeks on study treatment was deleted.

   Rationale for change: Because of the low incidence of Grade 3 or greater ALT and AST elevations seen on study, weekly monitoring of liver chemistry tests are not required. Additional monitoring of liver chemistries will occur every cycle while epacadostat is administered as combination therapy.

9. **Section 5.10, Concomitant Medications and Measures**

   Description of change: Text updated to indicate that concomitant medications administered as treatment prophylaxis (eg, for the management of infusion reactions) should be recorded in the CRF. A new table was added (Table 18) to provide warfarin dose modification guidance.

   Rationale for change: In the INCB 24360-102 study, PK [redacted] modeling showed that the observed extent of epacadostat interaction on multiple-dose warfarin PK is expected to cause greater INR increases in subjects on warfarin therapy; therefore, detailed coadministration guidance has been provided.

10. **Section 6, Study Assessments, Section 7.3.7, Pulmonary Function Tests**

    Description of change: The requirement for pulmonary function testing was deleted from Tables 20 and 21.

    Rationale for change: Because of the low incidence of Grade 3 or greater pulmonary events, the requirement for pulmonary function testing has been removed.

11. **Section 6, Study Assessments; Section 7.3.5, Twelve-Lead Electrocardiograms**

    Description of change: Timing of ECGs was clarified in Table 19 (footnote c) and a new table was added to Section 7.3.5 (Table 22) providing the schedule and timing of ECG assessments.

    Rationale for change: ECGs will be taken in conjunction with the updated timepoints for PK assessments.

12. **Section 6, Study Assessments; Section 7.6.1, Pharmacokinetics**

    Description of change: The PK sample collection timing for epacadostat and durvalumab PK was updated, and a new table was added (Table 25) providing sample collection windows for durvalumab PK assessments.

    Rationale for change: Pharmacokinetic assessments for the INCB24360 program were aligned to collect additional information at predose, C_{max}, and steady state.

13. **Section 7.4, Efficacy Assessments**

    Description of change: The tumor imaging sections were updated to indicate that imaging of the pelvis is only required for subjects with TCC of the GU tract but is strongly encouraged for all subjects.

    Rationale for change: Pelvic imaging is considered standard of care for TCC of the GU tract.

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

Amendment 3 (10 JUL 2015)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to remove the enrolment stagger and to remove the 200 mg dose-escalation cohort in Phase 1 of the study.

This amendment includes the changes to INCB 24360-203 Protocol Amendment 2 (20 FEB 2015) summarized below.

1. **Synopsis, Overall Study Design, Planned Number of Subjects, Statistical Methods; Section 1.4, Justification for Treatment Regimen; Section 4.1.1, Phase 1 Dose Escalation; Section 4.4, Number of Subjects; Section 5.6.2, Criteria and Procedures for Interruption or Dose Reduction (Table 8); Section 9.2.1, Cohort Size in Phase 1**

   Description of change: In Phase 1, the dose escalation cohort of 200 mg BID of epacadostat (INCB024360) will not be explored in combination with durvalumab (MEDI4736). The dose-escalation phase will now include up to 6 cohorts instead of 7, and the planned number of subjects for this phase is now 36 instead of 42. Section 1.4 has been revised with updated data from INCB 24360-101 and INCB 24360-201 to support the changes.

   Rationale for change: The results from Study INCB 24360-101 demonstrated that epacadostat displays mildly sublinear exposure-dose response. [redacted] Additionally, inhibition of IDO1 is well described by an E_{max} model that is fundamentally nonlinear, especially beyond the inhibition > 80%. Any incremental increase in IDO1 inhibition begins to plateau and would be insensitive to further increased epacadostat concentration. [redacted]

2. **Synopsis, Overall Study Design; Section 4.1.1, Phase I Dose Escalation**

   Description of change: The requirement to wait 1 week between subjects enrolling in successive weeks during Phase 1 has been removed from the Protocol.

   Rationale for change: The study currently includes a 42-day DLT evaluation period as well as weekly safety teleconferences with all participating study sites in the dose-escalation phase. No DLTs have been observed to date in the first 2 cohorts evaluated. Therefore, staggered enrollment is no longer considered to be necessary.

