Clinical Study Protocol

INCB 24360-207 / NCT03085914

A Phase 1/2, Open-Label, Safety, Tolerability, and Efficacy Study of Epacadostat in Combination With Pembrolizumab and Chemotherapy in Subjects With Advanced or Metastatic Solid Tumors (ECHO-207/KEYNOTE-723)

Product:	**Epacadostat (INCB024360)**
IND Number:	**132,309**
EudraCT Number:	**2016-004678-16**
Phase of Study:	**1/2**
Sponsor:	**Incyte Corporation 1801 Augustine Cut-Off Wilmington, DE 19803**
Original Protocol (Version 0):	**16 NOV 2016**
Amendment (Version) 1:	**10 JAN 2017**
Amendment (Version) 2:	**28 MAR 2017**
Amendment (Version) 3:	**18 MAY 2017**
Amendment (Version) 4:	**31 JUL 2017**
Amendment (Version) 5:	**02 FEB 2018**
Amendment (Version) 6:	**31 AUG 2018**
Amendment (Version) 7:	**14 FEB 2019**

INVESTIGATOR'S AGREEMENT

I have read the INCB 24360-207 Protocol Amendment 7 (Version 7 dated 14 FEB 2019) 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.

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(Printed Name of Investigator)

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(Signature of Investigator) (Date)

SYNOPSIS

Name of Investigational Product: Epacadostat (INCB024360)	
Title of Study: A Phase 1/2, Open-Label, Safety, Tolerability, and Efficacy Study of Epacadostat in Combination With Pembrolizumab and Chemotherapy in Subjects With Advanced or Metastatic Solid Tumors (ECHO-207/KEYNOTE-723)	
Protocol Number: INCB 24360-207	**Study Phase:** 1/2
Indication: Advanced or metastatic solid tumors (Phase 1); advanced or metastatic colorectal cancer (CRC), pancreatic ductal adenocarcinoma (PDAC), non–small cell lung cancer (NSCLC), urothelial carcinoma (UC), squamous cell carcinoma of the head and neck (SCCHN), or any advanced or metastatic solid tumor that progressed on previous therapy with a programmed cell death protein 1 (PD-1) or programmed cell death ligand 1 (PD-L1) inhibitor (Phase 2)	

Primary Objectives:

- Phase 1: To evaluate the safety, tolerability, and dose-limiting toxicities (DLTs) and to define a maximum tolerated dose (MTD) and/or pharmacologically active dose (PAD) of epacadostat in combination with pembrolizumab and chemotherapy in subjects with advanced or metastatic solid tumors.
- Phase 2: To evaluate the efficacy of epacadostat in combination with pembrolizumab and chemotherapy in subjects with advanced or metastatic CRC, PDAC, NSCLC, UC, SCCHN, or any advanced or metastatic solid tumor who progressed on previous therapy with a PD-1 or PD-L1 inhibitor by assessing objective response rate (ORR) per RECIST v1.1.

Secondary Objectives:

- Phase 1: To explore the efficacy of epacadostat in combination with pembrolizumab and chemotherapy in subjects with advanced or metastatic solid tumors by assessing ORR per RECIST v1.1.
- Phase 2: To further evaluate the safety and tolerability of epacadostat at the MTD and/or PAD in combination with pembrolizumab and chemotherapy in subjects with selected advanced or metastatic solid tumors.

[redacted]

Primary Endpoints:

- Phase 1: Safety and tolerability will be assessed by monitoring frequency, duration, and severity of adverse events (AEs) through physical examinations, by evaluating changes in vital signs and electrocardiograms (ECGs), and through clinical laboratory blood and urine sample evaluations.
- Phase 2: ORR, defined as the percentage of subjects having a complete response (CR) or partial response (PR), will be determined by investigator assessment of radiographic disease per RECIST v1.1.

Secondary Endpoints:

- Phase 1: ORR, defined as the percentage of subjects having a CR or PR, will be determined by investigator assessment of radiographic disease per RECIST v1.1.
- Phase 2: Safety and tolerability will be assessed by monitoring frequency, duration, and severity of AEs through physical examinations, by evaluating changes in vital signs and ECGs, and through clinical laboratory blood and urine sample evaluations.

[redacted]

Overall Study Design:

Note: As of 25 OCT 2018, this study is closed to enrollment. As of this date, no subjects were enrolled in Phase 2 efficacy expansion (all treatment groups) or Phase 2 mandatory biopsy Treatment Groups A, B, F, and G. Any text included in this Protocol synopsis that references these treatment groups and cohorts has not been deleted but should be disregarded.

This is an open-label, nonrandomized, Phase 1/2 study to determine the safety, tolerability, and efficacy of epacadostat when given in combination with pembrolizumab and 7 chemotherapy regimens. Phase 1 will consist of a 3 + 3 + 3 design and will determine the MTD or PAD of epacadostat when given in combination with pembrolizumab and chemotherapy; efficacy will also be explored. Subjects with advanced or metastatic solid tumors who have progressed after receiving at least 1 previous standard therapy for advanced or metastatic disease (or who are intolerant to or refuse standard of care) and for whom treatment with 1 of the chemotherapy regimens is appropriate will be enrolled in Phase 1. Phase 2 will further evaluate the safety, tolerability, and efficacy of the MTD or PAD of epacadostat selected in Phase 1 when given in combination with pembrolizumab and chemotherapy. Subjects with advanced or metastatic CRC, PDAC, NSCLC (squamous or nonsquamous), UC, or SCCHN who have not previously received chemotherapy as first-line therapy for advanced or metastatic disease and have not previously received immune checkpoint inhibitors nor an indoleamine 2,3-dioxygenase (IDO) inhibitor will be enrolled in Phase 2. A separate cohort of subjects with any advanced or metastatic solid tumor who progressed on previous therapy with a PD-1 or PD-L1 inhibitor will also be enrolled in Phase 2.

Phase 1:

A 3 + 3 + 3 design will be used in which 7 treatment groups will be explored in parallel. A minimum of 3 evaluable subjects will be enrolled in each treatment group beginning with Cohort 1 (epacadostat 100 mg twice daily [BID]; starting dose), and the first 3 evaluable subjects will be observed for a minimum of 28 days in the cohorts where mFOLFOX6 or *nab*-paclitaxel/gemcitabine are administered or 21 days for all other chemotherapy regimens. To be considered evaluable for dose tolerability, subjects should meet 1 of the following criteria: 1) received the cohort-specified dose of epacadostat, pembrolizumab, and chemotherapy for at least 80% of planned doses in the DLT observation period

(45 doses epacadostat/2 doses pembrolizumab for subjects who received mFOLFOX6 or *nab*-paclitaxel/gemcitabine; 34 doses epacadostat/1 dose pembrolizumab for subjects who received any other chemotherapy regimens) and completed the DLT observation period **or** 2) had a DLT during the DLT observation period. It is recognized that certain toxicities due to chemotherapy (eg, including but not limited to gastrointestinal toxicity, including diarrhea; renal insufficiency; high-grade laboratory abnormalities; hypersensitivity/rash) may initially be clinically indistinguishable from toxicities due to immunotherapy. Epacadostat will be held for these toxicities, and as a result, subjects may not receive at least 80% of the prescribed dose during Cycle 1. In these cases, the Safety Monitoring Committee (SMC) may assess subjects who receive dose intensities somewhat below 80% for the determination of DLTs, and consider in the adjudication process the specific toxicities encountered, likely cause of toxicities, and dose intensity and tolerability beyond Cycle 1. Additional subjects will be enrolled in a cohort to achieve the minimum of 3 evaluable subjects. Subjects who discontinue for reasons other than a DLT (eg, events clearly associated with the underlying disease, disease progression, concomitant medication, comorbidity, or an AE clearly unrelated to treatment) during the DLT observation period will be considered nonevaluable for DLTs and will be replaced.

The scenarios for expansion and de-escalation and the doses of epacadostat to be evaluated are summarized below:

1. If 0 DLTs occur in 3 subjects in Cohort 1, 3 additional subjects will be treated in Cohort 1. If there is ≤ 1 DLT in these 6 subjects, enrollment in Phase 2 for that treatment group may proceed.
2. If 1 of 3 subjects in Cohort 1 has a DLT, 3 additional subjects will be enrolled in Cohort 1. If there are no additional DLTs (≤ 1 DLT in 6 subjects), enrollment in Phase 2 for that treatment group may proceed.
3. If 2 of 6 subjects in Cohort 1 have a DLT, 3 additional subjects will be enrolled in Cohort 1. If there are no additional DLTs (≤ 2 DLTs in 9 subjects), enrollment in Phase 2 for that treatment group may proceed.
4. If ≥ 2 of 3, 3 of 6, or 3 of 9 subjects have DLTs within a cohort, de-escalation of epacadostat to 50 mg BID (Cohort –1) will be evaluated using the same criteria.

If Cohort –1 is not tolerated within a given treatment group, that treatment group will not be pursued further. The study will be terminated if Cohort –1 is not tolerated in all treatment groups.

Epacadostat Dose Cohort	Epacadostat Dose
–1	50 mg BID
1 (starting dose)	**100 mg BID**[a]

[a] If epacadostat 100 mg BID is not tolerated within a treatment group, epacadostat 50 mg BID will be evaluated.

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

Subjects will be assigned to a treatment group based on the chemotherapy regimen most appropriate for their tumor type as summarized below:

Treatment Group A	**Epacadostat**	**Pembrolizumab**	**mFOLFOX6**
	BID PO continuous daily dosing (see epacadostat dose cohort table)	200 mg IV Q3W	• Oxaliplatin 85 mg/m² IV on Day 1 and Day 15 • Leucovorin 400 mg/m² IV on Day 1 and Day 15 • 5-Fluorouracil 400 mg/m² IV bolus, then 1200 mg/m² per day IV infusion over 46 hours for a total dose of 2400 mg/m², on Day 1 and Day 15
Treatment Group B	**Epacadostat**	**Pembrolizumab**	***nab*-Paclitaxel and Gemcitabine**
	BID PO continuous daily dosing (see epacadostat dose cohort table)	200 mg IV Q3W	• *nab*-Paclitaxel 125 mg/m² IV on Days 1, 8, and 15 • Gemcitabine 1000 mg/m² IV on Days 1, 8, and 15
Treatment Group C	**Epacadostat**	**Pembrolizumab**	**Paclitaxel and Carboplatin**
	BID PO continuous daily dosing (see epacadostat dose cohort table)	200 mg IV Q3W	• Paclitaxel 200 mg/m² IV on Day 1 Q3W • Carboplatin AUC 6 IV on Day 1 Q3W
Treatment Group D	**Epacadostat**	**Pembrolizumab**	**Pemetrexed and Platinum Agent**
	BID PO continuous daily dosing (see epacadostat dose cohort table)	200 mg IV Q3W	• Pemetrexed 500 mg/m² IV on Day 1 Q3W • Investigators choice of platinum agent: Carboplatin AUC 5 IV on Day 1 Q3W or Cisplatin 75 mg/m² on Day 1 Q3W
Treatment Group E	**Epacadostat**	**Pembrolizumab**	**Cyclophosphamide**
	BID PO continuous daily dosing (see epacadostat dose cohort table)	200 mg IV Q3W	50 mg PO once daily
Treatment Group F	**Epacadostat**	**Pembrolizumab**	**Gemcitabine and Platinum Agent**
	BID PO continuous daily dosing (see epacadostat dose cohort table)	200 mg IV Q3W	• Gemcitabine 1000 mg/m² IV on Day 1 and Day 8 Q3W • Investigators choice of platinum agent: Carboplatin AUC 5 IV on Day 1 Q3W or Cisplatin 70 mg/m² on Day 1 Q3W
Treatment Group G	**Epacadostat**	**Pembrolizumab**	**Platinum Agent and 5-Fluorouracil**
	BID PO continuous daily dosing (see epacadostat dose cohort table)	200 mg IV Q3W	Investigator's choice of platinum agent: • Carboplatin AUC 5 IV on Day 1 Q3W or Cisplatin 100 mg/m² IV • 5-Fluorouracil 1000 mg/m² per day IV infusion on Days 1-4 (for a total dose of 4000 mg/m² over 96 hours) Q3W

IV = intravenous; PO = orally; Q3W = every 3 weeks.

Phase 2: Efficacy Expansion and Mandatory Biopsy Cohorts

Phase 2 efficacy expansion cohorts will evaluate the efficacy of the MTD or PAD of epacadostat determined in Phase 1 in combination with pembrolizumab and chemotherapy and further evaluate the safety and tolerability of the combination. The efficacy expansion cohorts will be limited to the following advanced or metastatic tumor types:

1. CRC (Treatment Group A: epacadostat + pembrolizumab + mFOLFOX6): Simon 2-Stage design
2. PDAC (Treatment Group B: epacadostat + pembrolizumab + *nab*-paclitaxel/gemcitabine): Simon 2-Stage design
3. Squamous NSCLC (Treatment Group C: epacadostat + pembrolizumab + paclitaxel/carboplatin)

4. Nonsquamous NSCLC (Treatment Group D: epacadostat + pembrolizumab + pemetrexed/platinum agent)
5. Any solid tumor that progressed on previous therapy with a PD-1 or PD-L1 inhibitor (Treatment Group E: epacadostat + pembrolizumab + cyclophosphamide)
6. UC (Treatment Group F: epacadostat + pembrolizumab+ gemcitabine/platinum agent)
7. SCCHN (Treatment Group G: epacadostat + pembrolizumab+ platinum agent/5-fluorouracil)

Enrollment in a specific efficacy expansion cohort in Phase 2 may begin after a minimum of 6 subjects have been treated with epacadostat 100 mg BID in the corresponding treatment group in Phase 1 and there is ≤ 1 DLT in these 6 subjects.

Continuous evaluation of toxicity events will be performed in the efficacy expansion cohorts. If the cumulative incidence of treatment-related serious AEs (SAEs) is > 40% and/or the cumulative incidence of ≥ Grade 3 immune-related AEs is > 40% after 10 subjects are enrolled in a specific Phase 2 efficacy expansion cohort, further enrollment in that cohort will be interrupted until the sponsor, investigators, and health authorities (if applicable) determine an appropriate course of action. If an efficacy expansion cohort is discontinued due to toxicity, a new cohort may be initiated at a lower dose of epacadostat.

In addition to the efficacy expansion cohorts listed above, separate mandatory biopsy cohorts will be enrolled to evaluate changes in the tumor microenvironment. For the cohorts where IV chemotherapy is administered, subjects will receive IV chemotherapy only during Cycle 1 followed by epacadostat + pembrolizumab + IV chemotherapy starting with Cycle 2 Day 1. For the CRC and PDAC cohorts, a minimum of 10 subjects with evaluable paired biopsy specimens will be enrolled. A fresh tumor biopsy will be collected during screening. On-treatment biopsies are mandatory and will be collected between Days 21 and 27 of Cycle 1 (IV chemotherapy only) and Cycle 2 (epacadostat + pembrolizumab + IV chemotherapy). For subjects with squamous NSCLC, nonsquamous NSCLC, UC, or SCCHN, a minimum of 10 subjects with evaluable paired biopsy specimens will be enrolled. A fresh tumor biopsy will be collected during screening. On-treatment biopsies are mandatory and will be collected between Days 14 and 20 of Cycle 1 (IV chemotherapy only) and Days 7 and 13 of Cycle 3 (epacadostat + pembrolizumab + IV chemotherapy). For subjects with any advanced or metastatic solid tumor that progressed on previous therapy with a PD-1 or PD-L1 inhibitor, a minimum of 5 subjects with evaluable paired biopsy specimens will be enrolled in the mandatory biopsy cohort; however, this cohort will be administered epacadostat, cyclophosphamide, and pembrolizumab starting on Cycle 1 Day 1. A fresh tumor biopsy will be collected during screening, and an on-treatment biopsy is mandatory and will be collected between Days 7 and 13 of Cycle 3.

If a subject is selected for inclusion in the mandatory biopsy cohort, and it is subsequently determined that tumor tissue cannot safely be obtained, or the biopsy does not meet the minimum standards for evaluation (as outlined in the Laboratory Manual), the subject may still enroll in the mandatory biopsy cohort and will be followed for efficacy and safety. The subject may be replaced in order to enroll sufficient numbers of subjects with paired biopsies.

Note: As of 25 OCT 2018, on-treatment tumor biopsies are no longer required for subjects who are already enrolled in the mandatory biopsy cohorts.

Study Population:

Phase 1: Subjects with histologically or cytologically confirmed advanced or metastatic solid tumors who have failed previous standard therapy (or who refuse or are intolerant to standard-of-care therapy).

Phase 2: Subjects with histologically or cytologically confirmed advanced or metastatic CRC, PDAC, squamous NSCLC, nonsquamous NSCLC, UC, SCCHN who have not received first-line therapy for advanced or metastatic disease; subjects with any advanced or metastatic solid tumor with confirmed progression on previous therapy with a PD-1 or PD-L1 inhibitor.

Key Inclusion Criteria:

- Men or women aged 18 years or older.
- Presence of measurable disease per RECIST v1.1. Tumor lesions located in a previously irradiated area, or in an area subjected to other loco-regional therapy, are considered measureable if progression has been demonstrated in the lesion.
- ECOG performance status of 0 or 1.
- Willing to avoid pregnancy or fathering children from screening through 120 days after the last dose of epacadostat and pembrolizumab based on criteria defined in the body of the Protocol.

Phase 1 subjects only:

- Subjects with locally advanced or metastatic solid tumors who have disease progression after treatment with available therapies that are known to confer clinical benefit, or who are intolerant to treatment, or subjects who refuse standard treatment. Locally advanced disease must not be amenable to resection with curative intent.

  Note: Subjects should not have received more than 2 previous therapies for advanced or metastatic disease. Subjects who received more than 2 previous therapies for advanced or metastatic disease must be discussed with medical monitor to confirm eligibility.
- Subjects must not have received therapy with an IDO inhibitor.

Phase 2 CRC subjects only:

- Histologically or cytologically confirmed advanced or metastatic adenocarcinoma of the colon or rectum.
- Subjects must not have received previous chemotherapy as first-line therapy for advanced or metastatic disease.

  Note: Subjects who completed a chemotherapy regimen as adjuvant, neoadjuvant, or part of a course of chemoradiation therapy and progressed ≥ 6 months after completing therapy will be eligible. If progression occurred < 6 months after completing therapy, the subject will not be eligible.
- Subjects must not have received previous immune checkpoint inhibitors (eg, cytotoxic T-lymphocyte–associated protein 4 [CTLA-4] inhibitor, PD-1 inhibitor, PD-L1 inhibitor, or any other antibody or drug specifically targeting T-cell costimulation), and/or an IDO inhibitor. Subjects who received other immunotherapies must be discussed with medical monitor to confirm eligibility.

Phase 2 PDAC subjects only:

- Histologically or cytologically confirmed advanced or metastatic PDAC.
- Subjects must not have received previous chemotherapy as first-line therapy for advanced or metastatic disease.
  Note: Subjects who completed a chemotherapy regimen as adjuvant, neoadjuvant, or part of a course of chemoradiation therapy and progressed ≥ 6 months after completing therapy will be eligible. If progression occurred < 6 months after completing therapy, the subject will not be eligible.
- Subjects must not have received previous immune checkpoint inhibitors (eg, CTLA-4 inhibitor, PD-1 inhibitor, PD-L1 inhibitor, or any other antibody or drug specifically targeting T-cell costimulation), and/or an IDO inhibitor. Subjects who received other immunotherapies must be discussed with medical monitor to confirm eligibility.

Phase 2 squamous or nonsquamous NSCLC subjects only:

- Histologically or cytologically confirmed Stage IIIB, Stage IV, or recurrent squamous or nonsquamous NSCLC.
- Subjects without driver mutations (eg, BRAF or epidermal growth factor receptor [EGFR] mutations, anaplastic lymphoma kinase (ALK) fusion oncogene or ROS1 rearrangements) must not have received previous chemotherapy as first-line therapy for Stage IIIB, Stage IV, or recurrent NSCLC.
  Note: Subjects who completed a chemotherapy regimen as adjuvant, neoadjuvant, or part of a course of chemoradiation therapy and progressed ≥ 6 months after completing therapy will be eligible. If progression occurred < 6 months after completing therapy, the subject will not be eligible.
- Subjects with driver mutations (eg, BRAF or EGFR mutations, ALK fusion oncogene or ROS1 rearrangements) must have received prior treatment only with an approved kinase inhibitor with subsequent disease progression.
- Subjects must not have received previous immune checkpoint inhibitors (eg, CTLA-4 inhibitor, PD-1 inhibitor, PD-L1 inhibitor, or any other antibody or drug specifically targeting T-cell costimulation), and/or an IDO inhibitor. Subjects who received other immunotherapies must be discussed with medical monitor to confirm eligibility.

Phase 2 subjects in the cohort of subjects with any solid tumor that progressed on previous therapy with a PD-1 or PD-L1 inhibitor only:

- Histologically or cytologically confirmed advanced or metastatic solid tumors that progressed (primary refractory or secondary relapsed) on previous monotherapy with a PD-1 or PD-L1 inhibitor or previous combination therapy that included a PD-1 or PD-L1 inhibitor in the advanced or metastatic setting.
  Note: Primary refractory subjects must have received at least 2 doses of PD-1 or PD-L1 inhibitor and have disease progression at least 8 weeks from the first dose of the PD-1 or PD-L1 inhibitor that is confirmed at least 4 weeks (no less than 28 days) later (confirmatory imaging may be performed during the screening period with medical monitor approval). The PD-1 or PD-L1 inhibitor does not need to be the last treatment received before signing informed consent. Subjects who received only 1 dose of the PD-1 or PD-L1 inhibitor or discontinued for toxicity without disease progression within 8 weeks of the first dose of the PD-1 or PD-L1 inhibitor are not eligible.
  Note: Secondary relapsed subjects must have had a PR or CR while on treatment with a PD-1 or PD-L1 inhibitor but later had disease progression that is confirmed at least 4 weeks (no less than 28 days) later. The PD-1 or PD-L1 inhibitor does not need to have been the last treatment received before signing informed consent.
- Subjects must not have received previous therapy with an IDO inhibitor.
- Subjects who received immunotherapies other than a PD-1 or PD-L1 inhibitor must be discussed with medical monitor to confirm eligibility.
- Subjects may have received previous chemotherapy for advanced or metastatic disease.
  Note: There is no limit to the number of previous chemotherapy regimens.

Phase 2 subjects in the mandatory biopsy cohort only:

- Willing to undergo pretreatment and on-treatment core or excisional tumor biopsies.
  Note: Fresh baseline tumor biopsies (defined as a biopsy specimen taken since completion of the most recent prior systemic regimen) are required for all Phase 2 mandatory biopsy subjects.

Phase 2 efficacy expansion subjects only:

- Willing to undergo pretreatment core or excisional tumor biopsies.
  Note: Fresh baseline tumor biopsies (defined as a biopsy specimen taken since completion of the most recent prior systemic regimen) are preferred. If a subject has inaccessible lesions, subject may be enrolled with medical monitor approval. In this case submission of archived tumor tissue may be acceptable. In all cases, biopsies will be confirmed to contain adequate tumor tissue by a local pathology review.

Phase 2 UC subjects only:

- Have histologically or cytologically confirmed advanced/unresectable (inoperable) or metastatic urothelial cancer of the renal pelvis, ureter, bladder, or urethra. Both transitional cell and mixed transitional/non-transitional (predominantly transitional) cell histologies are allowed.
- Subjects must not have received previous chemotherapy as first-line therapy for advanced or metastatic disease.
  Note: Adjuvant platinum-based chemotherapy, following radical cystectomy, with recurrence > 12 months from completion of therapy is permitted. Neoadjuvant platinum-based chemotherapy, with recurrence > 12 months since completion of therapy is permitted.
- Subjects must not have received previous immune checkpoint inhibitors (eg, CTLA-4 inhibitor, PD-1 inhibitor, PD-L1 inhibitor, or any other antibody or drug specifically targeting T-cell costimulation), and/or an IDO inhibitor. Subjects who received other immunotherapies must be discussed with medical monitor to confirm eligibility.

Phase 2 SCCHN subjects only:

- Histologically or cytologically-confirmed recurrent or metastatic SCCHN of the oral cavity, oropharynx, hypopharynx, and larynx that is considered incurable by local therapies.
  Note: Subjects with primary tumors of the nasopharynx, salivary gland, unknown primary origin, or nonsquamous histologies are not eligible.
- Documentation of results from testing of human papilloma virus (HPV) status for oropharyngeal cancer using p16 IHC testing.
  Note: Subjects with primary tumor site of the oral cavity, hypopharynx, and larynx are not required to undergo HPV testing by p16 IHC as these tumor locations are assumed to be HPV negative.
- Subjects must not have received previous chemotherapy as first-line therapy for recurrent or metastatic disease.
  Note: Systemic therapy completed > 6 months before signing consent if given as part of multimodal treatment for locally advanced disease is allowed.
- Subjects must not have received previous immune checkpoint inhibitors (eg, CTLA-4 inhibitor, PD-1 inhibitor, PD-L1 inhibitor, or any other antibody or drug specifically targeting T-cell costimulation), and/or an IDO inhibitor. Subjects who received other immunotherapies must be discussed with medical monitor to confirm eligibility.

Key Exclusion Criteria:

- Laboratory and medical history parameters not within the Protocol-defined range. If the screening laboratory tests below were conducted > 7 days before treatment initiation, they will need to be repeated on Cycle 1 Day 1 before initiation of treatment.
  - Absolute neutrophil count < 1.5×10^9/L.
  - Platelet count < 100×10^9/L.

- Hemoglobin < 9 g/dL or < 5.6 mmol/L.
- 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 creatinine clearance) < 50 mL/min for subjects with creatinine levels > 1.5 × institutional ULN.
- Aspartate aminotransferase, alanine aminotransferase (ALT), and alkaline phosphatase ≥ 2.5 × ULN.
  Note: Subjects with 1) bone metastases and 2) no hepatic parenchymal metastases on screening radiographic examinations may enroll if the alkaline phosphatase is ≤ 5 × ULN. Subjects with 1) bone metastases and 2) hepatic parenchymal metastases on screening radiographic examinations may enroll if the alkaline phosphatase is ≤ 5 × ULN only with medical monitor approval.
- Total bilirubin ≥ 1.2 × ULN.
  Note: If total bilirubin is ≥ 1.2 × ULN, conjugated (direct) bilirubin must be tested, and subjects will be excluded if the value is ≥ 2.0 × ULN or ≥ 40% of total bilirubin, if there is no institutional ULN.
- International normalized ratio (INR), prothrombin time, and activated partial thromboplastin time (aPTT) > 1.5 × ULN (unless the subject is receiving anticoagulant therapy, in which case the subject may be included as long as the INR, prothrombin time, and aPTT are within therapeutic range of intended use of anticoagulants).
  Note: Partial thromboplastin time may be used in place of aPTT per institutional standards.

- Receipt of anticancer medications or investigational drugs within the following intervals before Cycle 1 Day 1:
  - ≤ 14 days for chemotherapy or targeted small molecule therapy.
    Note: Bisphosphonates are permitted concomitant medications.
  - ≤ 28 days for previous monoclonal antibody used for anticancer therapy.
    Note: Use of denosumab is permitted.
  - ≤ 7 days for immune-suppressive–based treatment for any reason.
    Note: Use of inhaled or topical steroids, prophylactic corticosteroids for radiographic procedures, or systemic corticosteroid at doses of prednisone ≤10 mg/day or equivalent is permitted.
  - ≤ 28 days or 5 half-lives (whichever is longer) before Cycle 1 Day 1 for all other investigational agents or devices. For investigational agents with long half-lives (eg, > 5 days), enrollment before the fifth half-life requires medical monitor approval.
- Previous radiotherapy within 14 days of Cycle 1 Day 1 (except for radiation to the central nervous system [CNS], which requires a ≥ 28-day washout as described below). Subjects must also not require chronic use of corticosteroids and must not have had radiation pneumonitis as a result of treatment. A 1-week washout is permitted for palliative radiation to non–CNS disease with sponsor approval.
- Known active CNS metastases and/or carcinomatous meningitis.
  Note: Participants with previously-treated brain metastases may participate provided they are 1) radiologically stable (ie, without evidence of progression for at least 28 days by repeat imaging prior to the first dose of study treatment [repeat imaging may be performed during the screening period with medical monitor approval]), **and** 2) without requirement of steroid treatment for at least 14 days prior to first dose of study treatment, **and** 3) clinically stable, with any neurological signs or symptoms having returned to baseline. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.
  Note: Subjects with evidence of cerebral edema or those with < 28 days since radiation therapy to the CNS will be excluded from study.
- Has not recovered to ≤ Grade 1 from toxic effects of previous therapy and/or complications from previous surgical intervention before starting study therapy.
  Note: Subjects with stable chronic AEs (≤ Grade 2) not expected to resolve (eg, alopecia) are exceptions and may enroll.
  Note: Subjects with a history of peripheral neuropathy ≥ Grade 2 will be excluded.