3. **Synopsis, Key Inclusion Criteria and Key Exclusion Criteria; Section 3.2, Subject Inclusion Criteria; Section 3.3, Subject Exclusion Criteria**

   Description of change: Inclusion criterion 5b and exclusion criterion 4 have been updated to allow prior anti–PD-1 therapy for melanoma as well as any tumor type in which a PD-1 pathway targeted agent is approved.

   Rationale for change: PD-1 targeted agents have been approved for use in subjects with melanoma and have also been incorporated into the NCCN guidelines as an option for first-line treatment in melanoma. Incyte anticipates additional approvals for anti–PD-1 and anti–PD-L1 targeted agents in other tumor types during the conduct of this study.

4. **Synopsis, Key Inclusion Criteria; Section 3.2, Subject Inclusion Criteria**

   Description of change: Inclusion criterion 7 has been updated to allow subjects with exocrine pancreatic neoplasms to enroll in Part 1. Part 2 subjects must have adenocarcinoma of the pancreas.

   Rationale for change: The change was updated to allow for a broader population of pancreatic subjects to enroll in the study.

5. **Synopsis, Key Inclusion Criteria; Section 3.2, Subject Inclusion Criteria; Section 7.6.3.5, Analysis of Tumor Samples**

   Description of change: Fresh tumor biopsies are still required for all subjects at screening; however, subjects may now be enrolled if the tumor tissue is deemed inaccessible by the local interventional radiologist in consultation with the subject's treating physician. This exception requires medical monitor approval. Archival tumor tissue should be submitted if available; however, if archival tumor tissue is not available and the subject is able to undergo a fresh biopsy, the subject will be considered eligible.

   Rationale for change: Subjects with late-stage disease may have had any diagnostic archival specimens exhausted or have had their initial diagnosis made by fine-needle aspirate that would not be adequate for correlative studies. Therefore, if these subjects are willing and able to submit fresh biopsy samples they will not be excluded from the study (Administrative Change 2 dated 31 MAR 2015).

6. **Synopsis, Key Inclusion Criteria; Section 3.3, Subject Exclusion Criteria; Section 7.3.6, Twelve-Lead Electrocardiograms**

   Description of change: The average QTc of the 3 ECGs may be used for enrollment if a single QTc is > 470 milliseconds. In addition, subjects with an intraventricular conduction delay (eg, right bundle branch block), JTc < 340 milliseconds is acceptable; however, subjects with a left bundle branch block would be excluded.

   Rationale for change: Additional guidance was requested for situations when one of the 3 QTc measurements obtained at baseline exceeds > 470 milliseconds and for subjects with an intraventricular conduction delay.

7. **Synopsis, Study Drugs, Dosages, and Modes of Administration; Section 5.1.1, Epacadostat**

   Description of change: Instructions for epacadostat administration have been updated to specify that an additional dose should not be taken if a subject vomits.

   Rationale for change: Language was added to inform sites how to manage dosing if this event occurs in subjects dosed with epacadostat.

8. **Section 1.1, Pharmaceutical and Therapeutic Background**

   Description of change: New subsections containing background information for epacadostat (Section 1.1.3) and durvalumab (Section 1.1.4) have been added. Section 1.1.6 (Melanoma) was updated to include NCCN guidance and CHMP approval of PD-1 inhibitors for the treatment of melanoma. Section 1.1.10 (Preclinical and Clinical Trial Data) was updated to include a summary of epacadostat pharmacokinetic (PK) [redacted] data and durvalumab PK data in humans.

   Rational for change: Therapeutic background section was updated for consistency with the most recent information from the Investigator Brochures (IBs) for epacadostat and durvalumab.

9. **Section 1.3.1, Risks From Epacadostat**

   Description of change: Updated to report that in Study INCB 24360-201, 12 of the 48 subjects enrolled as of 29 OCT 2014 received concomitant treatment with an MAOI and epacadostat, and that 0 of the 12 subjects exhibited serotonin syndrome.