- Receipt of a live vaccine within 30 days of planned start of study therapy.
  Note: Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox/zoster, yellow fever, rabies, Bacillus Calmette-Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines are live attenuated vaccines and are not allowed.
- Active infection requiring systemic therapy.
- Subjects who have any active or inactive autoimmune disease or syndrome (ie, rheumatoid arthritis, moderate or severe psoriasis, multiple sclerosis, inflammatory bowel disease) that has required systemic treatment in the past 2 years or who are receiving systemic therapy for an autoimmune or inflammatory disease (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs).
  Note: Exceptions include subjects with vitiligo or resolved childhood asthma/atopy, hypothyroidism stable on hormone replacement, controlled asthma, Type I diabetes, Graves' disease, or Hashimoto's disease, or with medical monitor approval.
- History of (noninfectious) pneumonitis that required steroids or current pneumonitis or interstitial lung disease.
- History of 1) allogeneic stem cell or solid organ transplant that requires use of immunosuppressive therapy, 2) has a diagnosis of immunodeficiency, or 3) is receiving chronic systemic steroid therapy (in doses exceeding 10 mg daily of prednisone or its equivalent) or any other form of immunosuppressive therapy within 7 days before Cycle 1 Day 1.
  Note: The use of physiologic doses of corticosteroids may be approved after consultation with the sponsor.
- Known history of or screening test is positive for hepatitis B virus (HBV; eg, HBsAg reactive or HBV DNA detected) or hepatitis C virus (HCV; 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.
  Note: For Phase 2, treated hepatitis B subjects are eligible if there is no evidence of active infection (HBV DNA–negative and HBV DNA surface antigen–negative).
- Known history of human immunodeficiency virus (HIV; HIV 1/2 antibodies).
- History or presence of an ECG that, in the investigator's opinion, is clinically meaningful. Screening QTc interval > 480 milliseconds is excluded (corrected by Fridericia method). In the event that a single QTc is > 480 milliseconds, the subject may enroll if the average QTc for the 3 ECGs is < 480 milliseconds. For subjects with an intraventricular conduction delay (QRS interval > 120 milliseconds), the JTc interval may be used in place of the QTc with sponsor approval. The JTc must be ≤ 340 milliseconds if JTc is used in place of the QTc. Subjects with left bundle branch block are excluded.
  Note: QTc prolongation due to pacemaker may enroll if the JTc is normal or with medical monitor approval.
- Clinically significant cardiac disease, including unstable angina, acute myocardial infarction within 6 months of Cycle 1 Day 1, New York Heart Association Class III or IV congestive heart failure, and arrhythmia requiring therapy.
  Note: A subject with an arrhythmia may enroll if the subject is on antiarrhythmic medication and is in sinus rhythm on the screening ECG.
- Subjects with a history of bleeding related to cancer under study requiring a medical intervention (eg, embolization procedure, RBC transfusion, or hospitalization) within 30 days of study enrollment.
- Known allergy or severe hypersensitivity (≥ Grade 3) reaction to any component of epacadostat, pembrolizumab, or chemotherapy regimen components and/or their formulation excipients.

- Presence of a gastrointestinal condition (eg, inflammatory bowel disease, Crohn's disease, ulcerative colitis) that may affect drug absorption.

  Note: Subjects with feeding tubes are eligible.
- Receiving monoamine oxidase inhibitors (MAOIs) or drug that has significant MAOI activity (eg, meperidine, linezolid, methylene blue) within the 21 days before screening.
- Women who are pregnant or breastfeeding.

Phase 1 and 2 subjects in Treatment Group A and Treatment Group G only:

- Known dihydropyrimidine dehydrogenase deficiency (heterozygous or homozygous mutations).

Phase 2 subjects in the cohort of subjects with any solid tumor that progressed on previous therapy with a PD-1 or PD-L1 inhibitor only:

- History of any grade immune-related ocular AEs.
- History of a ≥ Grade 3 immune-related AE from previous immunotherapies.

  Note: Subjects with immune-related adrenal insufficiency because of previous immunotherapy who are medically stable and adequately managed on a stable dose of replacement therapy may be enrolled.
- Current urinary outflow obstruction.

Epacadostat, Dosage, and Mode of Administration:

In Phase 1, the dose of epacadostat will be dependent upon cohort assignment. In Phase 2, the dose of epacadostat will be dependent upon the MTD or PAD determined in Phase 1. Intrasubject dose-escalation is not permitted.

Epacadostat will be self-administered orally BID in 28- or 21-day cycles depending on the chemotherapy administered and will continue through the end of the cycle in which the 35th infusion of pembrolizumab is administered if, in the investigator's judgment, the subject is receiving benefit from therapy and has not met any criteria for treatment discontinuation. For Phase 1 and Phase 2 efficacy expansion subjects enrolled in Treatment Groups A, B, C, D, E, F, and G, and for Phase 2 mandatory biopsy subjects enrolled in Treatment Group E, epacadostat will be administered beginning on Cycle 1 Day 1 and continuously thereafter. For Phase 2 subjects enrolled in the mandatory biopsy cohorts where IV chemotherapy is administered (Treatment Groups A, B, C, D, F, and G), epacadostat will be administered beginning on Cycle 2 Day 1 and continuously thereafter. All BID doses will be taken in the morning and evening, approximately 12 hours apart without regard to food. If a dose is missed by more than 4 hours, then that dose should be skipped, and the next dose should be taken at the next scheduled timepoint.

Background Therapy, Dosage, and Mode of Administration:

Subjects will receive pembrolizumab and the assigned chemotherapy regimen as noted below. Intrasubject dose escalation of pembrolizumab or chemotherapy is not allowed.

Pembrolizumab will be administered as a 200 mg IV infusion over 30 minutes (-5 min/+10 min) every 3 weeks for a total of 35 infusions if, in the investigator's judgment, the subject is receiving benefit from therapy and has not met any criteria for treatment discontinuation. For Phase 1 and Phase 2 efficacy expansion subjects enrolled in Treatment Groups A, B, C, D, E, F, and G, and for Phase 2 mandatory biopsy subjects enrolled in Treatment Group E, pembrolizumab will be administered starting on Cycle 1 Day 1. For Phase 2 subjects enrolled in the mandatory biopsy cohorts where IV chemotherapy is administered (Treatment Groups A, B, C, D, F, and G), pembrolizumab will be administered starting on Cycle 2 Day 1.

Oxaliplatin, leucovorin, and 5-fluorouracil (mFOLFOX6) will be administered on Days 1 and 15 of each 28-day cycle. Subjects will receive oxaliplatin 85 mg/m² IV given concurrently with leucovorin 400 mg/m² IV over 2 hours (± 15 min; or equivalent dose and schedule based on institutional practice), followed by 5-fluorouracil 400 mg/m² IV bolus (administration time per institutional practice), then a 5-fluorouracil 1200 mg/m² per day IV infusion over 46 hours (for a total dose of 2400 mg/m²). There is no limit to the number of cycles of mFOLFOX6. Investigators may reduce or discontinue oxaliplatin for peripheral neuropathy; if discontinued, investigators have the option to discontinue 5-fluorouracil and leucovorin. Subjects may receive prophylactic granulocyte colony stimulating factor (G-CSF) support with filgrastim per institutional guidelines. Prophylactic G-CSF should not be given in the first cycle unless discussed with the medical monitor.

***nab*-Paclitaxel and Gemcitabine** will be administered on Days 1, 8, and 15 of each 28-day cycle. *nab*-Paclitaxel will be administered at 125 mg/m² IV over 30 minutes (± 5 min). Gemcitabine will be administered at 1000 mg/m² IV over 30 minutes (± 5 min). There is no limit to the number of cycles of *nab*-paclitaxel/gemcitabine. Subjects may receive prophylactic G-CSF support with filgrastim per institutional guidelines. Prophylactic G-CSF should not be given in the first cycle unless discussed with the medical monitor.

Paclitaxel and Carboplatin will be administered on Day 1 of each 21-day cycle for a minimum of 4 cycles and a maximum of 6 cycles. Paclitaxel will be administered at 200 mg/m² IV over 3 hours (± 15 min). Carboplatin will be administered at AUC 6 IV over 30 minutes (± 5 min). Subjects must receive premedications (IV or PO) with corticosteroids, H1- and H2-antagonists, and antiemetics based on institutional guidelines, investigator practice, or local prescribing information or standards of care. Subjects may receive prophylactic G-CSF support with filgrastim per institutional guidelines. Prophylactic G-CSF should not be given in the first cycle unless discussed with the medical monitor.

Pemetrexed and platinum agent will be administered on Day 1 of each 21-day cycle for a minimum of 4 cycles and a maximum of 6 cycles. Pemetrexed will be administered at 500 mg/m² IV over 10 minutes (± 5 min). Pemetrexed may continue as maintenance therapy after the 6 cycles. Investigators will have a choice of platinum agent: carboplatin, which will be administered at AUC 5 IV over 30 minutes (± 5 min), or cisplatin, which will be administered at 75 mg/m^2 over 2 hours (± 5 min). Subjects must receive premedications (IV or PO) with corticosteroids, antiemetics, and vitamin B12 and folic acid supplementation based on institutional guidelines, investigator practice, or local prescribing information or standards of care. Subjects receiving cisplatin must also receive hydration as per institutional guidelines. Subjects may receive prophylactic G-CSF support with filgrastim per institutional guidelines. Prophylactic G-CSF should not be given in the first cycle unless discussed with the medical monitor.

Cyclophosphamide will be self-administered 50 mg PO once daily beginning on Cycle 1 Day 1 and continuously thereafter in 21-day cycles. There is no limit to the number of cycles of cyclophosphamide. Subjects may receive prophylactic G-CSF support with filgrastim per institutional guidelines. Prophylactic G-CSF should not be given in the first cycle unless discussed with the medical monitor.

Gemcitabine and platinum agent will be administered in a 21-day cycle for a maximum of 6 cycles. Gemcitabine will be administered at 1000 mg/m² IV over 30 minutes (± 5 min) on Days 1 and 8. Investigators will have a choice of platinum agent to follow the gemcitabine infusion on Day 1: carboplatin, which will be administered at AUC 5 IV over 30 minutes (± 5 min), or cisplatin, which will be administered at 70 mg/m^2 over 2 hours (± 5 min). Subjects must receive premedications (IV or PO) with corticosteroids and antiemetics based on institutional guidelines, investigator practice, or local prescribing information or standards of care. Subjects receiving cisplatin must also receive hydration as per institutional guidelines. Subjects may receive prophylactic G-CSF support with filgrastim per institutional guidelines. Prophylactic G-CSF should not be given in the first cycle unless discussed with the medical monitor.

Platinum agent and 5-fluorouracil will be administered in a 21-day cycle for a maximum of 6 cycles. Investigators will have a choice of platinum agent: carboplatin, which will be administered at AUC 5 IV over 30 minutes (± 5 min), or cisplatin, which will be administered at 100 mg/m^2 over 60 minutes (± 5 min) on Day 1. The platinum agent will be followed by 5-fluorouracil 1000 mg/m^2 per day IV infusion over Days 1 through 4 (for a total dose of 4000 mg/m^2 over 96 hours). Subjects must receive premedications (IV or PO) with corticosteroids and antiemetics based on institutional guidelines, investigator practice, or local prescribing information or standards of care. Subjects receiving cisplatin must also receive hydration as per institutional guidelines. Subjects may receive prophylactic G-CSF support with filgrastim per institutional guidelines. Prophylactic G-CSF should not be given in the first cycle unless discussed with the medical monitor.

Study Schedule/Procedures:

The study comprises the following parts:

- **Screening:** Up to 28 days before enrollment. Screening will begin at the time that the subject signs the informed consent and will continue until the date the subject is enrolled in the study received the first dose of treatment in the study (Cycle 1 Day 1).
- **Treatment:** Begins on the day that the subject receives the first dose of treatment in the study on Cycle 1 Day 1 and may continue in 28-day cycles (mFOLFOX6 or *nab*-paclitaxel/gemcitabine) or 21-day cycles (all other chemotherapy regimens); additional site visits will occur during each cycle. Subjects will have regularly scheduled study visits on Day 1 (± 3 days) of each cycle. Additional study visits may be required during some cycles for safety, efficacy, [redacted] assessments as described below.
- **End of treatment:** Occurs when the subject permanently discontinues epacadostat and pembrolizumab (+ 7 days).
- **Safety follow-up:** 30 days (± 7 days) and 90 days (± 7 days) after the EOT visit.

Note: As of Amendment 7, disease status (if applicable) and survival follow-up visits are no longer required. The last study visit will be the 90-day safety follow-up visit.

Safety Assessments

NOTE: As of Amendment 7, the only safety data that will be collected will be related to SAEs and AEs leading to discontinuation of treatment. All safety procedures should be per standard of care for pembrolizumab and will not be collected in the database. Therefore, only safety labs required for pembrolizumab should be conducted at each cycle. No other assessments outside of standard of care are required.

Regular telephone conferences with study investigators will be scheduled by the sponsor in order to review cohort-specific data and overall safety data, agree on dose de-escalation, adjudicate individual high-grade AEs as potentially dose-limiting, and guide other major study decisions during Phase 1 and until the last subject has been treated for 3 months.

Efficacy Assessments

NOTE: As of Amendment 7, no further efficacy assessment will be required beyond Week 18. Imaging for the study will only be required at Week 9 and Week 18 per RECIST v1.1. Imaging should continue per standard of care for pembrolizumab after Week 18. If the subject has radiographic progression, they may have the option to continue treatment until confirmation of progression at least 4 weeks later (but no later than 6 weeks) where feasible, provided that the subject meets the definition of clinical stability defined as follows:

- Absence of clinically significant signs and symptoms (including worsening of laboratory values) indicating disease progression.
- No decline in ECOG performance status.

- Absence of rapid progression of disease.
- Absence of progressive tumors at critical anatomical sites (eg, spinal cord compression) requiring urgent alternative medical intervention.

[redacted]

Estimated Duration of Participation:

Up to 28 days for screening, continuous treatment in consecutive 28-day (mFOLFOX6 and *nab*-paclitaxel/gemcitabine) or 21-day cycles (all other chemotherapy regimens) as long as subjects are receiving benefit and do not met any criteria for discontinuation of epacadostat and pembrolizumab, and 30 and 90 days for safety follow-up. Study participation, including post-treatment follow-up, is expected to average 16 months for an individual subject.

Estimated Number of Subjects: Up to 421 subjects may be enrolled in the study.

Phase 1 – Approximately 42 to 126 evaluable subjects

Phase 2 (Efficacy Expansion + Mandatory Biopsy) – Approximately 237 to 295 evaluable subjects.

As of 25 OCT 2018, this study is closed to enrollment.

A total of 70 subjects have been enrolled. No subjects were enrolled in Phase 2 efficacy expansion (all treatment groups) or Phase 2 mandatory biopsy Treatment Groups A, B, F, and G.

Estimated Number of Study Sites: Approximately 25 sites

Principal Coordinating Investigator: [redacted], MD, [redacted]

Statistical Methods:

As of 25 OCT 2018, no subjects were enrolled in Phase 2 efficacy expansion (all treatment groups) or Phase 2 mandatory biopsy Treatment Groups A, B, F, and G. Any text included in this Protocol synopsis that references these treatment groups and cohorts has not been deleted but should be disregarded.

This is an open-label, nonrandomized, 7-parallel treatment group, Phase 1/2 study. Phase 1 consists of a 3 + 3 + 3 design for each of the 7 treatment groups. A minimum of 6 and up to 9 subjects will be enrolled in each dose level. The total number of subjects for Phase 1 will depend on the frequency of DLTs and the number of dose levels tested before the MTD or PAD is reached.

Phase 2 consists of expansion cohorts (efficacy and mandatory biopsy) in specific tumor types (advanced or metastatic CRC, PDAC, squamous or nonsquamous NSCLC, UC, SCCHN, or any advanced or metastatic solid tumor that progressed on previous therapy with a PD-1 or PD-L1 inhibitor). A Simon 2-stage design will be used for the CRC and PDAC efficacy expansion cohorts. A single-stage design will be used for all other efficacy expansion cohorts. The response rates for the historical control (p_0), desired response rates for the combination (p_1), number of subjects needed in Stage 1 (n_1) and Stage 2 (n_2), total number of subjects (n), first-stage threshold declaring cohort undesirable (r_1), and the upper-limit of the number of responses in n subjects such that futility of the drug is concluded (r) are provided for each expansion cohort in the table below.

Values for the CRC, PDAC, squamous NSCLC, and nonsquamous NSCLC, UC, and SCCHN efficacy expansion cohorts are calculated based on a 1-sided Type I error of 0.1 and power of 80%; values for the cohort enrolling solid tumors that progressed on prior PD-1/PD-L1 therapy are based on a 1-sided Type I error of 0.1 and power of approximately 98%.

Tumor Type	p_0	p_1	n_1	n_2	n	r_1	r
CRC	40%	60%	12	26	38	5	18
PDAC	25%	45%	15	12	27	4	9
Squamous NSCLC	30%	50%	-	-	33	-	13
Nonsquamous NSCLC	50%	70%	-	-	33	-	20
Solid tumors that progressed on previous therapy with a PD-1 or PD-L1 inhibitor	5%	25%	-	-	33	-	3
UC	60%	80%	-	-	33	-	23
SCCHN	50%	70%	-	-	33	-	20

In addition to the efficacy expansion cohorts listed above, separate mandatory biopsy cohorts will be enrolled to evaluate changes in the tumor microenvironment. Assuming the true rate of subjects positive for the biomarker is 50%, the probability of observing ≥ 4 subjects out of 10 with the biomarker is 83% for CRC, PDAC, squamous NSCLC, nonsquamous NSCLC, UC, and SCCHN cohorts, and the probability of observing ≥ 2 subjects out of 5 with the biomarker is 81% for previous PD-1 or PD-L1 inhibitor therapy cohort.

All statistical analyses are exploratory in nature. Descriptive statistics will be derived where appropriate. Continuous endpoints will be summarized with number of subjects, mean, standard deviation, minimum, median, and maximum for each cohort. Categorical endpoints will be summarized with frequency and percentage for each cohort. If data warrants, ORR will be estimated with 95% exact confidence interval.

Safety Monitoring Committee:

Due to the complexity of the study, an SMC will review safety data at regular intervals throughout the study. Details regarding membership, roles, and responsibilities of the committee are specified in the SMC charter.

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

Abbreviation	Definition
AE	adverse event
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
[redacted]	[redacted]
BCG	Bacillus Calmette-Guérin
BID	twice daily
CFR	Code of Federal Regulations
CI	confidence interval
[redacted]	[redacted]
[redacted]	[redacted]
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte–associated protein 4
DC	dendritic cells
DCR	disease control rate
DLT	dose-limiting toxicities
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
eIB	epacadostat Investigator's Brochure
EOS	end of study

Abbreviation	Definition
EOT	end of treatment
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin embedded
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HPV	human papilloma virus
HR	hazard ratio
ICD	immunogenic cell death
ICF	informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDO	indoleamine 2,3-dioxygenase
IDO1	indoleamine 2,3-dioxygenase 1
IEC	independent ethics committee
IN	Investigator Notification
INR	international normalized ratio
irAE	immune-related adverse event
IRB	institutional review board
irRC	immune-related response criteria
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
IV	intravenous
IRT	interactive response technology
LFT	liver chemistry test
mAb	monoclonal antibody
MAOI	monoamine oxidase inhibitors
M-CAVI	methotrexate, carboplatin, vinblastine
MedDRA	Medical Dictionary for Regulatory Activities
mFOLFOX6	5-fluorouracil, leucovorin, and oxaliplatin
MRI	magnetic resonance imaging
MSI	microsatellite-instability
MTD	maximum tolerated dose
MVAC	methotrexate, vinblastine, doxorubicin, and cisplatin
NSCLC	non–small cell lung cancer

Abbreviation	Definition
ORR	objective response rate
OS	overall survival
PAD	pharmacologically active dose
PD	progressive disease
PD-1	programmed cell death protein 1
PDAC	pancreatic ductal adenocarcinoma
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PI	prescribing information
pIB	pembrolizumab Investigator's Brochure
PK	pharmacokinetic
PO	orally
PR	partial response
PT-DC	platinum-based doublet chemotherapy
Q3W	every 3 weeks
RBC	red blood cell
RCC	renal cell carcinoma
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
SMC	Safety Monitoring Committee
SmPC	summary of product characteristics
SNRI	serotonin/norepinephrine reuptake inhibitor
SS	serotonin syndrome
SSRI	selective serotonin reuptake inhibitor
T1DM	Type 1 diabetes mellitus
TKI	tyrosine kinase inhibitor
TNBC	triple-negative breast cancer
Treg	regulatory T cells
UC	urothelial carcinoma
ULN	upper limit of normal

1. INTRODUCTION

1.1. Role of the Immune System in Cancer

Targeting the immune system is a proven and effective approach for the treatment of cancer, and immunotherapy is now an accepted standard of care in several tumor types. The blocking of immune cell coinhibitory receptors such as cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) by ipilimumab, programmed cell death protein 1 (PD-1) by pembrolizumab or nivolumab, and programmed cell death ligand 1 (PD-L1) by atezolizumab, avelumab, or durvalumab provide a critical mechanism for redirecting the host immune response against the tumor (Chen and Mellman 2013). Although these agents have antitumor activity when administered as monotherapy, multiple immune inhibitory mechanisms are present concurrently within the tumor microenvironment, suggesting that combination therapies may be required for optimal therapeutic effect (Quezada and Peggs 2013).

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

Recent interest has focused on the role of indoleamine 2,3-dioxygenase 1 (IDO1) as a mechanism of induction of tolerance to 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 catabolic pathways of tryptophan.

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

IDO1-driven oxidation of tryptophan results in a strong inhibitory effect on the development of T-cell–mediated responses by blocking T-cell activation and inducing T-cell apoptosis (Mellor et al 2003). Both the reduction in local tryptophan levels and the production of tryptophan catabolites that are inhibitory to cell proliferation contribute to the immunosuppressive effects (Frumento et al 2002) such as dendritic cell maturation and T-cell growth arrest and cell death (Mellor and Munn 1999). IDO1 activity also promotes the differentiation of naive T cells to cells with a regulatory phenotype (Treg; Fallarino et al 2006). Because increased Treg activity has been shown to promote tumor growth and Treg depletion has been shown to allow an otherwise ineffectual antitumor immune response to occur (Zou 2006), IDO1 expansion of Treg may provide an additional mechanism whereby IDO1 could promote an immunosuppressive environment.

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

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

Based on studies examining serum levels of tryptophan and kynurenine, IDO1 appears to be chronically activated in subjects with cancer, and IDO1 activation correlates with more extensive disease (Huang et al 2010, Weinlich et al 2007). IDO1 has subsequently been found to be overexpressed by a wide variety of human tumor cell types, as well as by the DCs that localize to the tumor-draining lymph nodes (Uyttenhove et al 2003, Munn et al 2004). Increased expression of IDO1 in tumor cells has been shown to be an independent prognostic variable for reduced overall survival (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 malignancies in combination with chemotherapeutics and/or immunotherapy-based strategies.

1.2. Overview of Epacadostat

Epacadostat is a novel, potent, and selective inhibitor of the IDO1 enzyme in both human tumor cells and human DCs. A Phase 1 monotherapy study in subjects with advanced solid tumors is complete and showed epacadostat monotherapy was generally well-tolerated at doses of up to 700 mg twice daily (BID). The most common adverse events (AEs) were Grade 1 or 2 fatigue and gastrointestinal disturbances. No responses were observed; however, 7 out of 52 subjects had stable disease (SD) for at least 16 weeks (Beatty et al 2017). With the recent emergence of immune-targeted agents (eg, PD-1, PD-L1, and CTLA-4 inhibitors), being investigated in several solid tumors and hematologic malignancies the combination of epacadostat with these agents was explored and several Phase 1 and Phase 2 studies are ongoing.

In a Phase 1 open-label, dose-escalation study (INCB 24360-201), epacadostat in combination with ipilimumab (3 mg/kg intravenous [IV]), was evaluated in 21-day cycles. The initial evaluation of epacadostat 300 mg BID in combination with ipilimumab was terminated due to the occurrence of clinically significant alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevations in 5 of 7 subjects treated at this dose level. These AEs were reversible in all subjects upon discontinuation of study therapy and administration of corticosteroids. Enrollment was restarted at lower doses, and 40 subjects were enrolled: 25 mg BID (n = 8), 50 mg BID continuous (n = 16), 50 mg BID intermittent dosing (2 weeks on and 1 week off; n = 9), and 75 mg total daily dose (50 mg q AM and 25 mg q PM; n = 7). The most common all grade immune-related AEs (irAEs) were rash (50%), pruritus (35%), diarrhea (28%), increased ALT/AST (23%), and hypothyroidism (10%). Immune-related AEs ≥ Grade 3 occurred in 23% of subjects. The most common ≥ Grade 3 irAEs were increased AST/ALT (10%) and colitis (5%). Among 30 immunotherapy-naive subjects, objective response rate (ORR) was 30% (9/30) per immune-related response criteria (irRC) and 27% (8/30) per RECIST. The disease control rate (DCR; complete response (CR) + partial response [PR] + SD) was 60% per irRC and 57% per RECIST. Median progression-free survival (PFS) was 8.3 months by irRC and 6.7 months by RECIST. Among 10 points previously treated with immunotherapy, the DCR by both criteria was 30% (all SDs; Gibney et al 2015).

A Phase 1/2 study is currently evaluating epacadostat in combination with pembrolizumab (INCB 24360-202). Epacadostat 25 mg BID, 50 mg BID, and 100 mg BID with pembrolizumab 2 mg/kg IV every 3 weeks and epacadostat 300 mg BID with pembrolizumab 200 mg IV every 3 weeks was evaluated in Phase 1 dose-escalation; epacadostat 50 mg BID, 100 mg BID, and 300 mg BID with pembrolizumab 200 mg IV every 3 weeks was evaluated in Phase 1 dose-expansion. The most common (≥ 15%) all-grade treatment-related AEs were fatigue, rash, arthralgia, pruritus, diarrhea, and nausea. Grade ≥ 3 treatment-related AEs were observed in 19% (most common: rash [8%] and increased lipase [3%]). There were no treatment-related deaths. Among 19 subjects who were treatment-naive for advanced melanoma (M1c 53%), 5 CRs, 6 PRs, and 3 SDs were observed. All responses are confirmed and ongoing (median follow-up in responders [minimum, maximum]: 56+ [46, 90+ weeks]). Median PFS has not been reached; the PFS rate was 74% at 6 months and 57% at 12 months. Responses were also observed in subjects previously treated for advanced melanoma (n = 3; 1 CR, 1 SD) and subjects with non–small cell lung cancer (NSCLC; n = 12; 5 PRs, 2 SDs), renal cell carcinoma (RCC; n = 11; 2 PRs, 5 SDs), endometrial adenocarcinoma (n = 7; 1 CR, 1 PR), urothelial carcinoma (UC; n = 5; 3 PRs), triple-negative breast cancer (TNBC; n = 3; 2 SDs), and squamous cell carcinoma of the head and neck (SCCHN; n = 2; 1 PR, 1 SD). Based on the overall safety and efficacy profile, epacadostat 100 mg BID was selected as the recommended dose for Phase 2 (Gangadhar et al 2016), and efficacy and safety of the combination is being investigated in tumor-specific cohorts of diffuse large B-cell lymphoma, melanoma, NSCLC, UC, TNBC, SCCHN, ovarian cancer, RCC, and microsatellite-instability (MSI) high colorectal cancer (CRC), gastric cancer, and hepatocellular carcinoma. Recently presented data from Phase 1 and Phase 2 subjects showed ORRs and DCRs, respectively, of 35% and 63% in 40 NSCLC subjects (Gangadhar et al 2017); 33% and 50% in 30 RCC subjects (Lara et al 2017); 35% and 53% in 40 UC subjects (Smith et al 2017); and 34% and 61% in 38 SCCHN subjects (Hamid et al 2017a).

A randomized, double-blind, Phase 3 study (INCB 24360-301) of pembrolizumab in combination with epacadostat or placebo in treatment-naive subjects with unresectable or metastatic melanoma was initiated based on results observed in the Phase 1 study. The dual primary endpoints of the study are PFS per RECIST v1.1 and OS. During an interim analysis, the external Data Monitoring Committee concluded that the study did not meet the primary endpoint of improving PFS in the combination compared to pembrolizumab monotherapy. Additionally, the external Data Monitoring Committee further determined that the OS endpoint was not expected to reach statistical significance. Of note, there were no new safety concerns. This study remains open so that subjects who are still on treatment will have continued access to open-label pembrolizumab monotherapy.

While the results from Study INCB 24360-301 are specific to melanoma and cannot be extrapolated to other tumor types, the sponsor, in collaboration with Merck, halted further enrollment in Phase 3 studies investigating epacadostat in combination with pembrolizumab in subjects with SCCHN, UC, and RCC. The remaining Phase 3 studies investigating epacadostat in combination with pembrolizumab in subjects with NSCLC were amended to become randomized Phase 2 studies.

For a thorough overview of the pharmacology of epacadostat and ongoing clinical studies, refer to the epacadostat Investigator's Brochure (eIB).

1.3. Overview of Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 monoclonal antibody (mAb) with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and programmed cell death ligand 2 (PD-L2). Based on preclinical *in vitro* data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Pembrolizumab is indicated for the treatment of patients across a number of indications. For more details on specific indications, refer to the pembrolizumab Investigator's Brochure (pIB).

Activity of pembrolizumab monotherapy over platinum-based doublet chemotherapy (PT-DC) in subjects with previously untreated advanced NSCLC subjects who were PD-L1+ (≥ 50% expression on tumor cells) was demonstrated in a Phase 3 study (Reck et al 2016). Median PFS was 10.3 months with pembrolizumab and 6.0 months with chemotherapy (hazard ratio [HR] = 0.50, 95% confidence interval [CI], 0.37 to 0.68; $p < 0.001$). Overall survival was significantly longer with pembrolizumab versus chemotherapy (HR = 0.60, 95% CI, 0.41 to 0.89; $p = 0.005$). Objective response rate was greater in subjects treated with pembrolizumab versus investigator's choice chemotherapy (45% vs 28%).

Activity of pembrolizumab monotherapy over chemotherapy in subjects with advanced UC that progressed during or after the receipt of platinum-based chemotherapy was investigated in the Phase 3 KEYNOTE-045 study (Bellmunt et al 2017). A statistically significant advantage in OS of pembrolizumab over chemotherapy was demonstrated (HR 0.73, 95% CI, 0.59 to 0.91; $p = 0.0022$). The median OS was 10.3 months with pembrolizumab and 7.4 months with chemotherapy. Notably, PFS for the 2 groups was similar (HR 0.98, 95% CI, 0.81 to 1.19) despite an ORR for pembrolizumab of 21.1% versus 11.4% for chemotherapy. The median time to response was 2.1 months with both pembrolizumab and chemotherapy. The median duration

response was not reached with pembrolizumab (range, 1.6+ to 15.6+ months) and was 4.3 months (range, 1.4+ to 15.4+) with chemotherapy. Interim analysis of the Phase 2 KEYNOTE-052 study demonstrated the activity of pembrolizumab monotherapy in cisplatin-ineligible subjects with unresectable or metastatic UC (Balar et al 2016). ORR was 24% (CR 6%) in all subjects, and favorable response rates were observed in subjects with high PD-L1 expression, defined as combined positive score of ≥ 10% (ORR 37%; CR 13%).