   Rationale for change: Theoretically, inhibition of IDO1 could cause an increase in serotonin levels that could precipitate a cluster of AEs termed serotonin syndrome (SS) when administered alone or in combination with other serotonergic agents. This rare syndrome has been associated with some monoamine oxidase inhibitors (MAOIs) and combinations of serotonergic drugs. MAOIs and serotonergic drugs are prohibited while on study however, data from the INCB 24360-201 study indicate that SS was not observed in 0 of 12 subjects who received concomitant treatment with an MAOI and epacadostat.

10. **Section 5.6.2, Criteria and Procedures for Interruption or Dose Reduction**

    Description of change: The infusion of durvalumab may be interrupted for up to 4 hours if an infusion reaction occurs.

    Rationale for change: Instructions in Table 7 were updated to make consistent with Section 5.1.2.2.

11. **Section 5.6.3, Criteria for Subjects Exhibiting Immune-Related Adverse Events**

    Description of change: The recommended approach to managing immune-related adverse events was updated.

    Rationale for change: The update provides additional guidance for supportive care measures for pneumonitis, enterocolitis, hepatitis, dermatitis, neuropathies, endocrinopathies other than hypothyroidism, and nephritis or renal dysfunction.

12. **Section 7.4.3, RECIST v1.1**

    Description of change: Updated to indicate that tumor lesions located in a previously irradiated area or in an area subjected to other locoregional therapy should not be selected as target lesions. In addition, tumor lesions that will be biopsied should not be selected as target lesions.

    Rationale for change: Lesions located in a previously irradiated area or in an area subjected to other locoregional therapy may confound the results of the overall response assessment for the subject.

13. **Incorporation of administrative changes and adoption and use of INN generic names for INCB024360 and MEDI4736 have been replaced throughout.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the attached red-line/strike-out version of the amendment.

Amendment 2 (20 FEB 2015)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to allow for the option of intrasubject dose escalation to 10 mg/kg for subjects who enroll in the initial dose cohort at MEDI4736 3 mg/kg in combination with INCB024360. This option will only be available when MEDI4736 10 mg/kg has been shown to be tolerable in combination with INCB024360 25 mg BID based on DLT rules.

This amendment includes the changes to INCB 24360-203 Protocol Amendment 1 (29 SEP 2014) summarized below.

1. **Synopsis, Study Drugs, Dosages, and Modes of Administration; Section 5.1.2, MEDI4736; Section 5.6.1, Planned Dose Increases**

   Description: Allow the option for subjects enrolled into the initial dose cohort of INCB024360 25 mg BID and MEDI4736 3 mg/kg to dose escalate to MEDI4736 10 mg/kg in combination with INCB024360 25 mg BID if a number of conditions are met.

   Rationale: MEDI4736 at a dose of 10 mg/kg has been shown to be well tolerated and is being carried forward as the dose in Phase 3 studies. If 10 mg/kg is found to be tolerable in combination with INCB024360 25 mg BID based on DLT rules, subjects who start at a dose of 3 mg/kg will be given the opportunity to escalate the dose to 10 mg/kg at the discretion of the investigator.

2. **Synopsis, Key Inclusion Criteria; Section 3.2, Subject Inclusion Criteria**

   Description of change to inclusion criterion #4: Added language to allow investigational agents in combination with standard therapies to be considered a line of therapy and also allow adjuvant, neoadjuvant, or chemoradiation regimens given within 6 months of screening to be considered a line of therapy.

   Rationale: Reorganization of inclusion criteria already present in the Protocol to clarify that these situations may apply to subjects of any disease indication.

   Description of change to inclusion criterion #5: Clarified that melanoma subjects may be treatment-naïve or have received prior anti–CTLA-4 therapy with the exception that in Phase 1, subjects with BRAF mutations must have received prior treatment with a BRAF inhibitor.

   Rationale: A recent update to the NCCN guidelines for melanoma has listed anti–PD-1 therapy as an option for first-line treatment. MEDI4736 is an anti-PD-L1 antibody and the mechanism of action is similar; therefore, it is reasonable to allow subjects to consider treatment in this study as appropriate first-line treatment.

Description of change to inclusion criterion #6: Removed the requirement for prior treatment with a platinum-based therapy. Clarified the requirement for subjects with driver mutations to have received and progressed or be intolerant to a targeted agent, if one is available.