Activity of pembrolizumab monotherapy in subjects with recurrent or metastatic non-nasopharyngeal SCCHN was demonstrated in 2 cohorts of the Phase 1/2 KEYNOTE-012 study (Seiwert et al 2016, Chow et al 2016) and in the Phase 2 KEYNOTE-055 study (Bauml et al 2017). In the expansion cohort of KEYNOTE-012, 132 subjects with recurrent and/or metastatic SCCHN regardless of PD-L1 expression received pembrolizumab 200 mg every 3 weeks. ORR was 18% by central review (Chow et al 2016). Median duration of response (DOR) was not reached (range: ≥ 2 months to ≥ 11 months) as of the data cutoff. Median PFS was 2 months, and the 6-month rates for PFS were 23%. Median OS was 8 months, and the 6-month OS rate was 59%. Responses were observed regardless of PD-L1 expression and association with human papilloma virus (HPV) status (Chow et al 2016).
In the KEYNOTE-055 study, 171 subjects with recurrent or metastatic SCCHN who were resistant to platinum agent and cetuximab received pembrolizumab 200 mg every 3 weeks. Objective response rate was 16% by central review with a median DOR of 8 months (range, 2+ to 12+ months). Median PFS was 2.1 months, and median OS was 8 months. Responses were observed regardless of PD-L1 expression and HPV status (Bauml et al 2017).

1.4. Overview of 5-Fluorouracil, Leucovorin, and Oxaliplatin in Colorectal Cancer

The mFOLFOX6 regimen is composed of 5-fluorouracil, leucovorin, and oxaliplatin. 5-Fluorouracil is a nucleoside metabolic inhibitor that interferes with the synthesis of DNA, and to a lesser extent RNA, leading to cell death in rapidly growing cells. When used in combination with leucovorin, the effect of FdUMP, an active metabolite of 5-fluorouracil, on inhibiting thymidylate synthase is enhanced. Oxaliplatin is a platinum agent that binds to DNA to form crosslinks that inhibit DNA replication and transcription. Of the 3 commercially available platinum agents, oxaliplatin is the preferred agent for the treatment of subjects with colorectal tumors.

In addition to mFOLFOX6, other common first-line oxaliplatin-based approaches in subjects with advanced CRC include CapeOX (capecitabine and oxaliplatin) or FOLFOXIRI with or without targeted agents (NCCN 2017a, Van Cutsem et al 2016). Historical data show that ORRs ranging from 35% to 55% with oxaliplatin-based regimens were observed in the first line-setting in subjects with metastatic CRC (Tournigand et al 2004, Saltz et al 2008, Bokemeyer et al 2009, Van Cutsem et al 2009, Douillard et al 2010).

1.5. Overview of *nab*-Paclitaxel/Gemcitabine in Pancreatic Cancer

Gemcitabine is a nucleoside metabolic inhibitor that kills cells undergoing DNA synthesis and blocks the progression of cells through the G1/S-phase boundary. *nab*-Paclitaxel is an albumin-bound formulation of paclitaxel, an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions.

Activity for gemcitabine in combination with *nab*-paclitaxel in subjects with advanced pancreatic cancer was demonstrated in a Phase 1/2 study (Von Hoff et al 2011) and in a Phase 3 study (Von Hoff et al 2013). In the Phase 1/2 study, among the 44 subjects treated at the maximum tolerated dose (MTD; gemcitabine 1000 mg/m^2 followed by *nab*-paclitaxel 125 mg/m^2 on Days 1, 8, and 15 of every 28-day cycle), the response rate was 48%, and median survival was 12.2 months. At this dose, Grade 3 or 4 toxicities included fatigue in 27%, neuropathy in 20%, and neutropenia in 49%. In the Phase 3 study, subjects treated with this combination showed a 31% reduction in the risk of progression or death with a median PFS of 5.5 versus 3.7 months and an ORR of 23% compared with 7% with gemcitabine alone. The most common Grade 3 or greater treatment-related AEs were neutropenia (38% vs 27%), fatigue (17% vs 7%), and neuropathy (17% vs 1%) in the combination treatment group versus the gemcitabine-only treatment group. There was no difference in serious life-threatening toxicity (4% in each treatment group). Based on results from this Phase 3 study, combination of *nab*-paclitaxel and gemcitabine is now accepted standard of care as first-line treatment for subjects with advanced/metastatic pancreatic cancer.

1.6. Overview of Platinum-Based Doublet Chemotherapy in Non–Small Cell Lung Cancer

Cisplatin and carboplatin binds to DNA to form crosslinks that inhibit DNA replication and transcription and are the more commonly used commercially available platinum agents for the treatment of subjects with non-colorectal tumors. Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization, resulting in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. Pemetrexed is a folate analog metabolic inhibitor that disrupts folate-dependent metabolic processes essential for cell replication. In combination with a platinum agent, paclitaxel and pemetrexed represent standard-of-care first-line therapy for NSCLC subjects (without sensitizing epidermal growth factor receptor [EGFR] mutations or anaplastic lymphoma kinase [ALK] translocation) with squamous and nonsquamous histologies, respectively (NCCN 2017c, Novello et al 2016).

Randomized studies comparing various PT-DC regimens in NSCLC have shown similar efficacy results, with ORRs ranging from 15% to 32%, median PFS of 4.0 to 5.1 months, and median OS from 8.1 to 10.3 months. One- and 2-year OS rates ranged from 30% to 44% and 10% to 19%, respectively (Kelly et al 2001, Sandler et al 2006, Scagliotti et al 2002, Scagliotti et al 2008, Schiller et al 2002). Bevacizumab and maintenance therapy with pemetrexed have improved clinical outcomes (Barlesi et al 2014, Scagliotti et al 2014, Patel et al 2013), but most subjects will eventually progress (Chang 2011).

1.7. Overview of Low-Dose Cyclophosphamide

Cyclophosphamide is an alkylating agent that is thought to exert its effect by cross-linking tumor cell DNA. Cyclophosphamide is primarily used at high doses for the treatment of hematologic malignancies (lymphomas, multiple myeloma, leukemias) but can be used for the treatment of ovarian and breast cancers. Additionally, cyclophosphamide can be used as an immunosuppressive agent for the treatment of autoimmune and immune-mediated diseases. Preclinical and clinical findings have demonstrated that cyclophosphamide is a potent immune modulator that targets suppressive regulatory immune cells within the tumor microenvironment while enhancing effector cells. Low doses of cyclophosphamide have been used to selectively deplete Tregs while enhancing effector and memory cytotoxic T cells within the tumor microenvironment, which resulted in suppressed tumor growth and enhanced survival (Abu Eid et al 2016, Ahlmann and Hempel 2016).

1.8. Overview of Gemcitabine/Platinum Agent in Urothelial Carcinoma

Activity of gemcitabine/cisplatin combination chemotherapy compared with methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) as first-line treatment for metastatic UC was investigated in a Phase 3 study in 405 subjects (von der Maase et al 2000). Overall survival was similar on both arms (HR = 1.04, 95% CI, 0.82 to 1.32; p = 0.75), as were time to progressive disease, time to treatment failure, and response rate (gemcitabine/cisplatin, 49%; MVAC, 46%); however, gemcitabine/cisplatin provided a better safety profile and tolerability. Unfortunately, cisplatin ineligibility is common in subjects with UC because of renal dysfunction (creatinine clearance < 60 mL/min) or performance status of 2, both, or additional comorbidity. Carboplatin provides an alternative for cisplatin in these subjects. Results from a Phase 3 study comparing gemcitabine/carboplatin with methotrexate/carboplatin/vinblastine (M-CAVI) in 238 cisplatin-ineligible subjects showed ORRs of 41.2% (36.1% confirmed response) with gemcitabine/carboplatin and 30.3% (21.0% confirmed response) with M-CAVI (p = 0.08 unconfirmed response; p = 0.01 confirmed response) and similar OS (HR = 0.94, 95% CI, 0.72 to 1.2; p = 0.64) and PFS (HR = 1.04; 95% CI, 0.80, 1.35). However, more subjects have severe acute toxicity (death resulting from toxicity, Grade 4 thrombocytopenia with bleeding, Grade 3 to 4 renal toxicity, neutropenic fever, or Grade 3 to 4 mucositis) with M-CAVI compared with gemcitabine-carboplatin (21.2% vs 9.3%; De Santis et al 2012). Results from these Phase 3 studies form the basis of combination therapy with gemcitabine and a platinum agent as first-line standard-of-care treatment for subjects with advanced/metastatic UC (NCCN 2017d, Bellmunt et al 2014).

1.9. Overview of Platinum Agent/5-Fluorouracil in Squamous Cell Carcinoma of the Head and Neck

Initial treatment options for patients with recurrent or metastatic SCCHN include various chemotherapy agents (platinum agent [cisplatin or carboplatin], 5-fluorouracil, or taxanes), either alone or in combination, and the biologic agent cetuximab (NCCN 2017b, Gregoire et al 2010). In Phase 3 studies cisplatin/5-fluourouracil, ORRs were 30% (Forastiere et al 1992, Jacobs et al 1992, Clavel et al 1994, Gibson et al 2005) while ORR with carboplatin/5-fluorouracil was 21% (Forastiere et al 1992). While these ORRs are considered significant improvements relative to single-agent platinum therapy, improvements in OS have not been observed. The addition of the EGFR-targeted monoclonal antibody cetuximab to platinum agent (cisplatin or carboplatin) and 5-fluorouracil (EXTREME regimen) prolonged median OS from 7.4 months to 10.1 months (HR = 0.80; p = 0.04) and median PFS from 3.3 months to 5.6 months (HR = 0.54; p < 0.001) compared with a platinum agent and 5-fluorouracil doublet. Additionally, ORR increased from 20% with platinum/5-fluorouracil to 36% with the EXTREME regimen (p < 0.001; Vermorken et al 2008). Based on these results, the EXTREME regimen is now the standard of care for patients with non-nasopharyngeal SCCHN in the recurrent and metastatic setting (NCCN 2017b, Gregoire et al 2010).

1.10. Study Rationale

While chemotherapy has largely been thought to be immunosuppressive and exert its effect via direct cytotoxicity, there is an emerging body of evidence to suggest that some chemotherapies may influence an immune response to tumors via induction of immunogenic cell death (ICD), elimination of immunosuppressive cells, or sensitization of tumor cells to immune effector cells (Apetoh et al 2015). FOLFOX-bevacizumab may induce a decrease in granulocytic myeloid-derived suppressor cells, high levels of which are associated with a poor prognosis (Limagne et al 2016). Gemcitabine and cyclophosphamide have been shown to improve antitumor immunity by depleting immunosuppressive Tregs (Ghiringhelli et al 2007, Le and Jaffee 2012, Shevchenko et al 2013). Platinum agents have demonstrated immunogenic effects via ICD and enhancement of effector immune response through PD-L1 receptor expression (Hato et al 2014). Paclitaxel and 5-fluorouracil have been shown to restore antitumor activity of CD8+ T cells (Sevko et al 2013, Vincent et al 2010). Given these findings, the combination of chemotherapy with immunotherapy is a rational choice, especially in subjects for whom these chemotherapies are the accepted standard of care.

Programmed cell death 1/PD-L1 blockade is being investigated in combination with chemotherapeutic agents in various tumor types. In a Phase 1 study (n = 56), nivolumab in combination with PT-DC in chemotherapy-naive NSCLC showed ORR ranging from 33% to 50% and PFS from 4.8 to 6.1 months, and ≥ Grade 3 treatment-related AEs were observed in 45% of subjects (Rizvi et al 2016). More promising efficacy signals have been observed in the KEYNOTE-021 study of pembrolizumab in combination with PT-DC from open-label cohorts (n = 74, ORR 48%-71%, PFS ~10 months, ≥ Grade 3 treatment-related AEs 56%-71%; Gadgeel et al 2016) and a randomized cohort of pembrolizumab/PT-DC versus PT-DC (n = 123, ORR 55% vs 29%, PFS 13 vs 8.9 months, ≥ Grade 3 treatment-related AEs 39% vs 26%; Langer et al 2016) as well as a Phase 1 study of atezolizumab (n = 58 safety evaluable, n = 41 efficacy evaluable, ORR 50%-77%, PFS immature at time of analysis;

Giaccone et al 2015). Confirmatory Phase 3 clinical studies in advanced/metastatic NSCLC are ongoing for these 3 therapies.

In addition to NSCLC, preliminary data of PD-1 or PD-L1 inhibitors in combination with chemotherapy in metastatic CRC and pancreatic cancer have been reported. In a Phase 1 study in subjects with previously untreated metastatic CRC (n = 23), atezolizumab in combination with FOLFOX and bevacizumab showed an ORR of 52% with a median PFS of 14.1 months. The regimen was well-tolerated, and no unexpected toxicities observed (Wallin et al 2016). In a Phase 1 investigator-initiated study of pembrolizumab in combination with mFOLFOX6 in subjects with advanced gastric malignancies (n = 10), the combination of pembrolizumab at doses of up to 200 mg given every 2 weeks with mFOLFOX6 was well-tolerated. Common ≥ Grade 3 AEs were neutropenia (40%) and hyponatremia (30%). Stable disease was observed in 4 of 7 CRC subjects (Stenehjem et al 2016). Preliminary data from a Phase 1/2 study of *nab*-paclitaxel ± gemcitabine with nivolumab in subjects with locally advanced or metastatic pancreatic cancer showed the addition of nivolumab to *nab*-paclitaxel or *nab*-paclitaxel/gemcitabine was tolerable. No dose-limiting toxicities (DLTs) were observed in the 11 subjects treated with nivolumab plus *nab*-paclitaxel, and the most common AEs were anemia, neutropenia, and pulmonary embolism (18% each). One DLT was observed in the 6 subjects treated with *nab*-paclitaxel/gemcitabine plus nivolumab, and the most common AE was anemia (33%). Two of 6 subjects treated with *nab*-paclitaxel and nivolumab had a PR and 4 had SD. Of the 11 subjects treated with *nab*-paclitaxel/gemcitabine and nivolumab, 3 subjects had a PR and 3 subjects had SD (George et al 2016).

The IDO pathway inhibitor indoximod has been evaluated in combination with chemotherapy in clinical studies. In a Phase 1 study (n = 27), indoximod in combination with docetaxel in pretreated subjects with metastatic solid tumors was well-tolerated with no unexpected toxicities and had a modest ORR of 18% (Soliman et al 2014). Based on encouraging activity observed in subjects with breast cancer from this study, a Phase 2 study of indoximod in combination with docetaxel or paclitaxel was initiated. Preliminary safety data showed AEs were similar to those typically seen with taxanes, and no unexpected AEs were observed (Tang et al 2016). Indoximod in combination with *nab*-paclitaxel and gemcitabine in subjects with metastatic pancreatic cancer was also well-tolerated in a Phase 1/2 study, and preliminary efficacy showed durable responses in 42% of subjects (Bahary et al 2016).

Combining the IDO1 inhibitor epacadostat, pembrolizumab, and chemotherapy may result in greater immunomodulatory effects in the tumor microenvironment, resulting in enhanced clinical benefit in subjects with advanced or metastatic solid tumors.

1.10.1. Justification for Treatment Regimen

The initial epacadostat dose selected for this study in combination with pembrolizumab and chemotherapy is 100 mg BID, with the option to de-escalate to 50 mg BID based on DLTs observed in the safety run-in. The initial dose selected is based on the preliminary observation that the average kynurenine inhibition at 6 hours after administration of epacadostat using a standardized whole blood assay is 89%, and the safety profile of this dose level has been well-tolerated. Pharmacokinetic (PK) and pharmacodynamic observations from studies INCB 24360-101 and INCB 24360-201 in subjects with cancer support the 25 mg BID to 300 mg BID dose levels, which provide a differential pharmacologic effect. Based on a 6-hour

observation period at steady state on Day 15 after administration of epacadostat and using a standardized whole blood assay, kynurenine levels are incompletely inhibited (66%), compared with baseline levels in subjects treated with 25 mg BID, but are nearly maximally inhibited (89%) in subjects treated with 100 mg BID. Complete inhibition of IDO1 is not required for maximally effective activity in preclinical models; however, maximally effective doses in nonclinical models result in exposures that are comparable to monotherapy doses of 50 mg BID to 300 mg BID in humans. Additionally, a detailed interrogation of the effect of dose and exposure on the pharmacodynamic effect of epacadostat on the tryptophan pathway was performed in Study INCB 24360-101. Using an *ex vivo* assay optimized for determining the inhibition of the metabolism of tryptophan to kynurenine by IDO1, epacadostat treatment produced significant dose-dependent reductions in plasma kynurenine levels and in the plasma kynurenine/tryptophan ratio at all doses and in all subjects. Near maximal changes were observed at doses of ≥ 100 mg BID with > 80% to 90% inhibition of IDO1 achieved throughout the dosing period (Beatty et al 2017).

Epacadostat doses of up to 700 mg BID as monotherapy have been well-tolerated. In the INCB 24360-202 study, epacadostat doses of up to 300 mg BID were evaluated in combination with pembrolizumab. The MTD was not exceeded in this study. While there was a higher incidence of Grade 3 rash in the 300 mg BID cohort than in the 100 mg BID cohort, these did not qualify as protocol-specified DLTs. The dose of epacadostat 300 mg BID is currently being investigated in other studies of epacadostat in combination with other checkpoint inhibitors.

In the Phase 3 INCB 24360-301 study, the combination of epacadostat 100 mg BID plus pembrolizumab 200 mg every 3 weeks (Q3W) was chosen based upon a benefit/risk assessment made specifically in melanoma in collaboration with Merck. In INCB 24360-202, there was evidence of improved efficacy in melanoma subjects at all doses of epacadostat from 50 mg to 300 mg BID. Given that melanoma is an immunotherapy responsive tumor, and lower doses of epacadostat appeared to have similar activity, epacadostat 100 mg BID dose was selected for evaluation in the INCB 24360-301 study because of the lower incidence of dose interruptions and dose reductions compared with the 300 mg BID dose observed in the INCB 24360-202 study.

The starting dose selected for the current study was formed on the basis of having a well-tolerated safety profile as monotherapy and in combination with other immunotherapy agents, as well as providing nearly maximum target inhibition of IDO1. Given that epacadostat was determined to be safe as monotherapy at doses up to 700 mg BID, the choice of the pharmacologically active dose (PAD) of 100 mg BID is justified as the starting dose in this combination study, and the dose range of 50 mg BID to 100 mg BID is justified as the dose range to potentially evaluate in this study.

1.10.2. Rationale for Efficacy Endpoints

RECIST v1.1 (Eisenhauer et al 2009) will be used by the local site to determine eligibility and evaluate disease status. However, because immunotherapeutic agents may produce antitumor effects by potentiating endogenous cancer-specific immune responses that may take weeks to emerge, the response patterns seen with immunotherapeutic agents may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest a clinical response after an initial increase in tumor burden or appearance of new lesions. As a result, RECIST v1.1 may not provide a comprehensive response assessment of immunotherapeutic agents; therefore, RECIST v1.1 will be used with the following adaptation:

> If radiologic imaging shows initial PD, tumor assessment should be repeated ≥ 4 weeks later (but no later than 6 weeks) to confirm PD with the option of continuing assigned treatment while awaiting radiologic confirmation of progression. If repeat imaging shows stability or reduction in tumor burden compared with the initial scan demonstrating PD, treatment may be continued or resumed. If repeat imaging confirms progressive PD, subjects will be discontinued from treatment. In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as nontarget lesions.

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

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

When feasible, subjects should not be discontinued until progression is confirmed. Subjects who are deemed clinically unstable are not required to have repeat imaging for confirmation of PD.

In all other instances, treatment decisions will be made based on investigator review of the clinical and radiographic data.

1.11. Potential Risks of the Treatment Regimen

1.11.2. Risks From Pembrolizumab

The most frequently reported adverse events (≥ 10%) in 2799 subjects treated with pembrolizumab were fatigue, nausea, decreased appetite, diarrhea, cough, pruritus, dyspnea, arthralgia, rash, constipation, headache, vomiting, asthenia, pyrexia, back pain, anemia, and peripheral edema. The 5 most frequently reported SAEs were pneumonia (3.0%), pleural effusion (1.7%), pneumonitis (1.6%), dyspnea (1.6%), and pulmonary embolism (1.5%). For full details and recommended management guidelines, refer to the pembrolizumab Investigator's Brochure (pIB).

It is unknown whether pembrolizumab is excreted in human milk. Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

1.11.3. Risks From mFOLFOX6

The most common adverse reactions (incidence ≥ 40%) of oxaliplatin were peripheral sensory neuropathy, neutropenia, thrombocytopenia, anemia, nausea, increase in transaminases and alkaline phosphatase (ALP), diarrhea, emesis, fatigue, and stomatitis. Serious adverse reactions including anaphylaxis and allergic reactions, neuropathy, pulmonary toxicities, and hepatotoxicity can occur. Anaphylactic reactions to oxaliplatin may occur within minutes of administration.

In clinical studies of oxaliplatin, the most common adverse reactions in previously untreated and treated subjects with advanced CRC were peripheral sensory neuropathies, fatigue, neutropenia, nausea, emesis, and diarrhea. Both 5-fluorouracil and oxaliplatin are associated with gastrointestinal and hematologic adverse reactions. When oxaliplatin is administered in combination with 5-fluorouracil, the incidence of these events is increased. Allergic sensitization, including anaphylactoid reactions and urticaria, has been reported after the administration of both oral and parenteral leucovorin.

1.11.4. Risks From *nab*-Paclitaxel/Gemcitabine

The most common (≥ 20%) adverse reactions of *nab*-paclitaxel in pancreatic ductal adenocarcinoma (PDAC) are neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash, and dehydration. Additionally, *nab*-paclitaxel causes myelosuppression. Sensory neuropathy occurs frequently and may require dose reduction or treatment interruption. Sepsis occurred in subjects with or without neutropenia who received *nab*-paclitaxel in combination with gemcitabine. Pneumonitis occurred with the use of *nab*-paclitaxel in combination with gemcitabine. Severe hypersensitivity reactions with fatal outcome have been reported. *nab*-Paclitaxel contains albumin derived from human blood, which has a theoretical risk of viral transmission. Refer to the US prescribing information (Abraxane PI 2015) or EU SmPC (Abraxane SmPC 2015) for *nab*-paclitaxel for full details.

1.11.5. Risks From Paclitaxel/Carboplatin

Bone marrow suppression (leukopenia, neutropenia, and thrombocytopenia) is dose-dependent and is also the DLT of carboplatin. Anaphylactic reactions to carboplatin may occur within minutes of administration. Carboplatin can induce emesis, which can be more severe in subjects previously receiving emetogenic therapy. Although peripheral neurotoxicity is infrequent, its incidence is increased in subjects older than 65 years and in subjects previously treated with cisplatin.

Bone marrow suppression (primarily neutropenia) is dose-dependent and is the DLT of paclitaxel. Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2% to 4% of subjects receiving paclitaxel in clinical studies. Fatal reactions have occurred in subjects despite premedication.

1.11.6. Risks From Pemetrexed/Platinum Agent

The most common adverse reactions (incidence ≥ 20% with single-agent use) with pemetrexed are fatigue, nausea, and anorexia. When pemetrexed is used in combination with a platinum agent, common adverse reactions include the following: vomiting (40%), nausea (56%), neutropenia (29%), leukopenia (18%), anemia (33%), stomatitis/pharyngitis (14%), thrombocytopenia (10%), and constipation (21%). Refer to the US prescribing information (Alimta PI 2013) or EU SmPC (Alimta SmPC 2016) for pemetrexed for full details.

1.11.7. Risks From Cyclophosphamide

The most often reported adverse reactions with cyclophosphamide are neutropenia, febrile neutropenia, fever, alopecia, nausea, vomiting, and diarrhea. Cyclophosphamide can cause myelosuppression (leukopenia, neutropenia, thrombocytopenia, and anemia), bone marrow failure, and severe immunosuppression, which may lead to serious and sometimes fatal infections, including sepsis and septic shock. Hemorrhagic cystitis, pyelitis, ureteritis, hematuria, and secondary malignancies (urinary tract cancer, myelodysplasia, acute leukemias, lymphomas, thyroid cancer, and sarcomas) have been reported. Myocarditis, myopericarditis, pericardial effusion including cardiac tamponade, and congestive heart failure, which may be fatal, have been reported. Pneumonitis, pulmonary fibrosis, pulmonary veno-occlusive disease, and other forms of pulmonary toxicity leading to respiratory failure have been reported during and after treatment with cyclophosphamide. Veno-occlusive liver disease including fatal outcome has been reported.

1.11.8. Risks From Gemcitabine/Platinum Agent

In the Phase 3 study of gemcitabine/cisplatin versus MVAC, ≥ Grade 3 anemia was more common with gemcitabine/cisplatin (27%) versus MVAC (18%); however, this did not result in an increase in RBC transfusion rates. Subjects treated with gemcitabine/cisplatin had more ≥ Grade 3 thrombocytopenia compared with MVAC (57% vs 21%, respectively); but there was no Grade 4 bleeding on either arm, and ≥ Grade 3 thrombocytopenia was infrequently associated with Grade 3 bleeding (2% for both treatment groups; von der Maase et al 2000). In the Phase 3 study in UC, severe acute toxicity (death, Grade 4 thrombocytopenia with bleeding, ≥ Grade 3 renal toxicity, neutropenic fever, or mucositis) was observed in 9.3% of subjects receiving gemcitabine-carboplatin and 21.2% of subjects receiving M-CAVI. The most common ≥ Grade 3 AEs were leukopenia (44.9%, 46.6%), neutropenia (52.5%, 63.5%), febrile neutropenia (4.2%, 14.4%), thrombocytopenia (48.3%, 19.4%), and infection (11.8%, 12.7%) in subjects treated with gemcitabine/carboplatin versus M-CAVI, respectively (De Santis et al 2012).

1.11.9. Risks From Platinum Agent/5-Fluorouracil

In a Phase 3 study of cisplatin/5-fluorouracil and carboplatin/5-fluorouracil versus single-agent methotrexate as first-line treatment for metastatic SCCHN, 33% of subjects treated with cisplatin/5-fluorouracil and 26% of subjects treated with carboplatin/5-fluorouracil had ≥ Grade 3 AEs. Compared with single-agent methotrexate, leukopenia was more frequent in cisplatin-treated subjects, and thrombocytopenia was more frequent in carboplatin-treated subjects. Stomatitis, nausea, and vomiting were common nonhematologic events with the platinum agent/5-fluorouracil regimens, and renal toxicity was more frequent in cisplatin-treated subjects (Forastiere et al 1992).

1.11.10. Risks From Combining an IDO Inhibitor With Chemotherapy

In a Phase 1 study of the IDO pathway inhibitor indoximod with docetaxel in advanced solid tumors, the most frequent AEs were fatigue (58.6%), anemia (51.7%), hyperglycemia, (48.3%), infection (44.8%), and nausea (41.4%; Soliman et al 2014). In a Phase 2 study of indoximod plus docetaxel in subjects with metastatic breast cancer, the most common indoximod-related AEs of any grade occurring in ≥ 10% of subjects were fatigue (20%), nausea (20%), diarrhea (13%), and headache (12%; Tang et al 2016).

Recently presented safety data from a Phase 1/2 study evaluating the combination of indoximod with *nab*-paclitaxel/gemcitabine in subjects with metastatic pancreatic cancer showed the most frequently reported AEs (regardless of attribution) occurring in ≥ 10% of subjects were anemia, constipation, diarrhea, nausea, vomiting, fatigue, peripheral edema, abdominal pain, decreased appetite, weight loss, dizziness, fever, peripheral neuropathy, alopecia, rash, hypotension, hypokalemia, hyponatremia, ALT increased, AST increased, ALP increased, platelet count decreased, white blood cell count decreased, and neutrophil count decreased (Bahary et al 2016).

1.11.11. Risks From Combining a PD-1 Inhibitor With Chemotherapy

In an investigator-initiated Phase 1 study of subjects with metastatic CRC, common AEs when pembrolizumab was combined with mFOLFOX6 were neutropenia (40%) and hyponatremia (30%; Stenehjem et al 2016). The most common AEs in 11 subjects with metastatic pancreatic cancer treated with *nab*-paclitaxel/gemcitabine plus nivolumab was anemia (33%; George et al 2016).

Recently presented safety data from a randomized cohort of the KEYNOTE-021 study where subjects with nonsquamous NSCLC were treated with pemetrexed/carboplatin plus pembrolizumab showed the most common ≥ Grade 3 treatment-related AEs were anemia (12%), decreased neutrophil count (5%), and acute kidney injury, decreased lymphocyte count, fatigue, neutropenia, sepsis, and thrombocytopenia (3% each; Langer et al 2016). In an open-label cohort from the same study, NSCLC subjects treated with paclitaxel/carboplatin plus pembrolizumab, treatment-related AEs ≥ Grade 3 occurred in 36% subjects; the most common events were anemia, neutropenia, and febrile neutropenia (n = 2 each; Gadgeel et al 2016).

1.11.12. Risks From Combining Epacadostat and Pembrolizumab

In the Phase 1 portion of the INCB 24360-202 study of epacadostat in combination with pembrolizumab, the most common all-grade treatment-related AEs were fatigue (29%), rash (29%), pruritus (23%), arthralgia (19%), diarrhea (18%), and nausea (16%). Treatment-related AEs ≥ Grade 3 were observed in 19% (most common: rash [8%] and increased lipase [3%]). Five subjects (8%) experienced treatment-related AEs that led to discontinuation, including Grade 3 arthralgia, Grade 3 AST increased/Grade 2 ALT increased, Grade 3 lipase increased, Grade 3 aseptic meningitis, and Grade 2 nervous system disorder. There were no treatment-related deaths (Gangadhar et al 2016).

Data from 294 subjects in the Phase 2 portion of the study (epacadostat 100 mg PO BID + pembrolizumab 200 mg IV Q3W) further support the acceptable safety and tolerability profile of this combination. The most common all-grade treatment-related AEs were fatigue (29%), rash (17%), nausea (11%), and pruritus (10%). Treatment-related AEs ≥ Grade 3 were observed in 18%. Treatment-related AEs leading to treatment discontinuations occurred in 11 subjects (4%); the most common were arthralgia and rash (n = 2 subjects each) and there was only 1 treatment-related AE that led to death (respiratory failure, secondary to aspiration pneumonia; pneumonitis could not be ruled out; Hamid et al 2017b).