Rationale: To allow NSCLC subjects who are not eligible for treatment with a platinum-based therapy the opportunity to enroll in the study and to clarify that subjects who have tumors with driver mutations should receive appropriate targeted therapy if one is available.

3. **Synopsis, Key Exclusion Criteria; Section 3.3, Subject Exclusion Criteria**

   Description of change to exclusion criterion #1b: Platelet count of $< 75 \times 10^9$/L at baseline is now considered exclusionary.

   Rationale: Heavily pretreated subjects may have persistent low-grade thrombocytopenia. As the risk of myelosuppression with the combination treatment given in this study is low, it is reasonable to allow subjects with Grade 1 thrombocytopenia to enroll.

   Description of change to exclusion criterion #21: Subjects with a QTc interval of > 470 ms are excluded.

   Rationale: Based on preclinical testing, there is no QTc liability for either INCB024360 or MEDI4736. The original QTc interval criterion was too strict in error and has been corrected to allow enrollment with a QTc interval of up to 470 msec.

   Description of change to exclusion criterion #25: Addition of an exclusion criterion that would require a conversation with the medical monitor to determine eligibility for a subject requiring ongoing thorocentesis or paracentesis for palliation.

   Rationale: Requirements for recurrent thorocentesis or paracentesis may be indicative of aggressive end-stage disease, and cases should be reviewed with the medical monitor to determine if the subject is an appropriate candidate for the study.

4. **Section 1.1.4, Melanoma; Section 1.3.2.2, Possible Risks Based on Clinical Data**

   Description: Added information on the recent FDA approval of anti–PD-1 antibodies for use in a subset of patients with metastatic melanoma and updated clinical data for MEDI4736 to reflect an IB update.

   Rationale: To provide investigators with the most updated information.

5. **Section 4.1.2, Phase 2**

   Description: Requirement for at least 5 subjects with PD-L1–positive tumors in each expansion cohort has been removed from the Protocol.

   Rationale: This requirement and the caveat to enroll additional subjects that express PD-L1 would have compromised the integrity of the Simon 2-stage design planned for Phase 2 of the study. Therefore, the requirement was removed.

6. **Section 5.5.1, Definition of Dose-Limiting Toxicities (Table 3: Criteria for Defining Dose-Limiting Toxicities)**

   Description: Additional criteria that would exclude certain types of Grade 3 rash as a DLT have been added to the nonhematologic toxicities section of Table 3.

   Rationale: Grade 3 rashes in the absence of desquamation, with no mucosal involvement, and that do not require systemic steroids or interfere with activities of daily living will not be considered a DLT.

7. **Section 5.6.2, Criteria and Procedures for Interruption or Dose Reduction**

   Description: Updated to indicate that there will be no dose reductions of MEDI4736 allowed for the management of toxicities of individual subjects and that doses of MEDI4736 may be delayed for toxicity management.

   Rationale: Language was added to clarify that dose reductions of MEDI4736 are not allowed (exception noted in Section 5.6.1).

8. **Section 5.10.1, Restricted Medications and Measures**

   Description: Doses of coumarin-based anticoagulants that will increase the INR will require a dose modification of approximately one-third upon initiation of therapy with INCB024360 (if alternative anticoagulants cannot be used).

   Rationale: Incyte investigated the potential interaction between INCB024360 and warfarin. Data from this study showed that administration of INCB024360 in combination with warfarin resulted in mild but statistically significant increase in INR; therefore, the guidance on the concomitant use of a coumarin-based anticoagulant has been modified.

9. **Section 5.10.2, Prohibited Medications and Measures**

   Description: Added a clause prohibiting administration of inactivated vaccines during the DLT observation period (42 days after Cycle 1 Day 1) for each subject.

   Rationale: To eliminate the possibility that side effects from vaccination (including inactivated vaccines such as the injectable influenza vaccination) may interfere with assessment of adverse events as DLTs during the study.

[redacted]

[redacted]theses linking changes in the tumor microenvironment with changes in peripheral blood.

11. **Section 7.3.7.1.1, Liver Chemistry Monitoring**

    Description: Added language that twice-weekly monitoring of liver chemistry tests for persistent low-grade abnormalities does not need to continue indefinitely.