In Study INCB 24360-301, the external Data Monitoring Committee found no new safety concerns with pembrolizumab plus epacadostat compared with pembrolizumab monotherapy. Treatment-related AEs ≥ Grade 3 occurred in 22% of subjects receiving epacadostat plus pembrolizumab and in 17% of subjects receiving placebo plus pembrolizumab. Treatment-related AEs leading to treatment discontinuations occurred in 11% and 10% of subjects treated with epacadostat plus pembrolizumab and placebo plus pembrolizumab, respectively (Long et al 2018).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objectives

- Phase 1: To evaluate the safety, tolerability, and DLTs and to define an MTD and/or PAD of epacadostat in combination with pembrolizumab and chemotherapy in subjects with advanced or metastatic solid tumors.
- Phase 2: To evaluate the efficacy of epacadostat in combination with pembrolizumab and chemotherapy in subjects with advanced or metastatic CRC, PDAC, NSCLC, UC, SCCHN, or any advanced or metastatic solid tumor who progressed on previous therapy with a PD-1 or PD-L1 inhibitor by assessing ORR per RECIST v1.1.

2.1.2. Secondary Objectives

- Phase 1: To explore the efficacy of epacadostat in combination with pembrolizumab and chemotherapy in subjects with advanced or metastatic solid tumors by assessing ORR per RECIST v1.1.
- Phase 2: To further evaluate the safety and tolerability of epacadostat at the MTD and/or PAD in combination with pembrolizumab and chemotherapy in subjects with selected advanced or metastatic solid tumors.

2.2. Study Endpoints

2.2.1. Primary Endpoints

- Phase 1: Safety and tolerability will be assessed by monitoring frequency, duration, and severity of AEs through physical examinations, by evaluating changes in vital signs and electrocardiograms (ECGs), and through clinical laboratory blood and urine sample evaluations.
- Phase 2: ORR, defined as the percentage of subjects having a CR or PR, will be determined by investigator assessment of radiographic disease per RECIST v1.1.

2.2.2. Secondary Endpoints

- Phase 1: ORR, defined as the percentage of subjects having a CR or PR, will be determined by investigator assessment of radiographic disease per RECIST v1.1.
- Phase 2: Safety and tolerability will be assessed by monitoring frequency, duration, and severity of AEs through physical examinations, by evaluating changes in vital signs and ECGs, and through clinical laboratory blood and urine sample evaluations.

3. SUBJECT ELIGIBILITY

Phase 1: Subjects with histologically or cytologically confirmed advanced or metastatic solid tumors who have failed previous standard therapy (or who refuse or are intolerant to standard-of-care therapy).

Phase 2: Subjects with histologically or cytologically confirmed advanced or metastatic CRC, PDAC, squamous NSCLC, nonsquamous NSCLC, UC, SCCHN who have not received first-line therapy for advanced or metastatic disease; subjects with any advanced or metastatic solid tumor with confirmed progression on previous therapy with a PD-1 or PD-L1 inhibitor.

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

3.1. Subject Inclusion Criteria

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

Phase 1 and Phase 2:

1. Ability to comprehend and willing to sign an informed consent form (ICF).
2. Men or women aged 18 years or older.
3. Presence of measurable disease per RECIST v1.1 (Appendix F). Tumor lesions located in a previously irradiated area, or in an area subjected to other loco-regional therapy, are considered measureable if progression has been demonstrated in the lesion.
4. ECOG performance status of 0 or 1 (Appendix C).
5. Willing to avoid pregnancy or fathering children based on the criteria below:
    a. Woman of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea and at least 51 years of age.)
    b. Woman of childbearing potential who has a negative serum pregnancy test at screening and before the first dose on Day 1 and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through 120 days after the last dose of epacadostat and pembrolizumab. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.
    Note: If a subject continues on chemotherapy after discontinuing epacadostat and pembrolizumab, contraception methods should continue for 180 days after the last dose of chemotherapy.

c. Man who agrees to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through 120 days after the last dose of epacadostat and pembrolizumab. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.
Note: If a subject continues on chemotherapy after discontinuing epacadostat and pembrolizumab, contraception methods should continue for 180 days after the last dose of chemotherapy.

6. Willing and able to comply with scheduled visits, the treatment plan, and laboratory tests.

Phase 1 subjects only:

7. Subjects with locally advanced or metastatic solid tumors who have disease progression after treatment with available therapies that are known to confer clinical benefit, who are intolerant to treatment, or who refuse standard treatment. Locally advanced disease must not be amenable to resection with curative intent.

   Note: Subjects should not have received more than 2 previous therapies for advanced or metastatic disease. Subjects who received more than 2 previous therapies for advanced or metastatic disease must be discussed with medical monitor to confirm eligibility.

8. Subjects must not have received therapy with an IDO inhibitor.

Phase 2 CRC subjects only:

9. Histologically or cytologically confirmed advanced or metastatic adenocarcinoma of the colon or rectum.

10. Subjects must not have received previous chemotherapy as first-line therapy for advanced or metastatic disease.

    Note: Subjects who completed a chemotherapy regimen as adjuvant, neoadjuvant, or part of a course of chemoradiation therapy and progressed ≥ 6 months after completing therapy will be eligible. If progression occurred < 6 months after completing therapy, the subject will not be eligible.

11. Subjects must not have received previous immune checkpoint inhibitors (eg, CTLA-4 inhibitor, PD-1 inhibitor, PD-L1 inhibitor, or any other antibody or drug specifically targeting T-cell costimulation) and/or an IDO inhibitor. Subjects who received other immunotherapies must be discussed with medical monitor to confirm eligibility.

Phase 2 PDAC subjects only:

12. Histologically or cytologically confirmed advanced or metastatic PDAC.

13. Subjects must not have received previous chemotherapy as first-line therapy for advanced or metastatic disease.

    Note: Subjects who completed a chemotherapy regimen as adjuvant, neoadjuvant, or part of a course of chemoradiation therapy and progressed ≥ 6 months after completing therapy will be eligible. If progression occurred < 6 months after completing therapy, the subject will not be eligible.

14. Subjects must not have received previous immune checkpoint inhibitors (eg, CTLA-4 inhibitor, PD-1 inhibitor, PD-L1 inhibitor, or any other antibody or drug specifically targeting T-cell costimulation) and/or an IDO inhibitor. Subjects who received other immunotherapies must be discussed with medical monitor to confirm eligibility.
15. Does not require recurrent paracentesis for management of ascites or thoracentesis for management of pleural effusion.
16. Albumin > 3.0 g/dL.
17. Absence of erosion into the stomach or other viscera by computed tomography scan.

Phase 2 squamous or nonsquamous NSCLC subjects only:

18. Histologically or cytologically confirmed Stage IIIB, Stage IV, or recurrent squamous or nonsquamous NSCLC.
19. Subjects without driver mutations (eg, BRAF or EGFR mutations, ALK fusion oncogene or ROS1 rearrangements) must not have received previous chemotherapy as first-line therapy for Stage IIIB, Stage IV, or recurrent NSCLC.

    Note: Subjects who completed a chemotherapy regimen as adjuvant, neoadjuvant, or part of a course of chemoradiation therapy and progressed ≥ 6 months after completing therapy will be eligible. If progression occurred < 6 months after completing therapy, the subject will not be eligible.
20. Subjects with driver mutations (eg, BRAF or EGFR mutations, ALK fusion oncogene or ROS1 rearrangements) must have received prior treatment only with an approved TKI with subsequent disease progression.
21. Subjects must not have received previous immune checkpoint inhibitors (eg, CTLA-4 inhibitor, PD-1 inhibitor, PD-L1 inhibitor, or any other antibody or drug specifically targeting T-cell costimulation) and/or an IDO inhibitor. Subjects who received other immunotherapies must be discussed with medical monitor to confirm eligibility.
22. For subjects with squamous histology, willing and able to take premedications to prevent hypersensitivity reactions.
23. For subjects with nonsquamous histology, willing and able to take vitamin B_{12} and folic acid supplements.

Phase 2 subjects in the cohort of subjects with any solid tumor that progressed on previous therapy with a PD-1 or PD-L1 inhibitor only:

24. Histologically or cytologically confirmed advanced or metastatic solid tumors that progressed (primary refractory or secondary relapsed) on previous monotherapy with a PD-1 or PD-L1 inhibitor or previous combination therapy that included a PD-1 or PD-L1 inhibitor in the advanced or metastatic setting.

    Note: Primary refractory subjects must have received at least 2 doses of PD-1 or PD-L1 inhibitor and have had disease progression at least 8 weeks from the first dose of the PD-1 or PD-L1 inhibitor that is confirmed at least 4 weeks (no less than 28 days) later (confirmatory imaging may be performed during the screening period with medical monitor approval). The PD-1 or PD-L1 inhibitor does not need to have been the last treatment received before signing informed consent. Subjects who received only 1 dose of the PD-1 or PD-L1 inhibitor or discontinued for toxicity without disease progression within 8 weeks of the first dose of the PD-1 or PD-L1 inhibitor are not eligible.

    Note: Secondary relapsed subjects must have had a PR or CR while on treatment with a PD-1 or PD-L1 inhibitor but later had disease progression that is confirmed at least 4 weeks (no less than 28 days) later. The PD-1 or PD-L1 inhibitor does not need to have been the last treatment received before signing informed consent. Subjects must not have received previous therapy with an IDO inhibitor.

25. Subjects who received immunotherapies other than a PD-1 or PD-L1 inhibitor must be discussed with medical monitor to confirm eligibility.

26. Subjects may have received previous chemotherapy for advanced or metastatic disease.

    Note: There is no limit to the number of previous chemotherapy regimens.

Phase 2 subjects in the mandatory biopsy cohort only:

27. Willing to undergo pretreatment and on-treatment core or excisional tumor biopsies.

    Note: Fresh baseline tumor biopsies (defined as a biopsy specimen taken since completion of the most recent prior systemic regimen) are required for all Phase 2 mandatory biopsy subjects.

Phase 2 efficacy expansion subjects only:

28. Willing to undergo pretreatment core or excisional tumor biopsies.

    Note: Fresh baseline tumor biopsies (defined as a biopsy specimen taken since completion of the most recent prior systemic regimen) are preferred. If a subject has inaccessible lesions, the subject may be enrolled with medical monitor approval. In this case, submission of archived tumor tissue may be acceptable. In all cases, biopsies will be confirmed to contain adequate tumor tissue by a local pathology review.

Phase 2 UC subjects only:

29. Have histologically or cytologically confirmed advanced/unresectable (inoperable) or metastatic urothelial cancer of the renal pelvis, ureter, bladder, or urethra. Both transitional cell and mixed transitional/nontransitional (predominantly transitional) cell histologies are allowed.
30. Subjects must not have received previous chemotherapy as first-line therapy for advanced or metastatic disease.

    Note: Adjuvant platinum-based chemotherapy, following radical cystectomy, with recurrence > 12 months from completion of therapy is permitted. Neoadjuvant platinum-based chemotherapy with recurrence > 12 months since completion of therapy is permitted.
31. Subjects must not have received previous immune checkpoint inhibitors (eg, CTLA-4 inhibitor, PD-1 inhibitor, PD-L1 inhibitor, or any other antibody or drug specifically targeting T-cell costimulation) and/or an IDO inhibitor. Subjects who received other immunotherapies must be discussed with medical monitor to confirm eligibility.

Phase 2 SCCHN subjects only:

32. Histologically or cytologically confirmed recurrent or metastatic SCCHN of the oral cavity, oropharynx, hypopharynx, and larynx that is considered incurable by local therapies.

    Note: Subjects with primary tumors of the nasopharynx, the salivary gland, unknown primary origin, or nonsquamous histologies are not eligible.
33. Documentation of results from testing of HPV status for oropharyngeal cancer using p16 IHC testing.

    Note: Subjects with primary tumor site of the oral cavity, hypopharynx, and larynx are not required to undergo HPV testing by p16 IHC, as these tumor locations are assumed to be HPV negative.
34. Subjects must not have received previous chemotherapy as first-line therapy for recurrent or metastatic disease.

    Note: Systemic therapy completed > 6 months before signing consent if given as part of multimodal treatment for locally advanced disease is allowed.
35. Subjects must not have received previous immune checkpoint inhibitors (eg, CTLA-4 inhibitor, PD-1 inhibitor, PD-L1 inhibitor, or any other antibody or drug specifically targeting T-cell costimulation) and/or an IDO inhibitor. Subjects who received other immunotherapies must be discussed with medical monitor to confirm eligibility.

3.2. Subject Exclusion Criteria

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

Phase 1 and Phase 2

1. Laboratory and medical history parameters not within the Protocol-defined range. If the screening laboratory tests below were conducted > 7 days before treatment initiation, they will need to be repeated on Cycle 1 Day 1 before initiation of treatment.
   a. Absolute neutrophil count (ANC) < 1.5×10^9/L.
   b. Platelet count < 100×10^9/L.
   c. Hemoglobin < 9 g/dL or < 5.6 mmol/L.
   d. 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 creatinine clearance) < 50 mL/min for subjects with creatinine levels > 1.5 × institutional ULN.
   e. AST, ALT, and ALP ≥ 2.5 × ULN.
      Note: Subjects with 1) bone metastases and 2) no hepatic parenchymal metastases on screening radiographic examinations may enroll if the ALP is ≤ 5 × ULN. Subjects with 1) bone metastases and 2) hepatic parenchymal metastases on screening radiographic examinations may enroll if the ALP is ≤ 5 × ULN only with medical monitor approval.
   f. Total bilirubin ≥ 1.2 × ULN.
      Note: If total bilirubin is ≥ 1.2 × ULN, conjugated (direct) bilirubin must be tested, and subjects will be excluded if the value is ≥ 2.0 × ULN or ≥ 40% of total bilirubin, if there is no institutional ULN.
   g. International normalized ratio (INR), prothrombin time, and activated partial thromboplastin time (aPTT) > 1.5 × ULN (unless the subject is receiving anticoagulant therapy, in which case the subject may be included as long as the INR, prothrombin time, and aPTT are within the therapeutic range of intended use of anticoagulants).
      Note: Partial thromboplastin time may be used in place of aPTT per institutional standards.
2. Receipt of anticancer medications or investigational drugs within the following intervals before Cycle 1 Day 1:
   a. ≤ 14 days for chemotherapy or targeted small molecule therapy.
      Note: Bisphosphonates are permitted concomitant medications.
   b. ≤ 28 days for previous monoclonal antibody used for anticancer therapy.
      Note: Use of denosumab is permitted.
   c. ≤ 7 days for immune-suppressive–based treatment for any reason.
      Note: Use of inhaled or topical steroids, prophylactic corticosteroids for radiographic procedures, or systemic corticosteroid at doses of prednisone ≤ 10 mg/day or equivalent is permitted.
   d. ≤ 28 days or 5 half-lives (whichever is longer) before Cycle 1 Day 1 for all other investigational agents or devices. For investigational agents with long half-lives (eg, > 5 days), enrollment before the fifth half-life requires medical monitor approval.

3. Previous radiotherapy within 14 days of Cycle 1 Day 1 (except for radiation to central nervous system (CNS), which requires a ≥ 28-day washout as described below). Subjects must also not require chronic use of corticosteroids and must not have had radiation pneumonitis as a result of treatment. A 1-week washout is permitted for palliative radiation to non-CNS disease with sponsor approval.
4. Known active CNS metastases and/or carcinomatous meningitis.

   Note: Participants with previously-treated brain metastases may participate provided they are 1) radiologically stable (ie, without evidence of progression for at least 28 days by repeat imaging prior to the first dose of study treatment [repeat imaging may be performed during the screening period with medical monitor approval]), **and** 2) without requirement of steroid treatment for at least 14 days prior to first dose of study treatment, **and** 3) clinically stable, with any neurological signs or symptoms having returned to baseline. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.

   Note: Subjects with evidence of cerebral edema or those with < 28 days since radiation therapy to the CNS will be excluded from study.
5. Has not recovered to ≤ Grade 1 from toxic effects of previous therapy and/or complications from previous surgical intervention before starting study therapy.

   Note: Subjects with stable chronic AEs (≤ Grade 2) not expected to resolve (eg, alopecia) are exceptions and may enroll.

   Note: Subjects with a history of peripheral neuropathy ≥ Grade 2 will be excluded.
6. Receipt of a live vaccine within 30 days of planned start of study therapy.

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

   Note: Exceptions include subjects with vitiligo or resolved childhood asthma/atopy, hypothyroidism stable on hormone replacement, controlled asthma, Type I diabetes, Graves' disease, or Hashimoto's disease, or with medical monitor approval.
9. History of (noninfectious) pneumonitis that required steroids or current pneumonitis or interstitial lung disease.

10. History of 1) allogeneic stem cell or solid organ transplant that requires use of immunosuppressive therapy, 2) has a diagnosis of immunodeficiency, or 3) is receiving chronic systemic steroid therapy (in doses exceeding 10 mg daily of prednisone or its equivalent) or any other form of immunosuppressive therapy within 7 days before Cycle 1 Day 1.

    Note: The use of physiologic doses of corticosteroids may be approved after consultation with the sponsor.

11. Known history of or screening test that is positive for hepatitis B virus (HBV; eg, HBsAg reactive or HBV DNA detected) or hepatitis C virus (HCV; 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.

    Note: For Phase 2, treated hepatitis B subjects are eligible if there is no evidence of active infection (HBV DNA–negative and HBV DNA surface antigen–negative).

12. Known history of human immunodeficiency virus (HIV; HIV 1/2 antibodies).

13. Known secondary malignancy that is progressing or requires active treatment. Exceptions include early stage cancers treated with curative intent, basal cell carcinoma of the skin, squamous cell carcinoma of the skin, *in situ* cervical cancer, or *in situ* breast cancer that has undergone potentially curative therapy.

14. History or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful. Screening QTc interval > 480 milliseconds is excluded (corrected by Fridericia method). In the event that a single QTc is > 480 milliseconds, the subject may enroll if the average QTc for the 3 ECGs is < 480 milliseconds. For subjects with an intraventricular conduction delay (QRS interval > 120 milliseconds), the JTc interval may be used in place of the QTc with sponsor approval. The JTc must be ≤ 340 milliseconds if JTc is used in place of the QTc. Subjects with left bundle branch block are excluded.

    Note: QTc prolongation due to pacemaker may enroll if the JTc is normal or with medical monitor approval.

15. Clinically significant cardiac disease, including unstable angina, acute myocardial infarction within 6 months of Cycle 1 Day 1, New York Heart Association Class III or IV congestive heart failure, and arrhythmia requiring therapy.

    Note: A subject with an arrhythmia may enroll if the subject is on antiarrhythmic medication and is in sinus rhythm on the screening ECG.

16. Subjects with a history of bleeding related to cancer under study requiring a medical intervention (eg, embolization procedure, RBC transfusion, or hospitalization) within 30 days of study enrollment.

17. Known allergy or severe hypersensitivity (≥ Grade 3) reaction to any component of epacadostat, pembrolizumab, or chemotherapy regimen components and/or their formulation excipients.

18. Presence of a gastrointestinal condition (eg, inflammatory bowel disease, Crohn's disease, ulcerative colitis) that may affect drug absorption.

    Note: Subjects with feeding tubes are eligible.

19. Receiving MAOIs or drug that has significant MAOI activity (eg, meperidine, linezolid, methylene blue) within the 21 days before screening. See Appendix D for prohibited medications associated with MAO inhibition.
20. Use of any UGT1A9 inhibitor from screening through safety follow-up period. See Section 5.10 for more details.
21. Any history of SS after receiving serotonergic drugs.
22. Women who are pregnant or breastfeeding.
23. Any condition that would jeopardize the safety of the subject or compliance with the Protocol.

Phase 1 and 2 subjects in Treatment Group A and Treatment Group G only:

24. Known dihydropyrimidine dehydrogenase deficiency (heterozygous or homozygous mutations).

Phase 2 subjects in the cohort of subjects with any solid tumor that progressed on previous therapy with a PD-1 or PD-L1 inhibitor only:

25. History of any grade immune-related ocular AEs.
26. History of a ≥ Grade 3 immune-related AEs from previous immunotherapies.

    Note: Subjects with immune-related adrenal insufficiency because of previous immunotherapy who are medically stable and adequately managed on a stable dose of replacement therapy may be enrolled.

27. Current urinary outflow obstruction.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

Note: As of 25 OCT 2018, this study is closed to enrollment. As of this date, no subjects were enrolled in Phase 2 efficacy expansion (all treatment groups) or Phase 2 mandatory biopsy Treatment Groups A, B, F, and G. Any text included in the body of this Protocol that references these treatment groups and cohorts has not been deleted but should be disregarded.

This is an open-label, nonrandomized, Phase 1/2 study to determine the safety, tolerability, and efficacy of epacadostat when given in combination with pembrolizumab and 7 chemotherapy regimens (Figure 1). Phase 1 will consist of a 3 + 3 + 3 design and will determine the MTD or PAD of epacadostat when given in combination with pembrolizumab and chemotherapy; efficacy will also be explored. Subjects with advanced or metastatic solid tumors who have progressed after receiving at least 1 previous standard therapy for advanced or metastatic disease (or who are intolerant to or refuse standard of care) and for whom treatment with 1 of the chemotherapy regimens is appropriate will be enrolled in Phase 1. Phase 2 will further evaluate the safety, tolerability, and efficacy of the MTD or PAD of epacadostat selected in Phase 1 when given in combination with pembrolizumab and chemotherapy. Subjects with advanced or metastatic CRC, PDAC, NSCLC (squamous or nonsquamous), UC, or SCCHN who have not previously received chemotherapy as first-line therapy for advanced or metastatic disease and have not previously received immune checkpoint inhibitors nor an IDO inhibitor will be enrolled in Phase 2. A separate cohort of subjects with any advanced or metastatic solid tumor who progressed on previous therapy with a PD-1 or PD-L1 inhibitor will also be enrolled in Phase 2.

4.1.1. Phase 1

A 3 + 3 + 3 design will be used in which 7 treatment groups will be explored in parallel. A minimum of 3 evaluable subjects will be enrolled in each treatment group beginning with Cohort 1 (epacadostat 100 mg BID; starting dose), and the first 3 evaluable subjects will be observed for a minimum of 28 days in the cohorts where mFOLFOX6 or *nab*-paclitaxel/gemcitabine are administered or 21 days for all other chemotherapy regimens. To be considered evaluable for dose tolerability, subjects should meet 1 of the following criteria: 1) received the cohort-specified dose of epacadostat, pembrolizumab, and chemotherapy for at least 80% of planned doses in the DLT observation period (45 doses epacadostat/2 doses pembrolizumab for subjects who received mFOLFOX6 or *nab*-paclitaxel/gemcitabine; 34 doses epacadostat/1 dose pembrolizumab for subjects who received any other chemotherapy regimens) and completed the DLT observation period **or** 2) had a DLT during the DLT observation period. It is recognized that certain toxicities due to chemotherapy (eg, including but not limited to gastrointestinal toxicity, including diarrhea; renal insufficiency; high-grade laboratory abnormalities; hypersensitivity/rash) may initially be clinically indistinguishable from toxicities due to immunotherapy. Epacadostat will be held for these toxicities, and as a result, subjects may not receive at least 80% of the prescribed dose during Cycle 1. In these cases, the Safety Monitoring Committee (SMC) may assess subjects who receive dose intensities somewhat below 80% for determining DLTs and consider in the

adjudication process the specific toxicities encountered, likely cause of toxicities, and dose intensity and tolerability beyond Cycle 1. Additional subjects will be enrolled in a cohort to achieve the minimum of 3 evaluable subjects. Subjects who discontinue for reasons other than a DLT (eg, events clearly associated with the underlying disease, disease progression, concomitant medication, comorbidity, or an AE clearly unrelated to treatment) during the DLT observation period will be considered nonevaluable for DLTs and will be replaced.

The scenarios for expansion and de-escalation are summarized below, and the doses of epacadostat to be evaluated are summarized in Table 1:

1. If 0 DLTs occur in 3 subjects in Cohort 1, 3 additional subjects will be treated in Cohort 1. If there is ≤ 1 DLT in these 6 subjects, enrollment in Phase 2 for that treatment group may proceed.
2. If 1 of 3 subjects in Cohort 1 has a DLT, 3 additional subjects will be enrolled in Cohort 1. If there are no additional DLTs (≤ 1 DLT in 6 subjects), enrollment in Phase 2 for that treatment group may proceed.
3. If 2 of 6 subjects in Cohort 1 have a DLT, 3 additional subjects will be enrolled in Cohort 1. If there are no additional DLTs (≤ 2 DLTs in 9 subjects), enrollment in Phase 2 for that treatment group may proceed.
4. If ≥ 2 of 3, 3 of 6, or 3 of 9 subjects have DLTs within a cohort, de-escalation of epacadostat to 50 mg BID (Cohort –1) will be evaluated using the same criteria.

If Cohort –1 is not tolerated within a given treatment group, that treatment group will not be pursued further. The study will be terminated if Cohort –1 is not tolerated in all treatment groups.

Table 1: Epacadostat Dose Cohorts

Epacadostat Dose Cohort	Epacadostat Dose
–1	50 mg BID
1 (starting dose)	**100 mg BID**[a]

[a] If epacadostat 100 mg BID is not tolerated within a treatment group, epacadostat 50 mg BID will be evaluated.

Dose interruptions and/or modifications may be implemented based on toxicity as described in Section 5.5.1.1. Dose modifications should not be made during the DLT observation period without discussion with the medical monitor. Intrasubject dose escalation is not permitted.

Subjects will be assigned to a treatment group (Table 2) based on the chemotherapy regimen most appropriate for their tumor type.

Table 2: Treatment Groups

Treatment Group A	**Epacadostat**	**Pembrolizumab**	**mFOLFOX6**
	BID PO continuous daily dosing (see Table 1)	200 mg IV Q3W	• Oxaliplatin 85 mg/m^2 IV on Day 1 and Day 15 • Leucovorin 400 mg/m^2 IV on Day 1 and Day 15 • 5-Fluorouracil 400 mg/m^2 IV bolus, then 1200 mg/m^2 per day IV infusion over 46 hours for a total dose of 2400 mg/m^2, on Day 1 and Day 15
Treatment Group B	**Epacadostat**	**Pembrolizumab**	***nab*-paclitaxel and Gemcitabine**
	BID PO continuous daily dosing (see Table 1)	200 mg IV Q3W	• *nab*-Paclitaxel 125 mg/m^2 IV on Days 1, 8, and 15 • Gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15
Treatment Group C	**Epacadostat**	**Pembrolizumab**	**Paclitaxel and Carboplatin**
	BID PO continuous daily dosing (see Table 1)	200 mg IV Q3W	• Paclitaxel 200 mg/m^2 IV on Day 1 Q3W • Carboplatin AUC 6 IV on Day 1 Q3W
Treatment Group D	**Epacadostat**	**Pembrolizumab**	**Pemetrexed and Platinum Agent**
	BID PO continuous daily dosing (see Table 1)	200 mg IV Q3W	• Pemetrexed 500 mg/m^2 IV on Day 1 Q3W • Investigators choice of platinum agent: Carboplatin AUC 5 IV on Day 1 Q3W or Cisplatin 75 mg/m^2 on Day 1 Q3W
Treatment Group E	**Epacadostat**	**Pembrolizumab**	**Cyclophosphamide**
	BID PO continuous daily dosing (see Table 1)	200 mg IV Q3W	50 mg PO once daily
Treatment Group F	**Epacadostat**	**Pembrolizumab**	**Gemcitabine and Platinum Agent**
	BID PO continuous daily dosing (see Table 1)	200 mg IV Q3W	• Gemcitabine 1000 mg/m^2 IV on Day 1 and Day 8 Q3W • Investigators choice of platinum agent: Carboplatin AUC 5 IV on Day 1 Q3W or Cisplatin 70 mg/m^2 on Day 1 Q3W
Treatment Group G	**Epacadostat**	**Pembrolizumab**	**Platinum Agent and 5-Fluorouracil**
	BID PO continuous daily dosing (see Table 1)	200 mg IV Q3W	Investigator's choice of platinum agent: • Carboplatin AUC 5 IV on Day 1 Q3W or Cisplatin 100 mg/m^2 IV • 5-Fluorouracil 1000 mg/m^2 per day IV infusion on Days 1-4 (for a total dose of 4000 mg/m^2 over 96 hours) Q3W

IV = intravenous; PO = orally.

4.1.2. Phase 2: Efficacy Expansion and Mandatory Biopsy Cohorts

Phase 2 efficacy expansion cohorts will evaluate the efficacy of the MTD or PAD of epacadostat determined in Phase 1 in combination with pembrolizumab and chemotherapy and to further evaluate the safety and tolerability of the combination. The efficacy expansion cohorts will be limited to the following advanced or metastatic tumor types:

1. CRC (Treatment Group A: epacadostat + pembrolizumab + mFOLFOX6): Simon 2-Stage design
2. PDAC (Treatment Group B: epacadostat + pembrolizumab + *nab*-paclitaxel/gemcitabine): Simon 2-Stage design
3. Squamous NSCLC (Treatment Group C: epacadostat + pembrolizumab + paclitaxel/carboplatin)
4. Nonsquamous NSCLC (Treatment Group D: epacadostat + pembrolizumab + pemetrexed/platinum agent)
5. Any solid tumor that progressed on previous therapy with a PD-1 or PD-L1 inhibitor (Treatment Group E: epacadostat + pembrolizumab + cyclophosphamide)
6. UC (Treatment Group F: epacadostat + pembrolizumab + gemcitabine/platinum agent)
7. SCCHN (Treatment Group G: epacadostat + pembrolizumab + platinum agent/5-fluorouracil)

Enrollment in a specific efficacy expansion cohort in Phase 2 may begin after a minimum of 6 subjects have been treated with epacadostat 100 mg BID in the corresponding treatment group in Phase 1 and there is ≤ 1 DLT in these 6 subjects.

Continuous evaluation of toxicity events will be performed in the efficacy expansion cohorts. If the cumulative incidence of treatment-related SAEs is > 40% and/or the cumulative incidence of ≥ Grade 3 irAEs is > 40% after 10 subjects are enrolled in a specific Phase 2 efficacy expansion cohort, further enrollment in that cohort will be interrupted until the sponsor, investigators, and health authorities (if applicable) determine an appropriate course of action. If an efficacy expansion cohort is discontinued due to toxicity, a new cohort may be initiated at a lower dose of epacadostat.

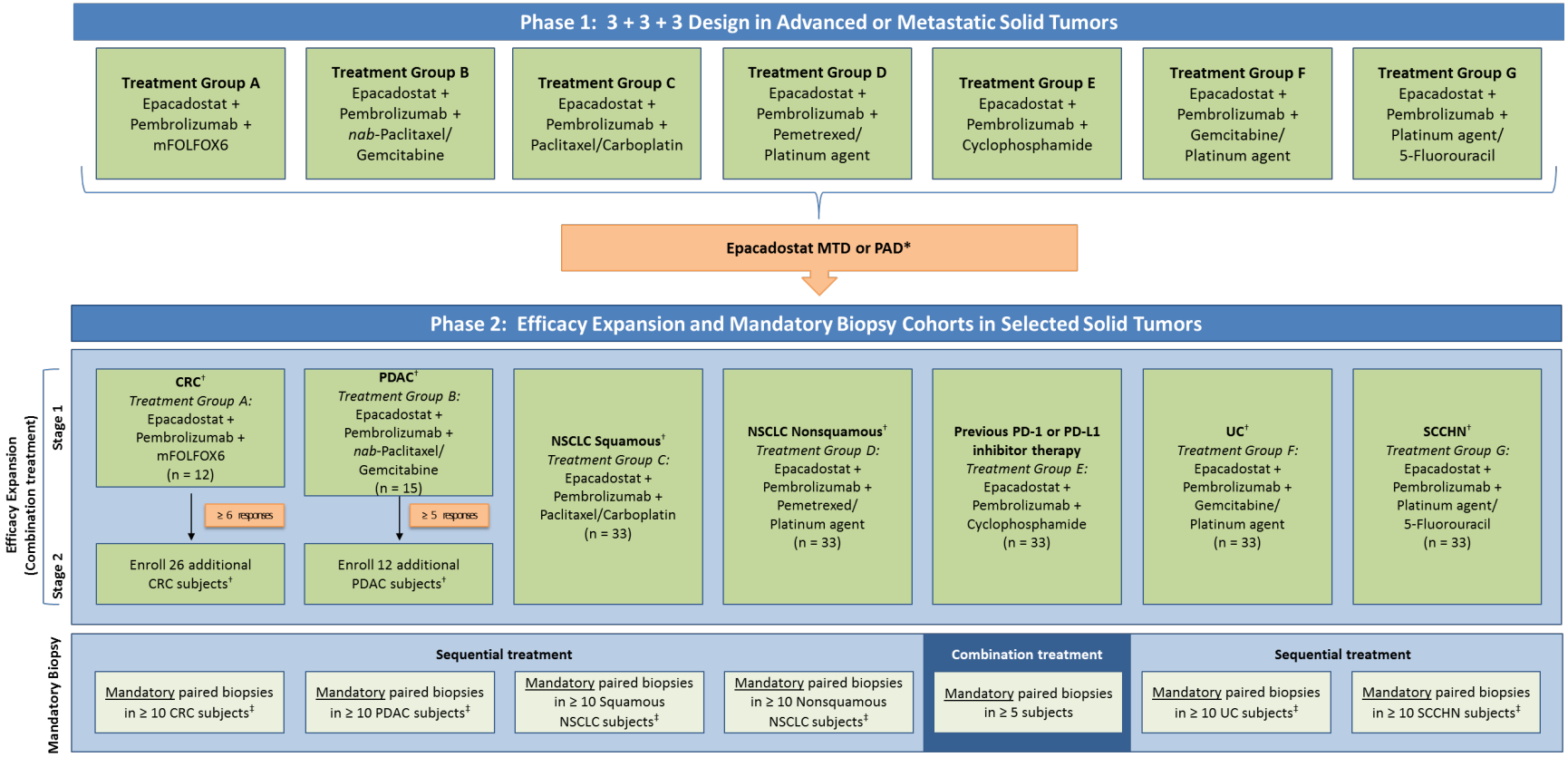
In addition to the efficacy expansion cohorts listed above, separate mandatory biopsy cohorts will be enrolled to evaluate changes in the tumor microenvironment. For the cohorts where IV chemotherapy is administered, subjects will receive IV chemotherapy only during Cycle 1 followed by epacadostat + pembrolizumab + IV chemotherapy starting with Cycle 2 Day 1. For the CRC and PDAC cohorts, a minimum of 10 subjects with evaluable paired biopsy specimens will be enrolled. A fresh tumor biopsy will be collected during screening. On-treatment biopsies are mandatory and will be collected between Days 21 and 27 of Cycle 1 (IV chemotherapy only) and Cycle 2 (epacadostat + pembrolizumab + IV chemotherapy). For the squamous NSCLC, nonsquamous NSCLC, UC, or SCCHN cohorts, a minimum of 10 subjects with evaluable paired biopsy specimens will be enrolled. A fresh tumor biopsy will be collected during screening. On-treatment biopsies are mandatory and will be collected between Days 14 and 20 of Cycle 1 (IV chemotherapy only) and Days 7 and 13 of Cycle 3 (epacadostat + pembrolizumab + IV chemotherapy). For subjects with any advanced or metastatic solid tumor that progressed on

previous therapy with a PD-1 or PD-L1 inhibitor, a minimum of 5 subjects with evaluable paired biopsy specimens will be enrolled in the mandatory biopsy cohort; however, this cohort will be administered epacadostat, pembrolizumab, and cyclophosphamide starting on Cycle 1 Day 1. A fresh tumor biopsy will be collected during screening, and an on-treatment biopsy is mandatory and will be collected between Days 7 and 13 of Cycle 3.

If a subject is selected for inclusion in the mandatory biopsy cohort, and it is subsequently determined that tumor tissue cannot safely be obtained, or if the biopsy does not meet minimum standards for evaluation (as outlined in the Laboratory Manual), the subject may still enroll in the mandatory biopsy cohort and will be followed for efficacy and safety. The subject may be replaced in order to enroll sufficient numbers of evaluable subjects with paired biopsies.

Note: As of 25 OCT 2018, on-treatment tumor biopsies are no longer required for subjects who are already enrolled in the mandatory biopsy cohorts.

Figure 1: Study Design



*If epacadostat 100 mg BID is not tolerated within a treatment group, epacadostat 50 mg BID will be evaluated. For all treatment groups, a minimum of 6 subjects must be treated with epacadostat 100 mg BID before opening Phase 2 at that dose.
†On-treatment biopsies are optional for all subjects enrolled in the Phase 2 efficacy expansion cohorts who receive IV chemotherapy.
‡For the Phase 2 mandatory biopsy cohorts with sequential treatment: IV chemotherapy only will be administered for Cycle 1; epacadostat, pembrolizumab, and IV chemotherapy will be administered starting on Cycle 2 Day 1.

4.2. Measures Taken to Avoid Bias

This is an open-label study. Assessment of safety using CTCAE v4.0 and efficacy using RECIST v1.1 are objective measurements, and only comparisons to pretreatment conditions will be made.

4.3. Number of Subjects

4.3.1. Planned Number of Subjects

Up to 421 subjects from up to 25 sites may be enrolled in the study:

- Phase 1 – Approximately 42 to 126 evaluable subjects.
- Phase 2 (Efficacy Expansion + Mandatory Biopsy) – Approximately 237 to 295 evaluable subjects.

As of 25 OCT 2018, this study is closed to enrollment. A total of 70 subjects were enrolled. No subjects were enrolled in Phase 2 efficacy expansion (all treatment groups) or Phase 2 mandatory biopsy Treatment Groups A, B, F, and G.

4.3.2. Replacement of Subjects

Subjects may be replaced for any of the following reasons:

- Subject is not evaluable for DLTs (see Section 5.5.1.1).
- In the Phase 2 mandatory biopsy cohorts, subject has not met the biopsy requirements for the study (ie, pre- and on-treatment samples).
- Subject does not meet the eligibility requirements of the study (eg, accidental enrollment).

4.4. Duration of Treatment and Subject Participation

After signing the ICF, screening assessments may be completed over a period of up to 28 days. Each subject enrolled in the study may receive treatment in continuous 28-day (mFOLFOX6 or *nab*-paclitaxel/gemcitabine) or 21-day cycles (all other chemotherapy regimens) if, in the judgment of the investigator, the subject is receiving benefit from treatment and has not met any criteria for treatment discontinuation.

Subjects who complete a standard duration of chemotherapy, or who must stop chemotherapy due to cumulative chemotherapy-related toxicities, may continue on pembrolizumab for a total of 35 pembrolizumab infusions and epacadostat through the end of the cycle in which the 35th pembrolizumab infusion is administered. Subjects may not start a new or different chemotherapy regimen during this period. Unless a maximum number of chemotherapy cycles are noted in the Protocol (see Section 5.3), subjects may continue chemotherapy beyond the maximum administration of epacadostat or pembrolizumab at the discretion of the treating physician in line with local prescribing labels, treatment guidelines, and/or standards of care. If subjects are continued on chemotherapy, contraception methods should continue for 180 days after the last dose of chemotherapy.

Subjects who must discontinue epacadostat due to epacadostat-related toxicities may continue pembrolizumab for a total of 35 pembrolizumab infusions. Unless a maximum number of chemotherapy cycles are noted in the Protocol (see Section 5.3), subjects may continue chemotherapy beyond the maximum administration of pembrolizumab at the discretion of the treating physician in line with local prescribing labels, treatment guidelines, and/or standards of care. If subjects are continued on chemotherapy, contraception methods should continue for 180 days after the last dose of chemotherapy.

Once a subject discontinues epacadostat and pembrolizumab, the subject will enter the follow-up period (see Section 6.4).

Study participation, including post-treatment follow-up, is expected to average 16 months for an individual subject (mFOLFOX6: 18-24 months, *nab*-paclitaxel/gemcitabine: 8-12 months; paclitaxel/carboplatin: 12-18 months; pemetrexed/platinum agent: 12-18 months; cyclophosphamide: 4-6 months; gemcitabine/platinum agent: 8-12 months; platinum agent/5-fluorouracil: 8-12 months).

4.5. Overall Study Duration

The study begins when the first subject signs the ICF. The end of the study will occur when all subjects have discontinued epacadostat and pembrolizumab and have completed the 30- and 90-day safety follow-up assessments or a minimum of 18 weeks after initial study medication administration. If by the end of the study there remains at least 1 subject still on study treatment for at least 18 weeks, the subject(s) may enter additional treatment cycles. At this point, a database lock of the study may occur to allow the analysis of the study data. Any remaining subjects may continue to receive study medications and be seen by the investigator per usual standard of care for this subject population. In addition, the investigator will be expected to monitor for and report any SAEs, AEs of special interest, and pregnancies, as detailed in Section 8. The remaining subjects are considered to be on study until a discontinuation criterion is met and written notification is provided to the sponsor.

4.6. Study Termination

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study contract. The investigator is to notify the institutional review board (IRB)/independent ethics committee (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, if required by regulatory decision, or upon review of emerging data. If the study is terminated prematurely, the sponsor will notify the investigators, the IRBs and IECs, and regulatory bodies of the decision and reason for termination of the study.

5. TREATMENT

5.1. Treatment Assignment

5.1.1. Subject Numbering and Treatment Assignment

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

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

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

5.1.2. Randomization and Blinding

Not applicable.

5.2. Study Drug

5.2.1. Epacadostat

5.2.1.1. Description and Administration

Epacadostat will be self-administered orally BID without regard to food. Doses will be taken in the morning and evening, approximately 12 hours apart. If a dose is missed by more than 4 hours, then that dose should be skipped, and the next dose should be taken at the next scheduled timepoint.

For Phase 1 and Phase 2 efficacy expansion subjects enrolled in Treatment Groups A, B, C, D, E, F, and G, and the Phase 2 mandatory biopsy subjects enrolled in Treatment Group E, epacadostat will be administered beginning on Cycle 1 Day 1 and continuously thereafter. For Phase 2 subjects enrolled in the mandatory biopsy cohorts where IV chemotherapy is administered (Treatment Groups A, B, C, D, F, and G), epacadostat will be administered beginning on Cycle 2 Day 1 and continuously thereafter. Treatment will continue through the end of the cycle in which the 35th pembrolizumab infusion is administered if, in the investigator's judgment, the subject is receiving benefit from therapy and has not met any criteria for treatment

discontinuation (see Section 5.6.1). Treatment will end the evening before the scheduled date of the subject's end-of-treatment (EOT) visit.

Phase 1 subjects enrolled in Treatment Groups A, B, C, D, E, F, and G and Phase 2 efficacy expansion subjects enrolled in Treatment Groups A, B, E, F, and G will self-administer epacadostat except for the morning dose on Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 2 Day 1, where epacadostat will be given at the study site, [redacted]. On days when epacadostat is administered in the clinic, epacadostat should be taken before beginning the infusion of pembrolizumab.

Phase 2 efficacy expansion subjects enrolled in Treatment Groups C and D will self-administer epacadostat except for the morning dose on Cycle 1 Day 1 and Cycle 2 Day 1, [redacted]. Subjects will skip their morning dose on Cycle 1 Day 1 dose and initiate epacadostat with the evening dose on Cycle 1 Day 1. For Cycle 2 Day 1, epacadostat will be administered in the clinic before infusion of the chemotherapy regimens and pembrolizumab.

5.2.1.2. Supply, Packaging, and Labeling

Epacadostat will be available as 100-mg tablets packaged in high-density polyethylene bottles. All tablet excipients comply with the requirements of the applicable compendial monographs (Ph. Eur., USP/NF; refer to the eIB).

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

5.2.1.3. Storage

Bottles should be stored at room temperature (15°C to 30°C [59°F to 86°F]) and closed tightly to protect the tablets from humidity.

5.3. Background Therapies

5.3.1. Pembrolizumab

5.3.1.1. Description and Administration

Subjects will receive pembrolizumab 200 mg as a 30-minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close as possible to 30 minutes (-5 min/+10 min).

For Phase 1 and Phase 2 efficacy expansion subjects enrolled in Treatment Groups A, B, C, D, E, F, and G, and for Phase 2 mandatory biopsy subjects enrolled in Treatment Group E, pembrolizumab will be administered starting on Cycle 1 Day 1. For subjects enrolled in the Phase 2 mandatory biopsy cohorts where IV chemotherapy is administered (Treatment Groups A, B, C, D, F, and G), pembrolizumab will be administered starting on Cycle 2 Day 1.

Treatment will continue for a total of 35 pembrolizumab infusions if, in the investigator's judgment, the subject is receiving benefit from therapy and has not met any criteria for treatment discontinuation (see Section 5.6.1). Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons (ie, elective surgery, unrelated medical events, subject vacation, holidays) not related to study therapy. Subjects should resume pembrolizumab within 3 weeks of the scheduled interruption. The reason for interruption should be documented in the eCRF.

Sites are instructed to consult the Pharmacy Manual for additional information and instructions for preparation and infusion of pembrolizumab.

5.3.1.2. Supply, Packaging, and Labeling

Pembrolizumab is available as a 100 mg/4 mL solution for injection and will be provided by Incyte. The contents of the label will be in accordance with all applicable regulatory requirements.

5.3.1.3. Storage

Vials should be stored under refrigeration at 2°C to 8°C (36°F to 46°F). Vials should be protected from light by being stored in the original package until time of use. Do not freeze or shake. Sites are instructed to consult the Pharmacy Manual for additional information on storage of pembrolizumab.

5.3.2. Oxaliplatin, Leucovorin, 5-Fluorouracil

5.3.2.1. Description and Administration

Subjects may receive premedications based on institutional guidelines, investigator practice, or local prescribing information or standards of care. All premedications must be recorded in the eCRF.

Subjects must meet minimum criteria for start of each chemotherapy cycle as outlined in Appendix H, Section H.1.

Subjects will receive oxaliplatin 85 mg/m^2 IV given concurrently with leucovorin 400 mg/m^2 IV over 2 hours (± 15 min; or equivalent dose and schedule based on institutional practice), followed by a 5-fluorouracil 400 mg/m^2 IV bolus (administration time per institutional practice), then a 5-fluorouracil 1200 mg/m^2 per day IV continuous infusion over 46 hours (for a total dose of 2400 mg/m^2). These 3 agents will be administered on Days 1 and 15 of each 28-day cycle. There is no limit to the number of cycles of mFOLFOX6. Investigators may reduce or discontinue oxaliplatin for peripheral neuropathy; if discontinued, investigators have the option to discontinue 5-fluorouracil and leucovorin.

In Phase 1 and Phase 2 efficacy expansion subjects enrolled in Treatment Group A, mFOLFOX6 will be administered after epacadostat and pembrolizumab (if applicable) on Cycle 1 Day 1 and Cycle 2 Day 1 [redacted].

For Phase 2 mandatory biopsy subjects enrolled in Treatment Group A, only IV chemotherapy will be administered during Cycle 1, and epacadostat, pembrolizumab, and IV chemotherapy will be administered starting on Cycle 2 Day 1.

Sites are instructed to consult local prescribing information for additional information and instructions for preparation and infusion of 5-fluorouracil, leucovorin, and oxaliplatin.

Subjects may receive prophylactic G-CSF support with filgrastim per institutional guidelines. Prophylactic G-CSF should not be given in the first cycle unless discussed with the medical monitor.

5.3.2.2. Supply, Packaging, and Labeling

In countries where 5-fluorouracil, leucovorin, oxaliplatin, or their generic equivalents are available, investigators are responsible for ensuring that subjects receive commercially available supplies of these therapies for the entire duration of study participation. Incyte may provide certain reference therapies where required by applicable law or regulation or under other limited circumstances when a subject may not otherwise have access to these therapies. The contents of the labels will be in accordance with all applicable regulatory requirements.

5.3.3. *nab*-Paclitaxel and Gemcitabine

5.3.3.1. Description and Administration

Subjects may receive premedications based on institutional guidelines, investigator practice, or local prescribing information or standards of care. All premedications must be recorded in the eCRF.

Subjects must meet minimum criteria for start of each chemotherapy cycle as outlined in Appendix I, Section I.1.

Subjects will receive *nab*-paclitaxel 125 mg/m^2 IV over 30 minutes (± 5 min) followed by gemcitabine 1000 mg/m^2 IV over 30 minutes (± 5 min) on Days 1, 8, and 15 of each 28-day cycle. The infusion of *nab*-paclitaxel should be completed before beginning the infusion of gemcitabine. There is no limit to the number of cycles of *nab*-paclitaxel/gemcitabine.

In Phase 1 and Phase 2 efficacy expansion subjects enrolled in Treatment Group B, *nab*-paclitaxel/gemcitabine will be administered after epacadostat and pembrolizumab (if applicable) on Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 2 Day 1 [redacted].

For Phase 2 mandatory biopsy subjects enrolled in Treatment Group B, only IV chemotherapy will be administered during Cycle 1, and epacadostat, pembrolizumab, and IV chemotherapy will be administered starting on Cycle 2 Day 1.

Sites are instructed to consult local prescribing information for additional information and instructions for preparation and infusion of *nab*-paclitaxel and gemcitabine.

Subjects may receive prophylactic G-CSF support with filgrastim per institutional guidelines. Prophylactic G-CSF should not be given in the first cycle unless discussed with the medical monitor.

5.3.3.2. Supply, Packaging, and Labeling

In countries where *nab*-paclitaxel or gemcitabine (or generic equivalent of gemcitabine) are available, investigators are responsible for ensuring that subjects receive commercially available supplies of these therapies for the entire duration of study participation. Incyte may provide certain reference therapies where required by applicable law or regulation or under other limited circumstances when a subject may not otherwise have access to these therapies. The contents of the labels will be in accordance with all applicable regulatory requirements.

5.3.4. Paclitaxel and Carboplatin

5.3.4.1. Description and Administration

Subjects must receive premedications (IV or PO) with corticosteroids, H1- and H2-antagonists, and antiemetics based on institutional guidelines, investigator practice, or local prescribing information or standards of care. All premedications must be recorded in the eCRF.

Subjects must meet minimum criteria for start of each chemotherapy cycle as outlined in Appendix J, Section J.1.

Subjects will receive paclitaxel 200 mg/m^2 IV over 3 hours (± 15 min) followed by carboplatin AUC 6 IV over 30 minutes (± 5 min) on Day 1 of each 21-day cycle for a minimum of 4 cycles and maximum of 6 cycles. The dose of carboplatin should be calculated based on local or institutional standards, and the maximum dose may be limited based on these standards. The infusion of paclitaxel should be completed before beginning the infusion of carboplatin.

In Phase 1 subjects enrolled in Treatment Group C, paclitaxel and carboplatin will be administered after epacadostat and pembrolizumab on Cycle 1 Day 1 and Cycle 2 Day 1 [redacted]. Premedications should be administered approximately 30 minutes after completion of the pembrolizumab infusion.

In Phase 2 efficacy expansion subjects enrolled in Treatment Group C, paclitaxel and carboplatin will be administered before pembrolizumab on Cycle 1 Day 1 and Cycle 2 Day 1 [redacted].

For Phase 2 mandatory biopsy subjects enrolled in Treatment Group C, only IV chemotherapy will be administered during Cycle 1, and epacadostat, pembrolizumab, and IV chemotherapy will be administered starting on Cycle 2 Day 1.

Sites are instructed to consult local prescribing information for additional information and instructions for preparation and infusion of paclitaxel and carboplatin.

Subjects may receive prophylactic G-CSF support with filgrastim per institutional guidelines. Prophylactic G-CSF should not be given in the first cycle unless discussed with the medical monitor.

5.3.4.2. Supply, Packaging, and Labeling

In countries where carboplatin, paclitaxel, or their generic equivalents are available, investigators are responsible for ensuring that subjects receive commercially available supplies of these therapies for the entire duration of study participation. Incyte may provide certain reference therapies where required by applicable law or regulation or under other limited circumstances when a subject may not otherwise have access to these therapies. The contents of the labels will be in accordance with all applicable regulatory requirements.

5.3.5. Pemetrexed and Platinum Agent

5.3.5.1. Description and Administration

Subjects must receive premedications (IV or PO) with corticosteroids, antiemetics, and vitamin B12 and folic acid supplementation based on institutional guidelines, investigator practice, or local prescribing information or standards of care. All premedications must be recorded in the eCRF. Subjects receiving cisplatin must also receive hydration as per institutional guidelines.

Subjects must meet minimum criteria for start of each chemotherapy cycle as outlined in Appendix K, Section K.1.

Subjects will receive pemetrexed 500 mg/m^2 IV over 10 minutes (± 5 min) followed by a platinum agent (carboplatin AUC 5 IV over 30 minutes [± 5 min] or cisplatin 75 mg/m^2 IV over 2 hours [± 5 min]) on Day 1 of each 21-day cycle for a minimum of 4 cycles and a maximum of 6 cycles. The dose of carboplatin should be calculated based on local or institutional standards, and the maximum dose may be limited based on these standards. Pemetrexed may continue as maintenance therapy after the 6 cycles.

In Phase 1 subjects enrolled in Treatment Group D, pemetrexed and platinum agent will be administered after epacadostat and pembrolizumab on Cycle 1 Day 1 and Cycle 2 Day 1 [redacted]. Premedications should be administered approximately 30 minutes after completion of the pembrolizumab infusion.

In Phase 2 efficacy expansion subjects enrolled in Treatment Group D, pemetrexed and platinum agent will be administered before pembrolizumab on Cycle 1 Day 1 and Cycle 2 Day 1 [redacted].

For Phase 2 mandatory biopsy subjects enrolled in Treatment Group D, only IV chemotherapy will be administered during Cycle 1, and epacadostat, pembrolizumab, and IV chemotherapy will be administered starting on Cycle 2 Day 1.

Sites are instructed to consult local prescribing information for additional information and instructions for preparation and infusion of pemetrexed and the applicable platinum agent.

Subjects may receive prophylactic G-CSF support with filgrastim per institutional guidelines. Prophylactic G-CSF should not be given in the first cycle unless discussed with the medical monitor.

5.3.5.2. Supply, Packaging, and Labeling

In countries where pemetrexed or carboplatin or cisplatin (or platinum agent generic equivalents) are available, investigators are responsible for ensuring that subjects receive commercially available supplies of these therapies for the entire duration of study participation. Incyte may provide certain reference therapies where required by applicable law or regulation or under other limited circumstances when a subject may not otherwise have access to these therapies. The contents of the labels will be in accordance with all applicable regulatory requirements.

5.3.6. Cyclophosphamide

5.3.6.1. Description and Administration

Subjects may receive premedications based on institutional guidelines, investigator practice, or local prescribing information or standards of care. All premedications must be recorded in the eCRF.

Subjects must meet minimum criteria for start of each chemotherapy cycle as outlined in Appendix L, Section L.1.

Subjects will self-administer cyclophosphamide 50 mg PO once daily of each 21-day cycle. There is no limit to the number of cycles of cyclophosphamide. Sites are instructed to consult local prescribing information for additional information on cyclophosphamide.

In Phase 1 and Phase 2 efficacy expansion subjects enrolled in Treatment Group E, cyclophosphamide will be administered after epacadostat and pembrolizumab (if applicable) on Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 2 Day 1 [redacted].

For Phase 1, Phase 2 efficacy expansion, and Phase 2 mandatory biopsy subjects enrolled in Treatment Group E, epacadostat, pembrolizumab, and cyclophosphamide will be administered starting on Cycle 1 Day 1.

Subjects may receive prophylactic G-CSF support with filgrastim per institutional guidelines. Prophylactic G-CSF should not be given in the first cycle unless discussed with the medical monitor.

5.3.6.2. Supply, Packaging, and Labeling

Cyclophosphamide will be obtained from commercial supplies and will be reimbursed by Incyte. Investigators are responsible for ensuring that subjects receive commercially available supplies of cyclophosphamide for the entire duration of study participation. Incyte may provide cyclophosphamide where required by applicable law or regulation or under other limited circumstances when a subject may not otherwise have access to these therapies. The contents of the label will be in accordance with all applicable regulatory requirements.

5.3.7. Gemcitabine and Platinum Agent

5.3.7.1. Description and Administration

Subjects must receive premedications (IV or PO) with corticosteroids and antiemetics based on institutional guidelines, investigator practice, or local prescribing information or standards of care. All premedications must be recorded in the eCRF. Subjects receiving cisplatin must also receive hydration as per institutional guidelines.

Subjects must meet minimum criteria for start of each chemotherapy cycle as outlined in Appendix M, Section M.1.

Gemcitabine and platinum agent will be administered in a 21-day cycle for a maximum of 6 cycles. Subjects will receive gemcitabine 1000 mg/m^2 over 30 minutes (± 5 min) on Days 1 and 8. Administration of a platinum agent (carboplatin AUC 5 IV over 30 minutes [± 5 min] or cisplatin 70 mg/m^2 IV over 2 hours [± 5 min]) will follow the gemcitabine infusion on Day 1. The dose of carboplatin should be calculated based on local or institutional standards, and the maximum dose may be limited based on these standards.

In Phase 1 and Phase 2 efficacy expansion subjects enrolled in Treatment Group F, applicable chemotherapy agent will be administered after epacadostat and pembrolizumab (if applicable) on Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 2 Day 1 [redacted].

For Phase 2 mandatory biopsy subjects enrolled in Treatment Group F, only IV chemotherapy will be administered during Cycle 1, and epacadostat, pembrolizumab, and IV chemotherapy will be administered starting on Cycle 2 Day 1.

Sites are instructed to consult local prescribing information for additional information and instructions for preparation and infusion of gemcitabine and the applicable platinum agent.

Subjects may receive prophylactic G-CSF support with filgrastim per institutional guidelines. Prophylactic G-CSF should not be given in the first cycle unless discussed with the medical monitor.

5.3.7.2. Supply, Packaging, and Labeling

In countries where carboplatin, cisplatin, gemcitabine, or their generic equivalents are available, investigators are responsible for ensuring that subjects receive commercially available supplies of these therapies for the entire duration of study participation. Incyte may provide certain reference therapies where required by applicable law or regulation or under other limited circumstances when a subject may not otherwise have access to these therapies. The contents of the labels will be in accordance with all applicable regulatory requirements.

5.3.8. Platinum Agent and 5-Fluorouracil

5.3.8.1. Description and Administration

Subjects must receive premedications (IV or PO) with corticosteroids and antiemetics based on institutional guidelines, investigator practice, or local prescribing information or standards of care. All premedications must be recorded in the eCRF. Subjects receiving cisplatin must also receive hydration as per institutional guidelines.

Subjects must meet minimum criteria for start of each chemotherapy cycle as outlined in Appendix N, Section N.1.

Subjects will receive a platinum agent (carboplatin AUC 5 IV over 30 minutes [± 5 min] or cisplatin 100 mg/m^2 IV over 60 minutes [± 5 min]) on Day 1 of each 21-day cycle followed by 5-fluorouracil 1000 mg/m^2 per day IV continuous infusion on Days 1 through 4 (for a total dose of 4000 mg/m^2 over 96 hours) of each 21-day cycle for a maximum of 6 cycles. The dose of carboplatin should be calculated based on local or institutional standards, and the maximum dose may be limited based on these standards.

In Phase 1 and Phase 2 efficacy expansion subjects enrolled in Treatment Group G, platinum agent/5-fluorouracil will be administered after epacadostat and pembrolizumab on Cycle 1 Day 1 and Cycle 2 Day 1 [redacted].

For Phase 2 mandatory biopsy subjects enrolled in Treatment Group G, only IV chemotherapy will be administered during Cycle 1, and epacadostat, pembrolizumab, and IV chemotherapy will be administered starting on Cycle 2 Day 1.

Sites are instructed to consult local prescribing information for additional information and instructions for preparation and infusion of applicable platinum agent and 5-fluorouracil.

Subjects may receive prophylactic G-CSF support with filgrastim per institutional guidelines. Prophylactic G-CSF should not be given in the first cycle unless discussed with the medical monitor.

5.3.8.2. Supply, Packaging, and Labeling

In countries where carboplatin, cisplatin, 5-fluourouracil, or their generic equivalents are available, investigators are responsible for ensuring that subjects receive commercially available supplies of these therapies for the entire duration of study participation. Incyte may provide certain reference therapies where required by applicable law or regulation or under other limited circumstances when a subject may not otherwise have access to these therapies. The contents of the labels will be in accordance with all applicable regulatory requirements.

5.4. Treatment Compliance

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

Pembrolizumab, 5-fluorouracil, leucovorin, oxaliplatin, carboplatin, cisplatin, paclitaxel, pemetrexed, gemcitabine, and *nab*-paclitaxel are administered as an IV infusion by site personnel. Receipt of infusions will be documented by the site staff and monitored by the sponsor/designee.