    Rationale: Clarify language to allow for reasonable monitoring that will not require subjects to be seen twice weekly indefinitely for low-grade abnormalities that have become the new baseline for a subject.

12. **Appendix F, Prohibited UGT-1A9 Inhibitors**

    Description: A new appendix was added listing prohibited UGT-1A9 inhibitors.

    Rationale: The use of UGT-1A9 inhibitors is prohibited while subjects are on study treatment per Section 5.10.2. A list of these agents was added as a reference for investigators.

13. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the red-line/strike-out version of the amendment.

Amendment 1 (29 SEP 2014)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to address FDA's 25 SEP 2014 clinical comments, including clarification and requested changes to the inclusion criteria, updates to the definition of dose-limiting toxicities, addition of dose levels to the dose-escalation portion of the study, and revision of the observation period for dose-limiting toxicities.

This amendment includes the changes to the INCB 24360-203 Protocol (dated 18 AUG 2014) summarized below.

1. **Synopsis; Section 1.4, Justification for Treatment Regimen; Section 4.1.1 Phase 1 Dose Escalation; Section 4.4 Number of Subjects; Section 5.1.2 MEDI4736; Section 5.6.2, Criteria and Procedures for Interruption; Section 9.2.1 Cohort Size in Phase 1**

   Description of change: The starting dose of MEDI4736 was adjusted in the dose-escalation portion of the study to 3 mg/kg. Additional dose-escalation cohorts of INCB024360 75 mg BID and 200 mg BID in combination with MEDI4736 were added to Phase 1 of the study.

   Rationale for change: FDA requested changes to the dose-escalation phase of the study.

2. **Synopsis; Section 3.2, Subject Inclusion Criteria**

   Description of change: The inclusion criteria for melanoma have been revised to require subjects with a BRAF-mutation to have received prior treatment with a BRAF inhibitor with or without a MEK inhibitor. The inclusion criteria have also been updated to clarify that subjects may not refuse standard treatment in Phase 1 of the study.

   Rationale for change: FDA requested changes to the inclusion criteria.

3. **Section 5.5.1, Definition of Dose-Limiting Toxicities**

   Description of change: The following have been added to the definition of DLT: Grade 4 thrombocytopenia related to either drug, ≥ Grade 3 neutropenia lasting > 5 days related to either drug, Grade 4 anemia related to either drug, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, disseminated intravascular coagulation, idiopathic thrombocytopenic purpura, ≥ Grade 3 hemolysis, and any drug-related toxicity that left the subject unable to receive 75% of INCB024360 or 3 doses of MEDI4736 during the DLT observation period.

   Rationale for change: The FDA requested modification of the criteria defining DLTs.

4. **Synopsis; Section 4.1.1, Phase 1 Dose Escalation; Section 5.5, Rationale for Dose Modification; Section 5.5.1, Definition of Dose-Limiting Toxicities**

   Description of change: The DLT observation period has been changed to 42 days (6 weeks) in the Phase 1 dose-escalation portion of the study. Text has also been added to limit enrollment to 2 subjects per week in Phase 1 of the study. Additionally, a 1-week interval will be required between subjects in successive weeks.

   Rationale for change: FDA requested change.

5. **Section 6, Study Assessments**

   Description of change: Table 14 and Table 15 were edited to clarify that liver function tests should be performed on a weekly basis for the first 8 weeks on study treatment. The chemistry panel and hematology panel are required to be performed at the start of every cycle.

   Rationale for change: FDA requested clarification of safety laboratory testing.

6. **Section 6, Study Assessments; Section 7.3.6, Twelve-Lead Electrocardiograms**

   Description of change: An electrocardiogram (ECG) was added at Cycle 2 Day 1 prior to administration of INCB024360 or infusion of MEDI4736 in addition to the scheduled assessment at 60 to 90 minutes after administration of INCB024360.

   Rationale for change: An additional time point was added to monitor the ECG at the anticipated steady state of INCB024360.

7. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the protocol and are noted in the attached red-line/strike-out version of the amendment.

Signature Manifest

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INCB 24360-203 Protocol AM7

Approval and Release

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