5.5. Treatment Interruptions and Adjustments

5.5.1. Dose Modifications

Modifications to epacadostat dosing are planned for the Phase 1 cohorts (see Section 4.1.1). Dose modifications in the form of reductions, interruption, or discontinuation of components of the chemotherapy regimen and/or interruption or discontinuation of pembrolizumab or epacadostat may also be needed for individual subjects in the event of a DLT or AE (related or unrelated to treatment). Intrasubject dose escalation for epacadostat, pembrolizumab, or any chemotherapy drug is not permitted.

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

A DLT will be defined as the occurrence of any of the toxicities in Table 3 occurring up to and including Day 28 for the cohorts where mFOLFOX6 and *nab*-paclitaxel/gemcitabine are administered and Day 21 for all other chemotherapy regimens in Phase 1, except those with a clear alternative explanation (eg, disease progression) or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms based on investigator determination. Immune-related AEs of Grade 3 that improve to Grade 1 or lower within 14 days after the initiation of supportive care or corticosteroid therapy can be deemed a non-DLT. All DLTs will be assessed by the investigator using CTCAE v4.0 criteria (Appendix E). To be considered evaluable for dose tolerability, subjects should meet 1 of the following criteria: 1) receive the cohort-specified dose of epacadostat, pembrolizumab, and chemotherapy for at least 80% of planned doses (45 doses epacadostat/2 doses pembrolizumab for subjects who receive mFOLFOX6 or *nab*-paclitaxel/gemcitabine; 34 doses epacadostat/1 dose pembrolizumab for subjects who receive any other chemotherapy regimen) and complete the DLT observation period, **or** 2) had a DLT during the DLT observation period. It is recognized that certain toxicities due to chemotherapy (eg, including but not limited to gastrointestinal toxicity, including diarrhea; renal insufficiency; high-grade laboratory abnormalities; hypersensitivity/rash) may initially be clinically indistinguishable from toxicities due to immunotherapy. Epacadostat will be held for these toxicities, and as a result, subjects may not receive at least 80% of the prescribed dose during Cycle 1. In these cases, the SMC may assess subjects who receive dose intensities somewhat below 80% for the determination of DLTs, and consider in the adjudication process the specific toxicities encountered, likely cause of toxicities, and dose intensity and tolerability beyond Cycle 1.

Individual subject dose reductions may be made based on events observed at any time during treatment with epacadostat; however, for the purposes of dose cohort de-escalation, expanding a dose cohort, and determining the MTD of epacadostat, decisions will be made based on events that are observed from the first day of epacadostat administration through and including the final day of Cycle 1 (Day 28 for the cohorts where mFOLFOX6 and *nab*-paclitaxel/gemcitabine are administered and Day 21 for all other chemotherapy regimens). A lower MTD of epacadostat may subsequently be determined based on relevant toxicities that become evident after Day 28 for the cohorts where mFOLFOX6 and *nab*-paclitaxel/gemcitabine are administered and Day 21 for all other chemotherapy regimens.

Table 3: Definition of Dose-Limiting Toxicity

Toxicity
Nonhematologic
• Grade 4 (life-threatening) irAE. • Grade 4 (life-threatening) vomiting or diarrhea. • Grade 4 (life-threatening) electrolyte abnormality. • Any ≥ Grade 3 nonhematologic toxicity EXCEPT: – Transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms. – Grade 3 nausea, vomiting, and diarrhea adequately controlled with medical therapy within 48 hours. – Grade 3 rash in the absence of desquamation, with no mucosal involvement, that does not require systemic steroids and that resolves to Grade 1 in ≤ 14 days. – An event clearly associated with the underlying disease, disease progression, a concomitant medication, or comorbidity. – Singular or nonfasting elevations in blood glucose (ie, blood glucose excursions will be considered toxicities if fasting blood glucose is elevated on 2 separate occasions). – Grade 3 irAE that improves to ≤ Grade 1 in ≤ 14 days by appropriate care or with corticosteroid therapy.
Hematologic
• ≥ Grade 3 thrombocytopenia with clinically significant bleeding (requires hospitalization, transfusion of blood products, or other urgent medical intervention). • Grade 4 thrombocytopenia of any duration. • Grade 4 neutropenia lasting > 3 days. • ≥ Grade 3 febrile neutropenia (ANC < 1.0×10^9/L and fever > 101°F/38.3°C). • Grade 4 anemia not explained by underlying disease.

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

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

5.5.1.1.2. Follow-Up of Dose-Limiting Toxicities

Any DLT should be followed until it resolves to baseline or appears to have stabilized for a minimum of 30 days, unless the subject discontinues epacadostat and pembrolizumab, in which case, the subject will be followed for 90 days after the last dose of epacadostat or pembrolizumab (whichever is later; see Section 8). During follow-up, subjects should be seen as often as medically indicated to ensure safety.

5.5.1.2. Procedures for Cohort Review and Dose De-Escalation

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

5.5.2. Criteria and Procedures for Dose Reductions or Interruptions of Epacadostat and/or Pembrolizumab

Dose reductions of epacadostat for the management of AEs are not permitted; however, administration may be delayed for management of toxicities (see Section 5.5.3 and Appendix G). 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 epacadostat that was temporarily interrupted because of an AE.

For specific guidance for interruption of epacadostat in the event of SS, see Section 5.5.6.

Dose reductions of pembrolizumab for the management of AEs is not permitted; however, administration may be delayed for management of toxicities (see Section 5.5.3 and Appendix G).

Dose interruptions of epacadostat and/or pembrolizumab may be permitted in the case of medical/surgical events or logistical reasons not related to study therapy (eg, elective surgery, unrelated medical events, subject vacation, and/or holidays). Subjects will be placed back on study therapy within 3 weeks of the scheduled interruption. The reason for interruption should be documented in the eCRF.

5.5.3. Management of Immune-Related Adverse Events

Adverse events associated with epacadostat and/or pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of epacadostat and/or pembrolizumab treatment and may affect more than 1 body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of epacadostat and/or pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue epacadostat and/or pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with epacadostat and/or pembrolizumab are provided in Appendix G. Subjects who develop a ≥ Grade 2 irAE should be discussed immediately with the sponsor.

It is important to note that some chemotherapy-related AEs will overlap with potential irAEs (including but not limited to gastrointestinal toxicity, including diarrhea; renal insufficiency; high-grade laboratory abnormalities; rash/hypersensitivity). In these cases, both the chemotherapy-related AE (see Section 5.5.4) and irAE management guidance (Appendix G) should be reviewed to determine the most appropriate management of therapy.

5.5.4. Management of Chemotherapy-Related Adverse Events

Dose modifications for hematologic and nonhematologic AEs related to chemotherapy may be managed per institutional guidelines. In the absence of these, recommendations for dose modifications for the applicable chemotherapy regimen in the event of hematologic and nonhematologic AEs are provided in the Protocol appendices:

- Appendix H for subjects who receive mFOLFOX6
- Appendix I for subjects who receive *nab*-paclitaxel/gemcitabine
- Appendix J for subjects who receive paclitaxel/carboplatin
- Appendix K for subjects who receive pemetrexed/platinum agent
- Appendix L for subjects who receive cyclophosphamide
- Appendix M for subjects who receive gemcitabine/platinum agent
- Appendix N for subjects who receive platinum agent/5-fluorouracil

It is important to note that some chemotherapy-related AEs will overlap with potential irAEs (including but not limited to gastrointestinal toxicity, including diarrhea; renal insufficiency; high-grade laboratory abnormalities; rash/hypersensitivity). In these cases, both the chemotherapy-related AE and irAE management guidance (Appendix G) should be reviewed to determine the most appropriate management of therapy.

5.5.5. Treatment After Initial Radiologic Evidence of Disease Progression

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

RECIST v1.1 will be adapted for defining PD to account for the unique tumor response seen with immunotherapies. This adaptation is known as irRECIST and will be used to guide treatment decisions for discontinuation of therapy due to disease progression. These disease assessments will be performed by the study site.

If radiographic imaging shows PD, it is at the discretion of the investigator to keep a subject on treatment or to stop treatment until imaging is repeated ≥ 4 weeks (but not ≥ 6 weeks) later in order to confirm PD. When feasible, subjects should not be discontinued until progression is confirmed. The decision to continue treatment after the first evidence of disease progression is at the investigator's discretion and should be based on the clinical status of the subject as described in Table 4.

Subjects may receive treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

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

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

In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging until the subject has confirmed PD, starts a new anticancer therapy, withdraws consent, or dies.

Table 4: Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD	Repeat imaging at ≥ 4 weeks to confirm PD.	May continue treatment at the investigator's discretion while awaiting confirmatory scan.	Repeat imaging at ≥ 4 weeks to confirm PD, if possible.	Discontinue treatment.
Repeat scan confirms PD	No additional imaging required.	Discontinue treatment.	No additional imaging required.	N/A
Repeat scan shows SD, PR, or CR	Continue regularly scheduled imaging assessments.	Continue treatment at the investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart treatment if condition has improved and/or is clinically stable per investigator's discretion.

5.5.6. Procedure for Subjects Exhibiting Serotonin Syndrome

There is a rare chance that epacadostat could cause an increase in serotonin levels in the brain that might trigger SS 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 (SSRIs) and selective serotonin/norepinephrine reuptake inhibitors (SNRIs) are permitted in the study.

Serotonin syndrome usually manifests with autonomic changes, mental status changes, and neurological findings. These mild, moderate, and severe signs and symptoms of SS (see Table 5) 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, including tremor; hyperreflexia; and spontaneous, ocular, or inducible clonus, together with agitation, fever, diaphoresis, or muscle rigidity:

- Immediately interrupt epacadostat, pembrolizumab, and chemotherapy (if applicable) 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, pembrolizumab and chemotherapy (if applicable) administration may be resumed unless other AE management guidelines apply for the specific event.

- If subject chooses to remain in the study, restart treatment 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 treatment MAY NOT be restarted.
- If subject chooses to withdraw from the study or must restart treatment with SSRI or SNRI, the subject should be scheduled for a follow-up visit. Treatment with SSRI or SNRI may be initiated 2 weeks after resolution of signs and symptoms of SS.
- If subject experiences moderate or severe unconfounded SS in the opinion of the investigator, without concomitant SSRI or SNRI usage, or serotonergic concomitant medications, only pembrolizumab administration may be resumed; epacadostat treatment should be permanently discontinued.

Table 5: Sign and Symptoms of Serotonin Syndrome

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

5.6. Discontinuation of Subjects From Study Treatment

5.6.1. Discontinuation Criteria

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

Subjects **must** be discontinued from treatment for the following reasons:

- Unacceptable AEs as described in Appendix G, Table G-1 with a requirement to permanently discontinue.
- The subject becomes pregnant.
- Consent is withdrawn by the subject.

  Note: Consent withdrawn means that the subject can no longer be followed and no additional data can be collected.
- Further participation would be injurious to the subject's health or well-being, in the investigator's medical judgment.
- Confirmed radiographic progression of disease per irRECIST. See Section 5.5.5, Section 7.6.2.1, and Appendix F.
- The subject has an unacceptable toxicity or a toxicity that does not recover in 12 weeks. Investigators who wish to continue treatment after a treatment delay of 12 weeks should consult with the sponsor's medical monitor for approval.
- The subject has completed 35 infusions of pembrolizumab and completed epacadostat treatment through the end of the cycle in which the 35th pembrolizumab infusion is administered. If the subject has discontinued epacadostat for epacadostat-related toxicities but continued on pembrolizumab monotherapy, the subject must be discontinued after 35 infusions of pembrolizumab.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

A subject may be discontinued from treatment as follows:

- The subject has attained a confirmed CR and has been treated for at least 24 weeks with epacadostat and pembrolizumab and had at least 2 infusions of pembrolizumab beyond the date of initial CR.
- 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 the study.
- If a subject is noncompliant with study procedures or epacadostat administration in the investigator's opinion, the sponsor should be consulted for instruction on handling the subject.

5.6.2. Discontinuation Procedures

Discontinuation of epacadostat and pembrolizumab does not constitute study withdrawal or completion. The subject will proceed to the safety follow-up period when epacadostat and pembrolizumab are permanently discontinued. The EOT visit should be conducted whenever possible except when subjects are physically unable to travel to the site for the EOT visit, have withdrawn consent, or are lost to follow up. Reasonable efforts should be made to have the subject return for the safety follow-up visit to have procedures completed as described in Section 6. The date the subject was discontinued from epacadostat and pembrolizumab and the specific reason for discontinuation will be recorded in the eCRF.

If a subject is discontinued from epacadostat and pembrolizumab:

- The study monitor or sponsor must be notified.
- The reason(s) for the discontinuation must be documented in the subject's medical record and in the eCRF.
- The EOT or early termination visit should be performed.
- The date epacadostat and pembrolizumab was discontinued should be recorded in the IRT.
- Subjects must be followed for safety until the time of the follow-up visit or until epacadostat–related or pembrolizumab–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer.

5.7. Procedures for Withdrawal From Study

If the subject discontinues epacadostat and pembrolizumab and actively withdraws consent for collection of follow-up data (ie, subsequent anticancer treatments and safety follow-up), then no additional data collection should occur. The date the subject was withdrawn from the study will be recorded in the eCRF.

5.8. Concomitant Medications

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

All concomitant medications received within 28 days before Cycle 1 Day 1 and 90 days after the last dose of epacadostat or pembrolizumab (whichever is later) should be recorded. Concomitant medications administered in the 90 days after the last dose of epacadostat or pembrolizumab (whichever is later) should be recorded for SAEs and AEs as defined in Section 8.

5.8.1. Permitted (Acceptable) Medications

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

5.9. Restricted Medications

- Systemic steroids may be used at doses ≤ 10 mg/day prednisone or equivalents.
- 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 may require dose modification. If an alternative to coumarin-based anticoagulants cannot be used, close INR monitoring is recommended.
- 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. Prohibited Medications/Treatment

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

- Any investigational medication other than epacadostat, pembrolizumab, or the assigned chemotherapy regimen.
- Any anticancer medications, including chemotherapy, immunotherapy, or biologic therapy other than epacadostat, pembrolizumab, or the assigned chemotherapy regimen.
- Any chronic immunosuppressive treatment for any reason.

  Note: Inhaled or topical steroids, systemic steroids at doses ≤ 10 mg/day of prednisone or equivalents, systemic steroids for short-term treatment of irAEs, or systemic steroids for prophylaxis of contrast allergy for imaging procedures, or systemic steroids for prophylaxis of chemotherapy-related AEs are allowed.
- Radiation therapy.

  Note: In the presence of a mixed response (some lesions improving or stable and other lesions progressing), radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after discussion with the medical monitor.
- Administration of a live attenuated vaccine within 30 days before the first dose of treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection

are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines are live attenuated vaccines and are not allowed.

- Any MAOI or drug associated with significant MAOI activity agents is prohibited from 21 days before Day 1 through 2 weeks after the final dose of epacadostat has been administered (see Appendix D).
- Any UGT1A9 inhibitor, including acitretin, amitriptyline, androsterone, cyclosporine, dasatinib, diclofenac, diflunisal, efavirenz, erlotinib, flutamide, gefitinib, gemfibrozil, glycyrrhetinic acid, glycyrrhizin, imatinib, imipramine, ketoconazole (systemic), linoleic acid supplements, mycophenolic acid, niflumic acid, nilotinib, phenobarbital, phenylbutazone, phenytoin, probenecid, quinidine, ritonavir, sorafenib, sulfinpyrazone, valproic acid, and verapamil.

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

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

5.10.1. Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Appendix G, Table G-1. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

The dose modification and supportive care guidelines are intended to be applied when the investigator determines the events to be related to epacadostat and/or pembrolizumab. If after the evaluation of the event, it is determined not to be related to pembrolizumab and/or epacadostat, the investigator does not need to follow the dose modification and supportive care guidelines.

Additionally, subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator, including, but not limited to, the items outlined below:

- Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.
- Diarrhea: See Appendix G, Table G-1.
- Infection: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.
- Infusion-related reactions with pembrolizumab: See Appendix G, Section G.3.

6. STUDY ASSESSMENTS

NOTE: As of Amendment 7, subjects will only be required to visit the clinic per standard of care. Safety (including laboratory analytes) assessments that are consistent with the standard of care for the subject's condition should be performed via local labs. Disease status should continue to be monitored by computerized tomography (CT), magnetic resonance imaging (MRI), or PET-CT scan as appropriate at a frequency consistent with the standard of care for the subject's disease.

As of Amendment 7, data will only be collected for informed consent, SAEs, AEs leading to discontinuation, EOT disposition (reason for discontinuation), drug accountability, dosing information, end of study (EOS) disposition (end of study form), and death if it occurs within the safety reporting period. See Table 6 for protocol-required assessments to limit clinic visits and procedures for subjects. **Only Table 6 should be followed by all subjects in all cohorts continuing on-treatment beyond Amendment 7. All other tables in this section may be disregarded.**

All study assessments will be performed as indicated in the schedule of assessments (Table 7, Table 9, Table 11, Table 12, and Table 14) and all laboratory assessments will be performed as indicated in Table 8, Table 10, Table 13, and Table 15. Table 16 presents a summary of clinical laboratory analytes to be assessed. See Section 7 for instructions on each assessment. Further details of study procedures and assessments can be found in the Study Reference Manual.

Table 6: Schedule of Assessments for ALL Ongoing Subjects After Amendment 7 Approval

Procedures	Treatment Period	EOT	Safety Follow Up 30-Day	Safety Follow up 90-Day	Comments
Informed consent	X				For subjects treated beyond initial progression the date of the consent will also be collected.
Concomitant medications	X	X			Review to ensure no prohibited medications are being used. Provide data to Sponsor about SAEs only.
Drug dispensing/contact IVRS	X				Dispense drug (epacadostat) on Day 1 of each cycle
Assess compliance	X	X			
Administer pembrolizumab	X				Pembrolizumab should be administered every 3 weeks per standard of care from Cycle 1 Day 1 for up to 35 infusions.
AE/SAE assessments	X	X	X	X	AEs that lead to the discontinuation of study treatment and all SAEs must be recorded in the CRFs, regardless of the causal relationship. *Sites should follow up with subjects 90 days post-treatment to confirm any SAEs that occurred during the 90-day safety reporting period have been submitted and entered into the EDC system.
Laboratory assessments	X				Local laboratory tests should be performed at each site as per standard of care for subject's condition and monitoring per investigator discretion (eg, hematology and chemistry). Data will not be collected unless related to an SAE.
Radiographic tumor assessments	X				Performed per standard of care schedule. Data will not be collected beyond Week 18.

Table 7: Schedule of Assessments for Phase 1 or Phase 2 Efficacy Expansion Subjects in Treatment Group A or Treatment Group B

Visit	Screening	Treatment[a]											EOT	Follow-Up				Comments
		Cycle 1, 4, 7+				Cycle 2, 5, 8+			Cycle 3, 6, 9+					Safety[b]		Disease Status	Survival	
		D1	D8	D15	D22	D1	D8	D15	D1	D8	D15	Q9W						
Evaluation Window	**Day -28 to -1**		**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**+7d**	**30 d After EOT (±7d)**	**90 d After EOT (±7d)**	**Q9W After EOT (±7d)**	**Q12W (±7d)**	
Administrative procedures																		
Informed consent	X																	
Contact IRT	X	X				X			X				X					
Inclusion/exclusion criteria	X	X																
Prior medical and cancer history (tumor-specific)	X																	
Concomitant medications	X	X	X*	X	X	X	X*	X	X	X*	X		X	X	X			* D8 for Cycles 1, 2, 3, 6, 9, 12, etc for all subjects. D8 for Cycles 4, 5, 7, 8, 10, 11, etc only for subjects who receive *nab*-paclitaxel/ gemcitabine.
Dispense epacadostat		X				X			X									
Post-treatment anticancer therapy status														X	X	X	X	
Survival follow-up (Phase 2 only)																	X	
Clinical procedures/assessments																		
Comprehensive physical examination and height	X																	
Targeted physical examination		X	X*	X	X	X	X*	X	X	X*	X		X	X	X			* D8 for Cycles 1, 2, 3, 6, 9, 12, etc for all subjects. D8 for Cycles 4, 5, 7, 8, 10, 11, etc only for subjects who receive *nab*-paclitaxel/ gemcitabine.
Vital signs and weight	X	X	X*	X	X	X	X*	X	X	X*	X		X	X	X			* D8 for Cycles 1, 2, 3, 6, 9, 12, etc for all subjects. D8 for Cycles 4, 5, 7, 8, 10, 11, etc only for subjects who receive *nab*-paclitaxel/ gemcitabine.
ECOG performance status	X	X				X			X				X	X	X			
Laboratory assessments	X	X	X*	X	X	X	X*	X	X	X*	X		X	X	X			* D8 for Cycles 1, 2, 3, 6, 9, 12, etc for all subjects. D8 for Cycles 4, 5, 7, 8, 10, 11, etc only for subjects who receive *nab*-paclitaxel/ gemcitabine.
Tumor biopsy (Phase 2 only)	X																	Tumor biopsy is required for Phase 2 efficacy expansion subjects at screening. See Section 7.9 for biopsy requirements.

Table 7: Schedule of Assessments for Phase 1 or Phase 2 Efficacy Expansion Subjects in Treatment Group A or Treatment Group B (Continued)

Visit	Screening	Treatment[a]											EOT	Follow-Up				Comments
		Cycle 1, 4, 7+				Cycle 2, 5, 8+			Cycle 3, 6, 9+			Q9W		Safety[b]		Disease Status	Survival	
		D1	D8	D15	D22	D1	D8	D15	D1	D8	D15							
Evaluation Window	**Day -28 to -1**		**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**+7d**	**30 d After EOT (±7d)**	**90 d After EOT (±7d)**	**Q9W After EOT (±7d)**	**Q12W (±7d)**	
12-lead ECG	X												X					All 12-lead ECGs will be performed with the subject in a recumbent or semirecumbent position after 5 minutes of rest and should not be performed within 15 minutes after a blood collection. Electrocardiograms may be performed throughout the treatment period as clinically indicated.
AE assessment	X	X	X*	X	X	X	X*	X	X	X*	X		X	X	X			* D8 for Cycles 1, 2, 3, 6, 9, 12, etc for all subjects. D8 for Cycles 4, 5, 7, 8, 10, 11, etc only for subjects who receive *nab*-paclitaxel/ gemcitabine.
Study drug or reference therapy administration																		
Administer epacadostat in clinic		X	X			X												Epacadostat will be administered in the clinic for any study visit [redacted]. Epacadostat should be administered before pembrolizumab and chemotherapy.
Administer pembrolizumab		X			X			X		X								Pembrolizumab should be administered every 3 weeks from Cycle 1 D1 and before IV chemotherapy (mFOLFOX6 or *nab*-paclitaxel/gemcitabine).
Administer mFOLFOX6		X		X		X		X	X		X							See Section 5.3 for order of administration.
Administer gemcitabine/ *nab*-paclitaxel		X	X	X		X	X	X	X	X	X							See Section 5.3 for order of administration.
Efficacy measurements																		
Radiologic tumor assessments	X											X	X			X		The same imaging technique should be used in a subject throughout the study. If imaging shows PD, an imaging assessment should be performed at a minimum of 4 weeks and maximum of 6 weeks later to confirm PD per irRECIST. See Section 7.6.2 for information on imaging frequency.

[a] Treatment cycles are every 28 days (± 3 days).

[b] The mandatory safety follow-up visits should be conducted approximately 30 days and 90 days after the EOT visit or before the initiation of a new anticancer treatment, whichever comes first. If an EOT visit was not conducted, the last dose of epacadostat or pembrolizumab (whichever is later) should be used as the start of the safety follow-up period.

Table 8: Laboratory Assessments for Phase 1 or Phase 2 Efficacy Expansion Subjects in Treatment Group A or Treatment Group B

Visit	Screening[a]	Treatment											EOT	Safety Follow-Up		Comments
		Cycle 1, 4, 7+				Cycle 2, 5, 8+			Cycle 3, 6, 9+			Q9W		30 d After EOT (±7d)	90 d After EOT (±7d)	
		D1	D8	D15	D22	D1	D8	D15	D1	D8	D15					
Evaluation Window	**Day -28 to -1**		**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**+7d**			
Laboratory assessments[b]																
Comprehensive serum chemistry	X	X	X*	X	X	X	X*	X	X	X*	X		X	X	X	Additional assessment of serum chemistry may be conducted as clinically indicated. * D8 for Cycles 1, 2, 3, 6, 9, 12, etc for all subjects. D8 for Cycles 4, 5, 7, 8, 10, 11, etc only for subjects who receive *nab*-paclitaxel/gemcitabine.
Hematology with differential	X	X	X*	X	X	X	X*	X	X	X*	X		X	X	X	Additional assessment of hematology with differential may be conducted as clinically indicated. * D8 for Cycles 1, 2, 3, 6, 9, 12, etc for all subjects. D8 for Cycles 4, 5, 7, 8, 10, 11, etc only for subjects who receive *nab*-paclitaxel/gemcitabine.
Liver chemistry tests	X	X	X*	X	X	X	X*	X	X	X*	X		X	X	X	Additional assessment of liver chemistry may be conducted as clinically indicated. * D8 for Cycles 1, 2, 3, 6, 9, 12, etc for all subjects. D8 for Cycles 4, 5, 7, 8, 10, 11, etc only for subjects who receive *nab*-paclitaxel/gemcitabine.
Coagulation panel	X	X*											X			More frequent monitoring during treatment is required if subject is on warfarin. * Not required on D1 of Cycles 4, 7, 10, etc.
Endocrine function tests	X	X				X			X							Required for D1 of Cycle 1, Cycle 2, and Cycle 3. For D1 of subsequent cycles, required every 3 cycles starting with Cycle 6 (ie, Cycles 6, 9, 12, etc). Not required for D1 on Cycles 4, 5, 7, 8, 10, 11, etc.
Urinalysis	X	X				X			X							Required for D1 of Cycle 1, Cycle 2, and Cycle 3. For D1 of subsequent cycles, required every 3 cycles starting with Cycle 6 (ie, Cycles 6, 9, 12, etc). Not required for D1 on Cycles 4, 5, 7, 8, 10, 11, etc.
Serum pregnancy test (childbearing females only)	X												X			A serum pregnancy test is required for all women of childbearing potential during screening and must be within 72 hours of Cycle 1 D1.
Urine pregnancy test (childbearing females only)		X*				X			X					X	X	* Not required on Cycle 1 D1. Required on D1 of each cycle starting on Cycle 2. See Section 7.5.5.7 for further details.
Serology	X															

Table 8: Laboratory Assessments for Phase 1 or Phase 2 Efficacy Expansion Subjects in Treatment Group A or Treatment Group B (Continued)

		Treatment												Safety Follow-Up		
		Cycle 1, 4, 7+				Cycle 2, 5, 8+			Cycle 3, 6, 9+							
Visit	Screening[a]	D1	D8	D15	D22	D1	D8	D15	D1	D8	D15	Q9W	EOT	30 d After EOT (±7d)	90 d After EOT (±7d)	Comments
Evaluation Window	Day -28 to -1		±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±7d	+7d			
[redacted]																

[a] If screening safety and eligibility laboratory assessments are performed within 7 days of Cycle 1 Day 1, then the Cycle 1 Day 1 assessments may be omitted.
[b] All safety laboratory assessments will be performed locally. See Table 16 for a list of analytes.

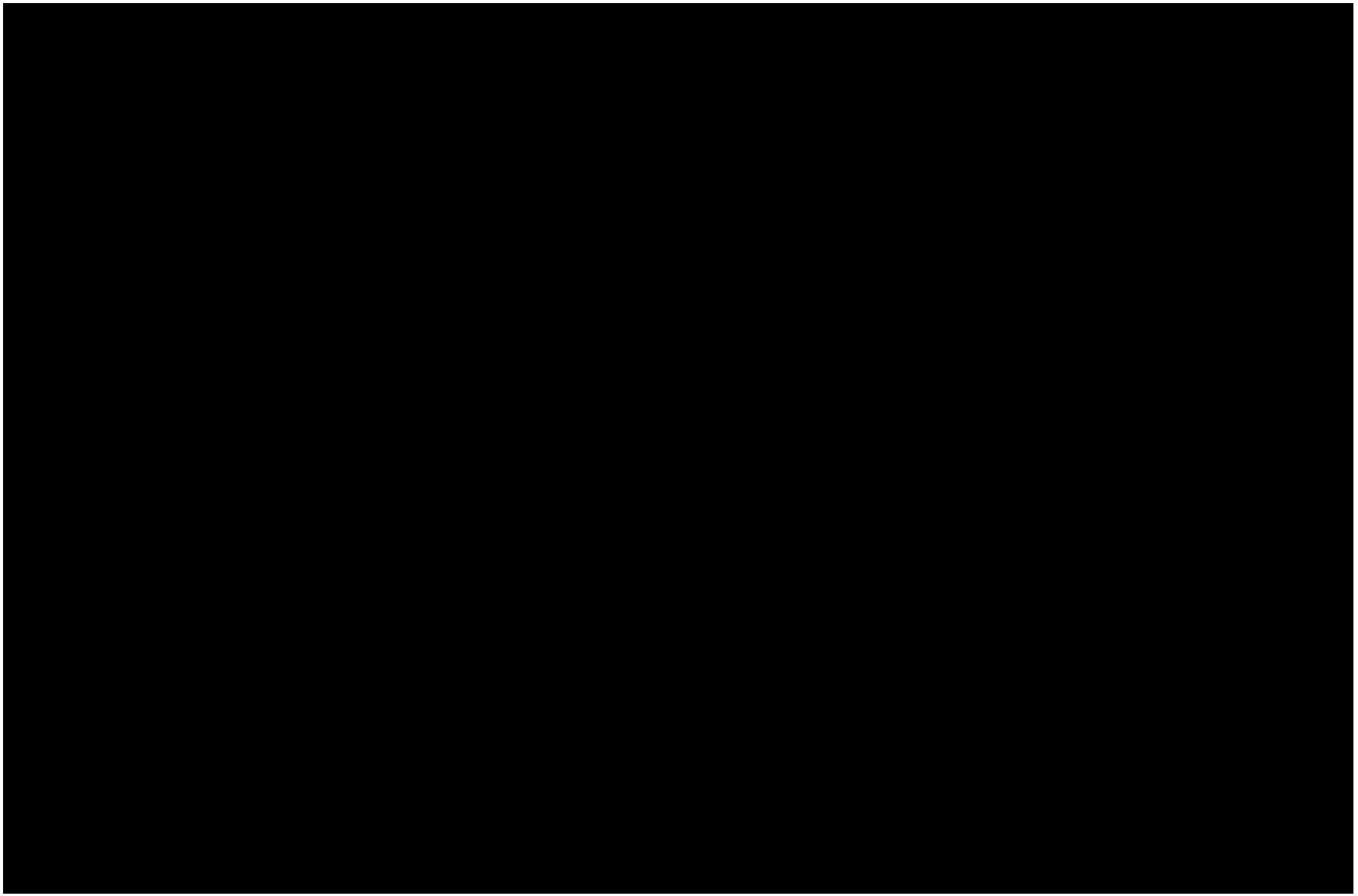


Table 9: Schedule of Assessments for Phase 2 Mandatory Biopsy Subjects in Treatment Group A or Treatment Group B (Continued)

Table 9: Schedule of Assessments for Phase 2 Mandatory Biopsy Subjects in Treatment Group A or Treatment Group B (Continued)

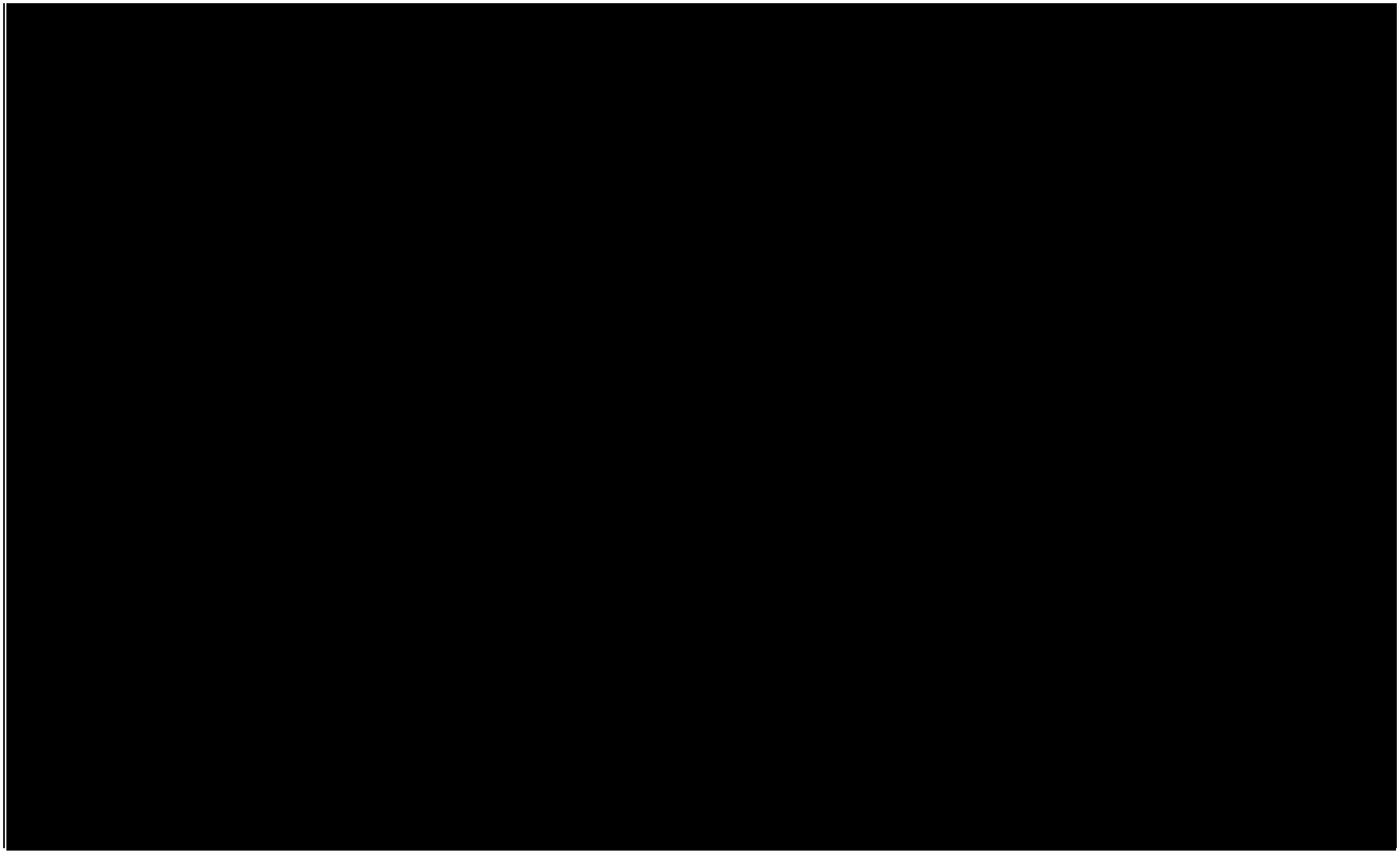


Table 9: Schedule of Assessments for Phase 2 Mandatory Biopsy Subjects in Treatment Group A or Treatment Group B (Continued)

Table 10: Laboratory Assessments for Phase 2 Mandatory Biopsy Subjects in Treatment Group A or Treatment Group B

Visit	Screening[a]	Treatment														EOT	Safety Follow-Up		Comments
		Cycle 1			Cycle 2, 5, 8+				Cycle 3, 6, 9+			Cycle 4, 7, 10+			Q9W		30 d After EOT (±7d)	90 d After EOT (±7d)	
		D1	D8	D15	D1	D8	D15	D22	D1	D8	D15	D1	D8	D15					
Evaluation Window	**Day -28 to -1**		**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**+7d**			
Laboratory assessments[b]																			
Comprehensive serum chemistry	X	X	X*	X	X	X*	X	X	X	X*	X	X	X*	X		X	X	X	Additional assessment of serum chemistry may be conducted as clinically indicated. * D8 for Cycles 1, 2, 3, 4, 7, 10, 13, etc for all subjects. D8 for Cycles 5, 6, 8, 9, 11, 12, etc only for subjects who receive *nab*-paclitaxel/ gemcitabine.
Hematology with differential	X	X	X*	X	X	X*	X	X	X	X*	X	X	X*	X		X	X	X	Additional assessment of hematology with differential may be conducted as clinically indicated. * D8 for Cycles 1, 2, 3, 4, 7, 10, 13, etc for all subjects. D8 for Cycles 5, 6, 8, 9, 11, 12, etc only for subjects who receive *nab*-paclitaxel/ gemcitabine.
Liver chemistry tests	X	X	X*	X	X	X*	X	X	X	X*	X	X	X*	X		X	X	X	Additional assessment of liver chemistry may be conducted as clinically indicated. * D8 for Cycles 1, 2, 3, 4, 7, 10, 13, etc for all subjects. D8 for Cycles 5, 6, 8, 9, 11, 12, etc only for subjects who receive *nab*-paclitaxel/ gemcitabine.
Coagulation panel	X	X														X			More frequent monitoring during treatment is required if subject is on warfarin.
Endocrine function tests	X	X			X				X										Required for D1 of Cycle 1, Cycle 2, and Cycle 3. For D1 of subsequent cycles, required every 3 cycles starting with Cycle 6 (ie, Cycles 6, 9, 12, etc). Not required for D1 on Cycles 5, 8, 11, etc.
Urinalysis	X	X			X				X										Required for D1 of Cycle 1, Cycle 2, and Cycle 3. For D1 of subsequent cycles, required every 3 cycles starting with Cycle 6 (ie, Cycles 6, 9, 12, etc). Not required for D1 on Cycles 5, 8, 11, etc.

Table 10: Laboratory Assessments for Phase 2 Mandatory Biopsy Subjects in Treatment Group A or Treatment Group B (Continued)

Visit	Screening[a]	Treatment														EOT	Safety Follow-Up		Comments
		Cycle 1			Cycle 2, 5, 8+				Cycle 3, 6, 9+			Cycle 4, 7, 10+					30 d After EOT (±7d)	90 d After EOT (±7d)	
		D1	D8	D15	D1	D8	D15	D22	D1	D8	D15	D1	D8	D15	Q9W				
Evaluation Window	**Day -28 to -1**		**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**+7d**			
Serum pregnancy test (childbearing females only)	X															X			A serum pregnancy test is required for all women of childbearing potential during screening and must be within 72 hours of Cycle 1 D1.
Urine pregnancy test (childbearing females only)					X				X			X					X	X	Required on D1 of each cycle starting on Cycle 2. See Section 7.5.5.7 for further details.
Serology	X																		
[redacted]																			
Correlative samples																			
Whole blood for correlative studies		X	X	X	X				X										Required for Cycle 1 (D1, D8, D15), Cycle 2 (D1), and Cycle 3 (D1). For D1 of subsequent cycles, required every 3 cycles starting with Cycle 6 (ie, Cycles 6, 9, 12, etc). Not required for D1 on Cycles 5, 8, 11, etc.
Plasma for correlative studies		X	X	X	X				X										Required for Cycle 1 (D1, D8, D15), Cycle 2 (D1), and Cycle 3 (D1). For D1 of subsequent cycles, required every 3 cycles starting with Cycle 6 (ie, Cycles 6, 9, 12, etc). Not required for D1 on Cycles 5, 8, 11, etc.

[a] If screening safety and eligibility laboratory assessments are performed within 7 days of Cycle 1 Day 1, then the Cycle 1 Day 1 assessments may be omitted.
[b] All safety laboratory assessments will be performed locally. See Table 16 for a list of analytes.

Table 11: Schedule of Assessments for Phase 1 or Phase 2 Efficacy Expansion Subjects in Treatment Group C, Treatment Group D, Treatment Group F, and Treatment Group G

Visit	Screening	Treatment[a]									EOT	Follow-Up				Comments
		Cycle 1			Cycle 2			Cycle 3+				Safety[b]		Disease Status	Survival	
		D1	D8	D15	D1	D8	D15	D1	D8	Q9W						
Evaluation Window	**Day -28 to -1**		**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**+7d**	**30 d After EOT (±7d)**	**90 d After EOT (±7d)**	**Q9W After EOT (±7d)**	**Q12W (±7d)**	
Administrative procedures																
Informed consent	X															
Contact IRT	X	X			X			X			X					
Inclusion/exclusion criteria	X	X														
Prior medical and cancer history (tumor-specific)	X															
Concomitant medications	X	X	X	X	X	X	X	X	X*		X	X	X			* D8 visit for Cycles 3-6 is required for subjects in Treatment Group F only. D8 visits from Cycle 7 onwards are not required, as subjects receive gemcitabine on D8 for a maximum of 6 cycles.
Dispense epacadostat		X			X			X								
Post-treatment anticancer therapy status												X	X	X	X	
Survival follow-up (Phase 2 only)															X	
Clinical procedures/assessments																
Comprehensive physical examination and height	X															
Targeted physical examination		X	X	X	X	X	X	X	X*		X	X	X			* D8 visit for Cycles 3-6 is required for subjects in Treatment Group F only. D8 visits from Cycle 7 onwards are not required, as subjects receive gemcitabine on D8 for a maximum of 6 cycles.
Vital signs and weight	X	X	X	X	X	X	X	X	X*		X	X	X			* D8 visit for Cycles 3-6 is required for subjects in Treatment Group F only. D8 visits from Cycle 7 onwards are not required, as subjects receive gemcitabine on D8 for a maximum of 6 cycles.
ECOG performance status	X	X			X			X			X	X	X			
Laboratory assessments	X	X	X	X	X	X	X	X	X*		X	X	X			* D8 visit for Cycles 3-6 is required for subjects in Treatment Group F only. D8 visits from Cycle 7 onwards are not required, as subjects receive gemcitabine on D8 for a maximum of 6 cycles.
Tumor biopsy (Phase 2 only)	X															Tumor biopsy is required for Phase 2 efficacy expansion subjects at screening. See Section 7.9 for biopsy requirements.
12-lead ECG	X										X					All 12-lead ECGs will be performed with the subject in a recumbent or semirecumbent position after 5 minutes of rest and should not be performed within 15 minutes after a blood collection. Electrocardiograms may be performed throughout the treatment period as clinically indicated.

Table 11: Schedule of Assessments for Phase 1 or Phase 2 Efficacy Expansion Subjects in Treatment Group C, Treatment Group D, Treatment Group F, and Treatment Group G (Continued)

Visit	Screening	Treatment[a]									EOT	Follow-Up				Comments
		Cycle 1			Cycle 2			Cycle 3+		Q9W		Safety[b]		Disease Status	Survival	
Evaluation Window	Day -28 to -1	D1	D8	D15	D1	D8	D15	D1	D8	±7d	+7d	30 d After EOT (±7d)	90 d After EOT (±7d)	Q9W After EOT (±7d)	Q12W (±7d)	
AE assessment	X	X	X	X	X	X	X	X	X*		X	X	X			* D8 visit for Cycles 3-6 is required for subjects in Treatment Group F only. D8 visits from Cycle 7 onwards are not required, as subjects receive gemcitabine on D8 for a maximum of 6 cycles.
Study drug or reference therapy administration																
Administer epacadostat in clinic		X	X		X											For all Phase 1 subjects and Phase 2 efficacy expansion subjects in Treatment Groups F and G. See Section 7.5.4 and Section 7.8.1.1 for further details.
Administer epacadostat in clinic			X		X											For Phase 2 efficacy expansion subjects in Treatment Group C and D. See Section 7.5.4, Section 7.8.1.2, and Section 7.8.1.3 for further details.
Administer pembrolizumab		X			X			X								For all Phase 1 subjects and Phase 2 efficacy expansion subjects in Treatment Groups F and G, pembrolizumab should be administered before IV chemotherapy. For Phase 2 efficacy expansion subjects in Treatment Groups C and D, pembrolizumab should be administered after IV chemotherapy.
Administer carboplatin or cisplatin		X			X			X								See Section 5.3 for order of administration and maximum number of cycles.
Administer paclitaxel		X			X			X								See Section 5.3 for order of administration and maximum number of cycles.
Administer pemetrexed		X			X			X								See Section 5.3 for order of administration and maximum number of cycles.
Administer gemcitabine		X	X		X	X		X	X							See Section 5.3 for order of administration and maximum number of cycles.
Administer 5-fluorouracil		X			X			X								See Section 5.3 for order of administration and maximum number of cycles.
Efficacy measurements																
Radiologic tumor assessments	X									X	X			X		The same imaging technique should be used in a subject throughout the study. If imaging shows PD, an imaging assessment should be performed at a minimum of 4 weeks and maximum of 6 weeks later to confirm PD per irRECIST. See Section 7.6.2 for information on imaging frequency.

[a] Treatment cycles are every 21 days (± 3 days).

[b] The mandatory safety follow-up visits should be conducted approximately 30 days and 90 days after the EOT visit or before the initiation of a new anticancer treatment, whichever comes first. If an EOT visit was not conducted, the last dose of epacadostat or pembrolizumab (whichever is later) should be used as the start of the safety follow-up period.

Table 12: Schedule of Assessments for Phase 1, Phase 2 Efficacy Expansion, or Phase 2 Mandatory Biopsy Subjects in Treatment Group E

Visit	Screening	Treatment[a]									EOT	Follow-Up				Comments
		Cycle 1			Cycle 2			Cycle 3+		Q9W		Safety[b]		Disease Status	Survival	
		D1	D8	D15	D1	D8	D15	D1	D10							
Evaluation Window	**Day -28 to -1**		**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**+7d**	**30 d After EOT (±7d)**	**90 d After EOT (±7d)**	**Q9W After EOT (±7d)**	**Q12W (±7d)**	
Administrative procedures																
Informed consent	X															
Contact IRT	X	X			X			X			X					
Inclusion/exclusion criteria	X	X														
Prior medical and cancer history (tumor-specific)	X															
Concomitant medications	X	X	X	X	X	X	X	X			X	X	X			
Dispense epacadostat		X			X			X								
Dispense cyclophosphamide		X			X			X								There is no limit to the maximum number of cycles of cyclophosphamide.
Post-treatment anticancer therapy status												X	X	X	X	
Survival follow-up (Phase 2 only)															X	
Clinical procedures/assessments																
Comprehensive physical examination and height	X															
Targeted physical examination		X	X	X	X	X	X	X			X	X	X			
Vital signs and weight	X	X	X	X	X	X	X	X			X	X	X			
ECOG performance status	X	X			X			X			X	X	X			

Table 12: Schedule of Assessments for Phase 1, Phase 2 Efficacy Expansion, or Phase 2 Mandatory Biopsy Subjects in Treatment Group E (Continued)

Visit	Screening	Treatment[a]									EOT	Follow-Up				Comments
		Cycle 1			Cycle 2			Cycle 3+		Q9W		Safety[b]		Disease Status	Survival	
		D1	D8	D15	D1	D8	D15	D1	D10							
Evaluation Window	**Day -28 to -1**		**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**+7d**	**30 d After EOT (±7d)**	**90 d After EOT (±7d)**	**Q9W After EOT (±7d)**	**Q12W (±7d)**	
Laboratory assessments	X	X	X	X	X	X	X	X			X	X	X			
Tumor biopsy (Phase 2 only)	X								X*							Screening biopsy is required for all Phase 2 efficacy expansion and mandatory biopsy subjects. * On-treatment biopsy is required for Phase 2 mandatory biopsy subjects only and will occur during Cycle 3 between D7 and D13. See Section 7.9 for biopsy requirements.
12-lead ECG	X										X					All 12-lead ECGs will be performed with the subject in a recumbent or semirecumbent position after 5 minutes of rest and should not be performed within 15 minutes after a blood collection. Electrocardiograms may be performed throughout the treatment period as clinically indicated.
AE assessment	X	X	X	X	X	X	X	X			X	X	X			
Study drug or reference therapy administration																
Administer epacadostat in clinic (Phase 1 and Phase 2 efficacy expansion only)		X	X		X											Section 7.8.1.1 for further details.
Administer pembrolizumab		X			X			X								
Efficacy measurements																
Radiologic tumor assessments	X									X	X			X		The same imaging technique should be used in a subject throughout the study. If imaging shows PD, an imaging assessment should be performed at a minimum of 4 weeks and maximum of 6 weeks later to confirm PD per irRECIST. See Section 7.6.2 for information on imaging frequency.

[a] Treatment cycles are every 21 days (± 3 days).

[b] The mandatory safety follow-up visits should be conducted approximately 30 days and 90 days after the EOT visit or before the initiation of a new anticancer treatment, whichever comes first. If an EOT visit was not conducted, the last dose of epacadostat or pembrolizumab (whichever is later) should be used as the start of the safety follow-up period.

Table 13: Laboratory Assessments for Phase 1 or Phase 2 Efficacy Expansion Subjects in Treatment Group C, Treatment Group D, Treatment Group E, Treatment Group F, and Treatment Group G

Visit	Screening[a]	Treatment									EOT	Safety Follow-Up		Comments
		Cycle 1			Cycle 2			Cycle 3+						
		D1	D8	D15	D1	D8	D15	D1	D8	Q9W		30 d After EOT (±7d)	90 d After EOT (±7d)	
Evaluation Window	**Day -28 to -1**		**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**+7d**			
Laboratory assessments[b]														
Comprehensive serum chemistry	X	X	X	X	X	X	X	X	X*		X	X	X	Additional assessment of serum chemistry may be conducted as clinically indicated. * D8 visit for Cycles 3-6 is required for subjects in Treatment Group F only. D8 visits from Cycle 7 onwards are not required, as subjects receive gemcitabine on D8 for a maximum of 6 cycles.
Hematology with differential	X	X	X	X	X	X	X	X	X*		X	X	X	Additional assessment of hematology with differential may be conducted as clinically indicated. * D8 visit for Cycles 3-6 is required for subjects in Treatment Group F only. D8 visits from Cycle 7 onwards are not required, as subjects receive gemcitabine on D8 for a maximum of 6 cycles
Liver chemistry tests	X	X	X	X	X	X	X	X	X*		X	X	X	Additional assessment of liver chemistry may be conducted as clinically indicated. * D8 visit for Cycles 3-6 is required for subjects in Treatment Group F only. D8 visits from Cycle 7 onwards are not required, as subjects receive gemcitabine on D8 for a maximum of 6 cycles
Coagulation panel	X	X									X			
Endocrine function tests	X	X			X			X						Required for D1 of Cycle 1, Cycle 2, and Cycle 3. For D1 of subsequent cycles, required every 3 cycles starting with Cycle 6 (ie, Cycles 6, 9, 12, etc).
Urinalysis	X	X			X			X						Required for D1 of Cycle 1, Cycle 2, and Cycle 3. For D1 of subsequent cycles, required every 3 cycles starting with Cycle 6 (ie, Cycles 6, 9, 12, etc).
Serum pregnancy test (childbearing females only)	X										X			A serum pregnancy test is required for all women of childbearing potential during screening and must be within 72 hours of Cycle 1 D1.
Urine pregnancy test (childbearing females only)					X			X				X	X	See Section 7.5.5.7 for further details.
Serology	X													
[redacted]														

Table 13: Laboratory Assessments for Phase 1 or Phase 2 Efficacy Expansion Subjects in Treatment Group C, Treatment Group D, Treatment Group E, Treatment Group F, and Treatment Group G (Continued)

Visit	Screening[a]	Treatment									EOT	Safety Follow-Up		Comments
		Cycle 1			Cycle 2			Cycle 3+						
		D1	D8	D15	D1	D8	D15	D1	D8	Q9W		30 d After EOT (±7d)	90 d After EOT (±7d)	
Evaluation Window	Day -28 to -1		±3d	±3d	±3d	±3d	±3d	±3d	±3d	±7d	+7d			
[redacted]														

[a] If screening safety and eligibility laboratory assessments are performed within 7 days of Cycle 1 D1, then the Cycle 1 D1 assessments may be omitted.
[b] All safety laboratory assessments will be performed locally. See Table 16 for a list of analytes.

Table 14: Schedule of Assessments for Phase 2 Mandatory Biopsy Subjects in Treatment Group C, Treatment Group D, Treatment Group F, and Treatment Group G

Visit	Screening	Treatment[a]											EOT	Follow-Up				Comments
		Cycle 1				Cycle 2			Cycle 3+					Safety[b]		Disease Status	Survival	
		D1	D8	D15	D17	D1	D8	D15	D1	D8	D10	Q9W						
Evaluation Window	**Day -28 to -1**		**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**+7d**	**30 d After EOT (±7d)**	**90 d After EOT (±7d)**	**Q9W After EOT (±7d)**	**Q12W (±7d)**	
Administrative procedures																		
Informed consent	X																	
Contact IRT	X	X				X			X				X					
Inclusion/exclusion criteria	X	X																
Prior medical and cancer history (tumor-specific)	X																	
Concomitant medications	X	X	X	X		X	X	X	X	X*			X	X	X			* D8 visit for Cycles 3-6 is required for subjects in Treatment Group F only. D8 visits from Cycle 7 onwards are not required, as subjects receive gemcitabine on D8 for a maximum of 6 cycles.
Dispense epacadostat						X			X									
Post-treatment anticancer therapy status														X	X	X	X	
Survival follow-up																	X	
Clinical procedures/assessments																		
Comprehensive physical examination and height	X																	
Targeted physical examination		X	X	X		X	X	X	X	X*			X	X	X			* D8 visit for Cycles 3-6 is required for subjects in Treatment Group F only. D8 visits from Cycle 7 onwards are not required, as subjects receive gemcitabine on D8 for a maximum of 6 cycles.
Vital signs and weight	X	X	X	X		X	X	X	X	X*			X	X	X			* D8 visit for Cycles 3-6 is required for subjects in Treatment Group F only. D8 visits from Cycle 7 onwards are not required, as subjects receive gemcitabine on D8 for a maximum of 6 cycles.
ECOG performance status	X	X				X			X				X	X	X			
Laboratory assessments	X	X	X	X		X	X	X	X	X*			X	X	X			* D8 visit for Cycles 3-6 is required for subjects in Treatment Group F only. D8 visits from Cycle 7 onwards are not required, as subjects receive gemcitabine on D8 for a maximum of 6 cycles.

Table 14: Schedule of Assessments for Phase 2 Mandatory Biopsy Subjects in Treatment Group C, Treatment Group D, Treatment Group F, and Treatment Group G (Continued)

Visit	Screening	Treatment[a]											EOT	Follow-Up				Comments
		Cycle 1				Cycle 2			Cycle 3+			Q9W		Safety[b]		Disease Status	Survival	
		D1	D8	D15	D17	D1	D8	D15	D1	D8	D10							
Evaluation Window	Day -28 to -1		±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±7d	+7d	30 d After EOT (±7d)	90 d After EOT (±7d)	Q9W After EOT (±7d)	Q12W (±7d)	
Tumor biopsy	X				X						X							Tumor biopsy is required for Phase 2 mandatory biopsy subjects at screening and on-treatment. Biopsies will occur during Cycle 1 between D14 and D20 and Cycle 3 between D7 and D13. See Section 7.9 for biopsy requirements.
12-lead ECG	X												X					All 12-lead ECGs will be performed with the subject in a recumbent or semirecumbent position after 5 minutes of rest and should not be performed within 15 minutes after a blood collection. Electrocardiograms may be performed throughout the treatment period as clinically indicated.
AE assessment	X	X	X	X		X	X	X	X	X*			X	X	X			* D8 visit for Cycles 3-6 is required for subjects in Treatment Group F only. D8 visits from Cycle 7 onwards are not required, as subjects receive gemcitabine on D8 for a maximum of 6 cycles.
Study drug or reference therapy administration																		
Administer pembrolizumab						X			X									Pembrolizumab should be administered before IV chemotherapy.
Administer carboplatin or cisplatin		X				X			X									See Section 5.3 for order of administration and maximum number of cycles.
Administer paclitaxel		X				X			X									See Section 5.3 for order of administration and maximum number of cycles.
Administer pemetrexed		X				X			X									See Section 5.3 for order of administration and maximum number of cycles.
Administer gemcitabine		X	X			X	X		X	X								See Section 5.3 for order of administration and maximum number of cycles.
Administer 5-fluorouracil		X				X			X									See Section 5.3 for order of administration and maximum number of cycles.

Table 14: Schedule of Assessments for Phase 2 Mandatory Biopsy Subjects in Treatment Group C, Treatment Group D, Treatment Group F, and Treatment Group G (Continued)

Visit	Screening	Treatment[a]											EOT	Follow-Up				Comments
		Cycle 1				Cycle 2			Cycle 3+					Safety[b]		Disease Status	Survival	
		D1	D8	D15	D17	D1	D8	D15	D1	D8	D10	Q9W						
Evaluation Window	Day -28 to -1		±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±7d	+7d	30 d After EOT (±7d)	90 d After EOT (±7d)	Q9W After EOT (±7d)	Q12W (±7d)	
Efficacy measurements																		
Radiologic tumor assessments	X											X	X			X		The same imaging technique should be used in a subject throughout the study. If imaging shows PD, an imaging assessment should be performed at a minimum of 4 weeks and maximum of 6 weeks later to confirm PD per irRECIST. See Section 7.6.2 for information on imaging frequency.

[a] Treatment cycles are every 21 days (± 3 days).

[b] The mandatory safety follow-up visits should be conducted approximately 30 days and 90 days after the EOT visit or before the initiation of a new anticancer treatment, whichever comes first. If an EOT visit was not conducted, the last dose of epacadostat or pembrolizumab (whichever is later) should be used as the start of the safety follow-up period.

Table 15: Laboratory Assessments for Phase 2 Mandatory Biopsy Subjects in Treatment Group C, Treatment Group D, Treatment Group E, Treatment Group F, and Treatment Group G

Visit	Screening[a]	Treatment									EOT	Safety Follow-Up		Comments
		Cycle 1			Cycle 2			Cycle 3+				30 d After EOT (±7d)	90 d After EOT (±7d)	
		D1	D8	D15	D1	D8	D15	D1	D8	Q9W				
Evaluation Window	**Day -28 to -1**		**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**+7d**			
Laboratory assessments[b]														
Comprehensive serum chemistry	X	X	X	X	X	X	X	X	X*		X	X	X	Additional assessment of serum chemistry may be conducted as clinically indicated. * D8 visit for Cycles 3-6 is required for subjects in Treatment Group F only. D8 visits from Cycle 7 onwards are not required, as subjects receive gemcitabine on D8 for a maximum of 6 cycles.
Hematology with differential	X	X	X	X	X	X	X	X	X*		X	X	X	Additional assessment of hematology with differential may be conducted as clinically indicated. * D8 visit for Cycles 3-6 is required for subjects in Treatment Group F only. D8 visits from Cycle 7 onwards are not required, as subjects receive gemcitabine on D8 for a maximum of 6 cycles.
Liver chemistry tests	X	X	X	X	X	X	X	X	X*		X	X	X	Additional assessment of liver chemistry may be conducted as clinically indicated. * D8 visit for Cycles 3-6 is required for subjects in Treatment Group F only. D8 visits from Cycle 7 onwards are not required, as subjects receive gemcitabine on D8 for a maximum of 6 cycles.
Coagulation panel	X	X									X			
Endocrine function tests	X	X			X			X						Required for D1 of Cycle 1, Cycle 2, and Cycle 3. For D1 of subsequent cycles, required every 3 cycles starting with Cycle 6 (ie, Cycles 6, 9, 12, etc).
Urinalysis	X	X			X			X						Required for D1 of Cycle 1, Cycle 2, and Cycle 3. For D1 of subsequent cycles, required every 3 cycles starting with Cycle 6 (ie, Cycles 6, 9, 12, etc).
Serum pregnancy test (childbearing females only)	X										X			A serum pregnancy test is required for all women of childbearing potential during screening and must be within 72 hours of Cycle 1 D1.
Urine pregnancy test (childbearing females only)					X			X				X	X	See Section 7.5.5.7 for further details.
Serology	X													
[redacted]														

Table 15: Laboratory Assessments for Phase 2 Mandatory Biopsy Subjects in Treatment Group C, Treatment Group D, Treatment Group E, Treatment Group F, and Treatment Group G (Continued)

Visit	Screening[a]	Treatment									EOT	Safety Follow-Up		Comments
		Cycle 1			Cycle 2			Cycle 3+				30 d After EOT (±7d)	90 d After EOT (±7d)	
		D1	D8	D15	D1	D8	D15	D1	D8	Q9W				
Evaluation Window	**Day -28 to -1**		**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**+7d**			
Correlative samples														
Whole blood for correlative studies		X	X	X	X			X						Required for Cycle 1 (D1, D8, D15), Cycle 2 (D1), and Cycle 3 (D1). For D1 of subsequent cycles, required every 3 cycles starting with Cycle 6 (ie, Cycles 6, 9, 12, etc).
Plasma for correlative studies		X	X	X	X			X						Required for Cycle 1 (D1, D8, D15), Cycle 2 (D1), and Cycle 3 (D1). For D1 of subsequent cycles, required every 3 cycles starting with Cycle 6 (ie, Cycles 6, 9, 12, etc).

[a] If screening safety and eligibility laboratory assessments are performed within 7 days of Cycle 1 Day 1, then the Cycle 1 Day 1 assessments may be omitted.
[b] All safety laboratory assessments will be performed locally. See Table 16 for a list of analytes.

Table 16: Clinical Laboratory Analytes

Serum Chemistries	Hematology	Other
Albumin Amylase Bicarbonate Blood urea nitrogen Calcium Chloride Creatinine Glucose Iron Lactate dehydrogenase Lipase Magnesium Phosphate Potassium Sodium 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 Absolute values must be provided for the following WBC differential laboratory results: • White blood cell count • Lymphocytes • Neutrophils	**Pregnancy test:** Female subjects of childbearing potential only require a serum test at screening. Pregnancy tests (urine or serum) should be repeated on Day 1 of each cycle. **Coagulation:** PT aPTT or PTT INR **Liver Chemistry Tests** ALP ALT AST Total bilirubin Direct bilirubin (only if total bilirubin is elevated above ULN at screening)
Urinalysis	**Hepatitis Screening Tests**	**Endocrine Monitoring**
Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein Urobilinogen	Hepatitis B surface antigen HBV-DNA HCV-RNA HCV antibody	Thyroid stimulating hormone Free thyroxine Total triiodothyronine

6.1. Screening

Screening is the interval between the signing of the ICF and the day that the subject is enrolled and received the first dose of treatment in the study (Cycle 1 Day 1) and must not exceed 28 days. The ICF 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 screening process.

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

Results from the screening visit evaluations will be reviewed to confirm subject eligibility before enrollment or the administration of epacadostat, pembrolizumab, or chemotherapy regimen. Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the results to be in error. For screening assessments that are repeated, the most recent available result before treatment assignment will be used to determine subject eligibility. Treatment should start as soon as possible but within 7 days after the date of enrollment. Additionally, a subject who fails screening may repeat the screening process 1 time if the investigator believes that there has been a change in eligibility status.

6.2. Treatment

The treatment period begins on the day that the subject receives the first dose of treatment in the study on Cycle 1 Day 1 and may continue in 28-day cycles (mFOLFOX6 or *nab*-paclitaxel/gemcitabine) or 21-day cycles (all other chemotherapy regimens) if, in the judgment of the investigator, the subject is receiving benefit from treatment and has not met any criteria for treatment discontinuation. See Section 4.4 for details on the maximum duration of treatment.

Cycle 1 Day 1 must be no more than 28 days after the subject has signed the ICF.

6.3. End of Treatment

The EOT visit will be conducted when the subject permanently discontinues epacadostat and pembrolizumab (+ 7 days). As the discontinuation date of epacadostat may differ from that of pembrolizumab, the EOT visit should be conducted on the latter of the 2 dates.

If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data will be entered in the EOT page in the eCRF. The subject should be encouraged to return for the follow-up visits.

6.4. Follow-Up

6.4.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled safety follow-up visit(s), which should occur 30 days (± 7 days) and 90 days (± 7 days) after the EOT visit. Adverse events and SAEs must be reported up until at least 90 days (120 days for pregnancy) after the EOT visit, the date of the follow-up visit, or until epacadostat- or pembrolizumab-related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. If an EOT visit was not conducted, the last dose of epacadostat or pembrolizumab (whichever is later) should be used as the start of the safety follow-up period.

Reasonable efforts should be made to have the subject return for the follow-up visit and report any AEs that may occur during this period. If the subject cannot return to the site for the safety

follow-up visit, the subject should be contacted by telephone for assessment of AEs and SAEs, and this should be documented in the eCRF.

Adverse events and SAEs before the start of the new anticancer therapy must be reported. If a subject begins a new anticancer therapy before the end of the 30-day or 90-day safety follow-up period, the safety follow-up visit should be performed before the new anticancer therapy is started.

6.4.2. Disease Status Follow-Up

As of Amendment 7, disease status follow-up visits for subjects who discontinued for any reason other than disease progression are no longer required. The last study visit will be the 90-day safety follow-up visit.

6.4.3. Survival Follow-Up

As of Amendment 7, survival follow-up visits for Phase 2 subjects are no longer required. The last study visit will be the 90-day safety follow-up visit.

6.5. End of Study

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

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

  Note: Every effort must be made to obtain the date of death.
- Consent is withdrawn for any further contact related to this study.
  - Subjects may choose to withdraw from the study at any time without penalty of jeopardizing their health care or loss of benefits to which 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 eCRF.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority or IRB or IEC.

NOTE: As of Amendment 7, the 90-day safety follow-up visit will be considered the EOS for an individual subject unless any of the above conditions have been met before this visit.

6.6. Unscheduled Visits

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

7. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

7.1. Administration of Informed Consent Form

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

7.2. Interactive Response Technology Procedure

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

7.3. Demography and Medical History

7.3.1. Demographics and General Medical History

Demographic data and a complete medical and medication history will be collected at screening by the investigator or qualified designee and will include date of birth, race, ethnicity (where allowed by local regulations), medical and surgical history, and concurrent illnesses assessed using the NCI CTCAE v4.0 (NCI 2010). Medical history should include all active conditions and any condition considered to be clinically significant by the investigator.

7.3.2. Disease Characteristics and Treatment History

Details regarding the disease for which the subject has enrolled in this study (eg, date of diagnosis, primary tumor histology, previous systemic therapies, surgeries, radiation therapy, and stage of cancer) will be collected at screening. [redacted]

7.4. Prior and Concomitant Medications and Procedures

NOTE: As of Amendment 7, use of concomitant medications should be monitored for subjects to verify that subjects are not taking any concomitant medication prohibited per protocol; however, concomitant medications no longer need to be collected in the eCRF.

Prior and concomitant medications and procedures will be reviewed to determine subject eligibility. All concomitant medications and measures must be recorded in the eCRF, and any medication received or procedure performed within 28 days before enrollment and up until the subject discontinues from the study will be recorded in the eCRF. The medication record will be maintained after signing the ICF to document concomitant medications, including any changes to the dose or regimen. Concomitant medications include any prescription, over-the-counter medications, or natural/herbal preparations taken or administered during the study period. Concomitant treatments and/or procedures that are required to manage a subject's medical condition during the study will also be recorded in the eCRF.

7.5. Safety Assessments

NOTE: As of Amendment 7, safety assessments should be as per site standard of care. Only AEs leading to discontinuation and SAEs will be collected in the eCRF.

7.5.1. Adverse Events

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

All AEs of unknown etiology associated with epacadostat or pembrolizumab exposure should be evaluated to determine if it is possibly an irAE. See Section 5.5.3 and Appendix G regarding the identification, evaluation, and management of AEs of potential immunologic etiology.

7.5.2. Physical Examinations

7.5.2.1. 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 height and the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; lymph nodes; and a brief neurologic examination. Clinically significant abnormal findings during screening should be recorded as medical history.

7.5.2.2. Targeted Physical Examination

The investigator or qualified designee will perform a directed physical examination as clinically indicated before treatment administration. A targeted physical examination will be a symptom-directed evaluation conducted by the investigator or designee. The targeted physical examination will include assessment(s) of the body systems or organs, as indicated by subject symptoms, AEs, or other findings. New clinically significant abnormal findings should be recorded as AEs.

7.5.3. Vital Signs

Vital sign measurements include blood pressure, pulse, respiratory rate, body temperature, and weight. Clinically significant abnormal findings during screening should be recorded as medical history. New clinically significant abnormal findings should be recorded as AEs.

7.5.4. Electrocardiograms

All 12-lead ECGs will be performed with the subject in a recumbent or semirecumbent position after 5 minutes of rest and should not be performed within 15 minutes after a blood collection. Electrocardiograms must be obtained at screening for all subjects; subsequent ECGs may be obtained during the treatment period as clinically indicated.

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. Clinically significant abnormal findings during screening should be recorded as medical history. New clinically significant abnormal findings should be recorded as AEs.

7.5.5. Laboratory Assessments

NOTE: As of Amendment 7, laboratory assessments only need to be performed in accordance with standard of care at each investigational site for the subject's condition and monitoring. Laboratory results do not need to be reported in the CRF, but all laboratory results corresponding with an SAE will be reported on the SAE form.

Laboratory tests for screening period should be performed by the site's local laboratory within 7 days before the first dose of treatment. Clinically significant abnormal findings during screening should be recorded as medical history. After Cycle 1, predose laboratory procedures can be conducted up to 72 hours before administration of epacadostat, pembrolizumab, and/or chemotherapy regimen. Results must be reviewed by the investigator or qualified designee and found to be acceptable before each dose of treatment. New clinically significant abnormal findings should be recorded as AEs.

7.5.5.1. Serum Chemistry

A comprehensive serum chemistry will be performed as clinically indicated. Appropriate monitoring intervals should be discussed with the medical monitor in these circumstances. Serum chemistry tests will be performed by the site's local laboratory.

7.5.5.2. Hematology

Hematology with differential will be performed as clinically indicated. Appropriate monitoring intervals should be discussed with the medical monitor in these circumstances. Hematology with differential will be performed by the site's local laboratory.

7.5.5.3. Liver Chemistry

Liver chemistry tests will be performed as clinically indicated. Appropriate monitoring intervals should be discussed with the medical monitor in these circumstances. Liver chemistry tests will be performed by the site's local laboratory.

7.5.5.4. Coagulation Panel

A coagulation panel will be performed as clinically indicated. The coagulation panel will be performed by the site's local laboratory.

7.5.5.5. Endocrine Function

Endocrine function tests will be performed as clinically indicated. Endocrine function testing analysis will be performed by the site's local laboratory.

7.5.5.6. Urinalysis

Urinalysis will be performed as clinically indicated. Urinalysis will be performed by the site's local laboratory.

7.5.5.7. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential during screening and as clinically indicated.

If a subject inadvertently becomes pregnant while on study, the subject will immediately be discontinued from study treatment. The site will contact the subject at least monthly and document the subject's status until the first well-baby visit 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. The outcome of the pregnancy will be reported to the sponsor without delay and within 24 hours if the outcome is an SAE (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the sponsor. If a male subject impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy reported to the sponsor and followed as described above and in Section 8.5.

7.5.5.8. Serology

Serology will be performed at screening only to assess eligibility for inclusion in the study.

[redacted]

7.6. Efficacy Assessments

NOTE: As of Amendment 7, no further efficacy assessment will be required beyond Week 18. Imaging for the study will only be required at Week 9 and Week 18 per RECIST v1.1. After Week 18, CT/MRI or PET-CT assessments are only required to be performed as per standard of care guidelines for the subject's condition and monitoring. Subjects must be withdrawn from the study if, in the opinion of the investigator, the disease has progressed and the subject is no longer having clinical benefit from the study treatment.

7.6.1. Initial Tumor Imaging

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

Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days before the first dose of treatment. **The same imaging technique should be used in a subject throughout the study.** Baseline scan must be a contrast CT or MRI, except in circumstances where there is a contrast allergy or with medical monitor approval. When the CT component of a positron emission tomography/CT uses higher energy and thinner slices, it may be acceptable (with medical monitor approval). A standard, full assessment for lesions should be conducted at baseline, including CT or MRI scans of chest, abdomen, and pelvis. The same modality (CT or MRI) should be used for follow-up assessments every 9 weeks, including radiologic assessments of all sites of disease present at baseline. In addition to radiologic monitoring, all other lesions observed at the screening visit should be followed.

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

7.6.2. Tumor Imaging During the Study

Tumor imaging should be continued on treatment and assessed per RECIST v1.1, and the same imaging technique should be used in a subject throughout the study. Imaging should be performed every 9 weeks (± 7 days) from Cycle 1 Day 1 for the first 12 months of treatment. After 12 months of treatment, the assessments should be performed every 12 weeks (± 7 days). Assessments should continue to be performed until disease progression, the start of new anticancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs

first. More frequent scanning is allowed, if clinically indicated. **Imaging should not be delayed for delays in cycle starts or extension of combination treatment cycle intervals.**

Response should be confirmed by a repeat radiographic assessment not less than 4 weeks from the date the response was first documented. The scan for confirmation of response may be performed at the earliest of 4 weeks after the first indication of response or at the next scheduled scan (9 weeks later), whichever is clinically indicated.

Disease progression should be confirmed at least 4 weeks (but not later than 6 weeks) after the first scan indicating PD in clinically stable subjects. Subjects who have unconfirmed disease progression may continue on treatment until progression is confirmed provided that they have met the conditions detailed in Section 7.6.2.1.

7.6.2.1. Assessment of Progressive Disease According to Immune-Related RECIST Criteria

RECIST v1.1 will be adapted for defining PD to account for the unique tumor response seen with immunotherapies. This adaptation is known as irRECIST and will be used to guide treatment decisions for discontinuation of therapy due to disease progression.

If imaging shows PD, it is at the discretion of the investigator to keep a subject on treatment or to stop treatment until imaging is repeated ≥ 4 weeks later, but not ≥ 6 weeks later, to confirm PD. When feasible, subjects should not be discontinued until progression is confirmed; however, the decision to continue treatment after the first evidence of disease progression is at the investigator's discretion based on the clinical status of the subject.

Subjects may continue to receive treatment while waiting for confirmation of PD (see Table 4) if they are clinically stable as defined by the following criteria:

- Absence of clinically significant signs and symptoms (including worsening of laboratory values) indicating disease progression.
- No decline in ECOG performance status.
- 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. If radiologic progression is confirmed, then the subject will be discontinued from treatment as specified in the Protocol, and the first radiographic evidence of PD should be the date of progression. If radiologic progression is not confirmed, then the subject should resume/continue treatment and have their next scan according to the Protocol-specified schedule. If progression is not confirmed and the subject continues on treatment, the next scan that documents disease progression (and is confirmed by a second scan at least 4 weeks later) will be considered the date of disease progression.

Note: If a subject with confirmed radiographic progression (ie, 2 scans ≥ 4 weeks apart demonstrating progressive disease) is clinically stable or clinically improved, and there is no further increase in the tumor dimensions at the confirmatory scan, an exception may be considered to continue treatment upon consultation with the sponsor. Clinically stable subjects

should also have at the confirmatory scan no further increase in the target lesions, no unequivocal increase in nontarget lesions, and no additional new lesions develop (nonworsening PD) to continue treatment.

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

Progressive disease is confirmed if ANY of the following conditions are met on the subsequent confirmatory scan:

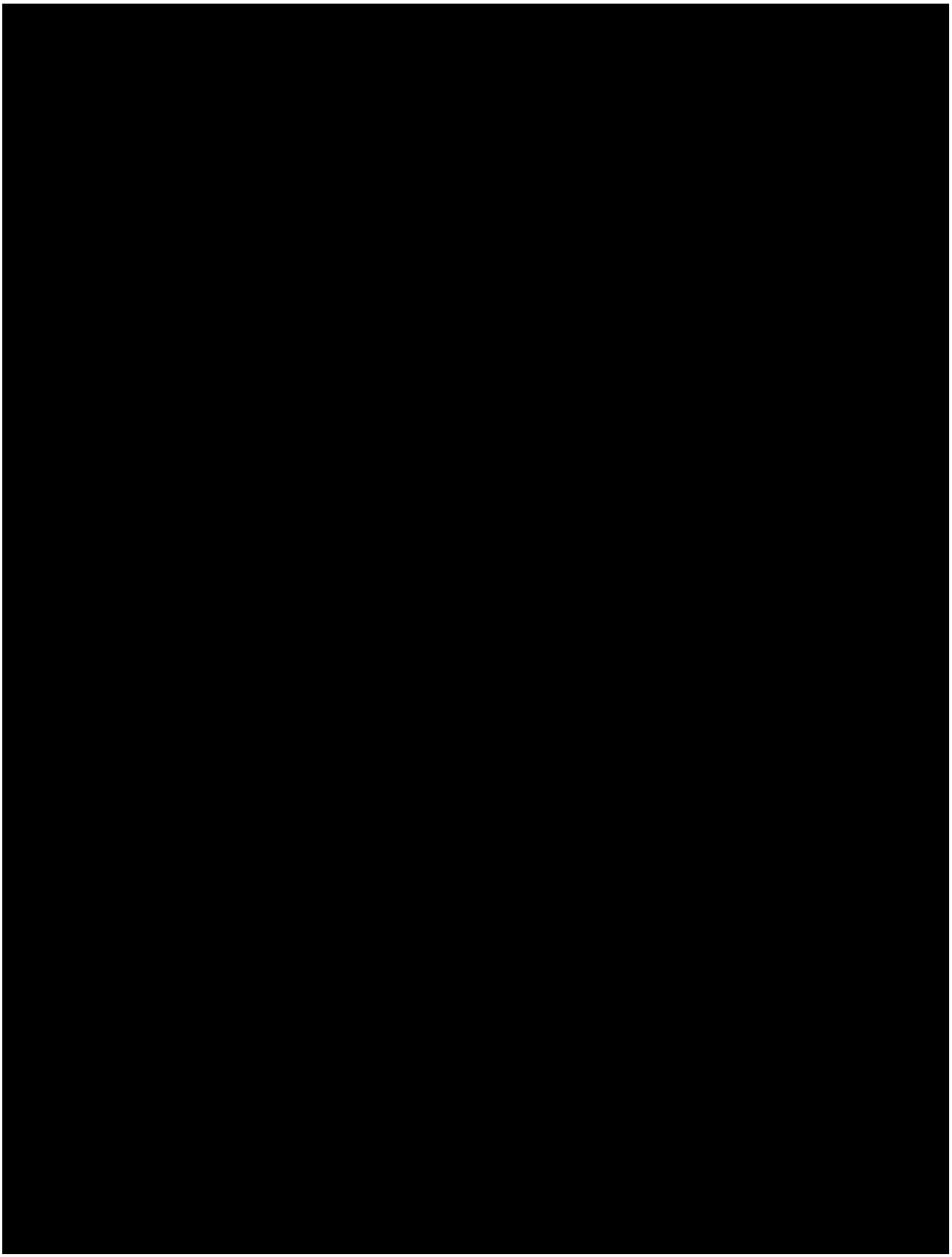
- Target lesions reach the PD threshold (increase in tumor burden ≥ 20% and absolute increase of at least 5 mm relative to nadir), OR if the threshold has already been reached on the initial scan showing PD, they remain above the threshold.
- Nontarget lesions show unequivocal progression.
- New lesions appear, OR if they appeared on the initial scan showing PD, they have grown.

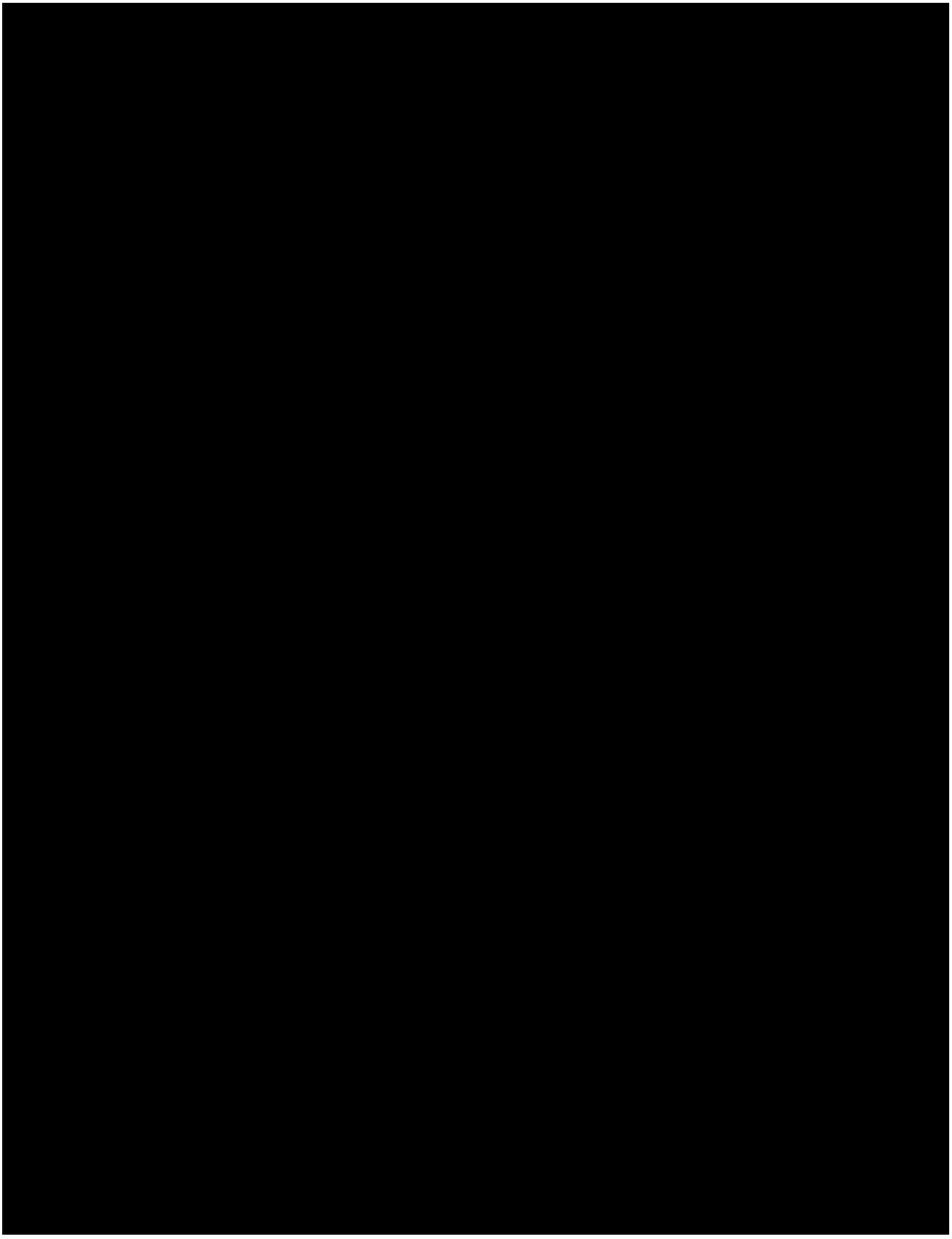
7.7. Performance and Quality-of-Life Assessments

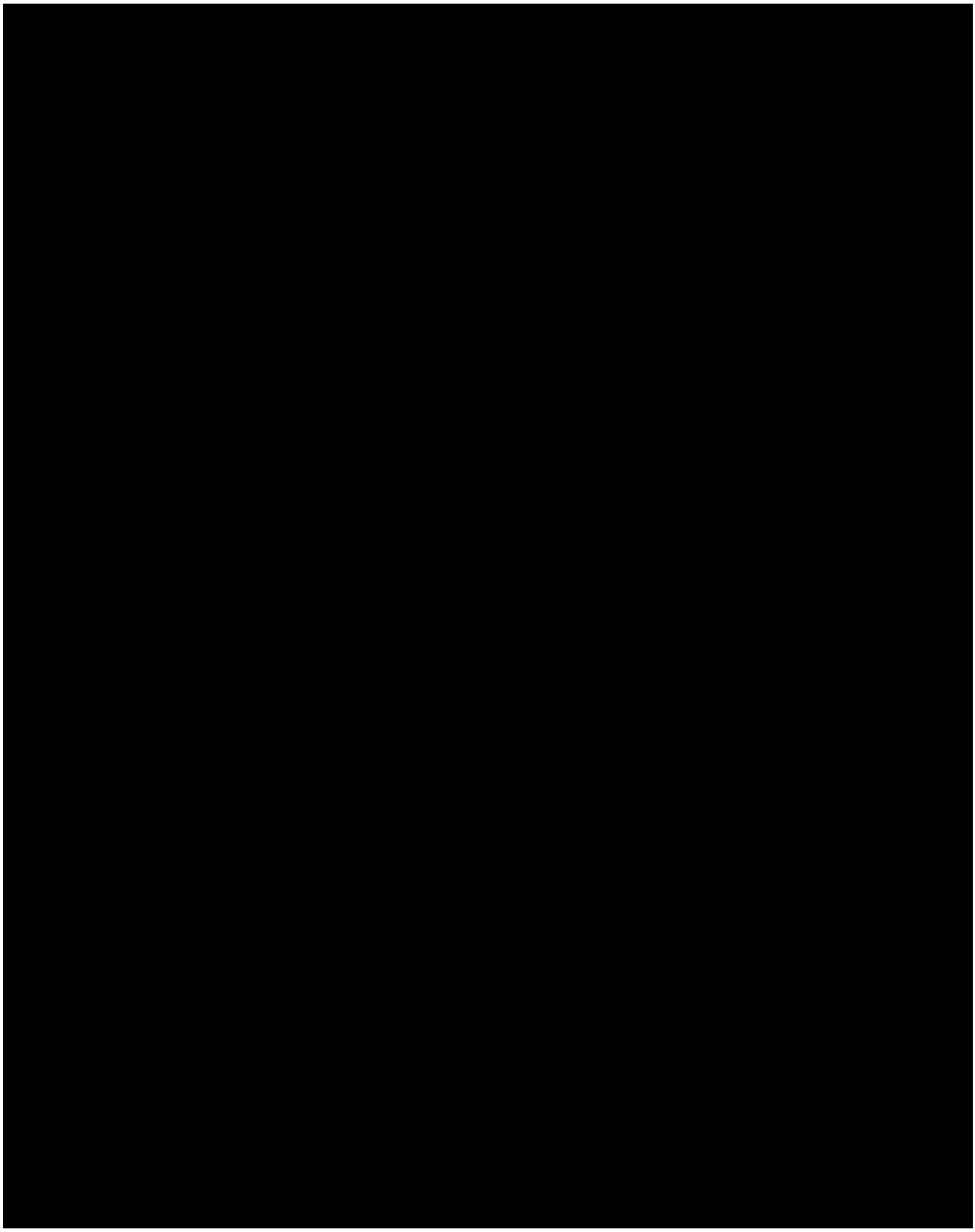
NOTE: As of Amendment 7, ECOG performance status will no longer be collected and should be monitored only per the site's standard of care, if applicable.

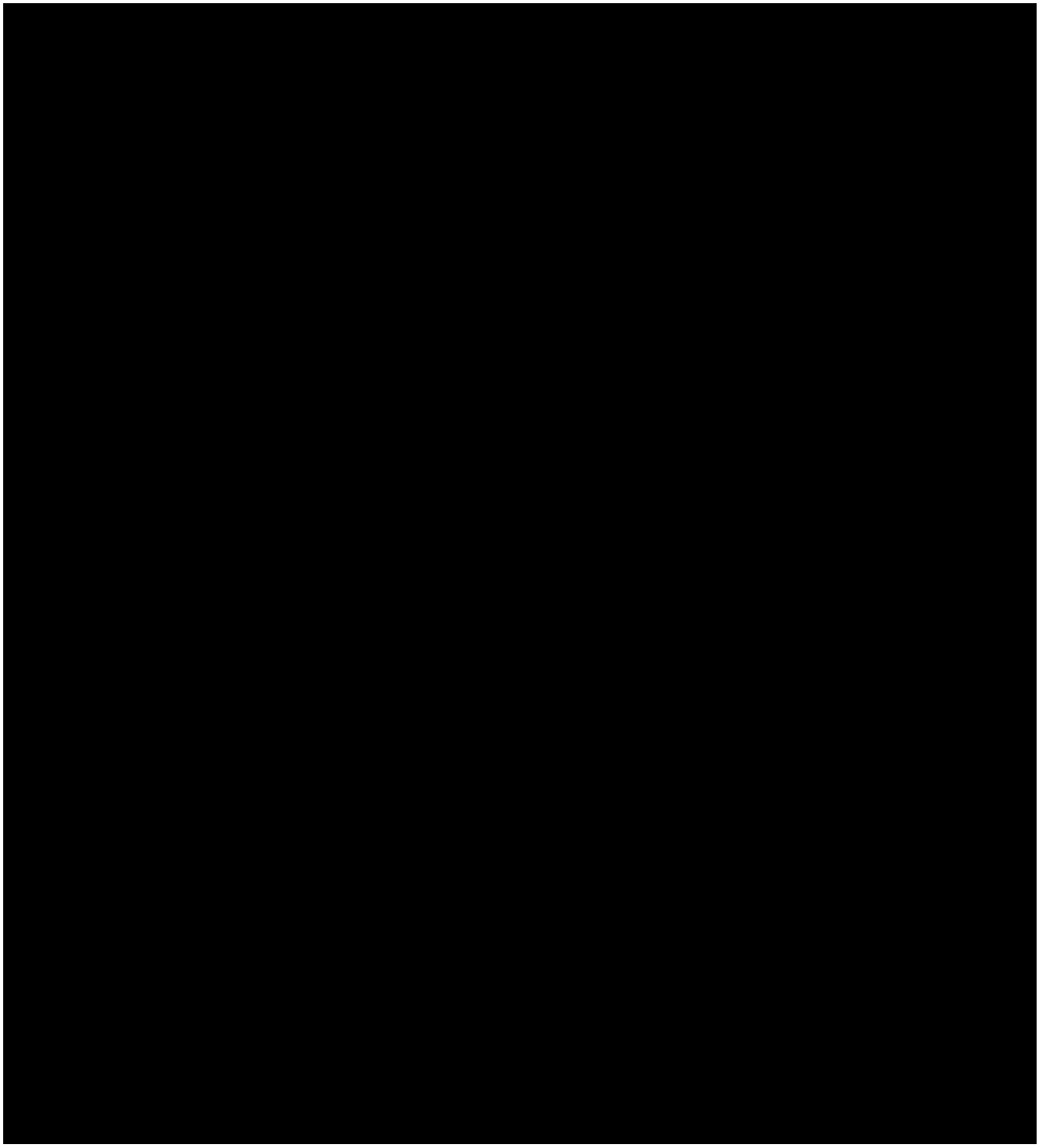
7.7.1. Eastern Cooperative Oncology Group Performance Status

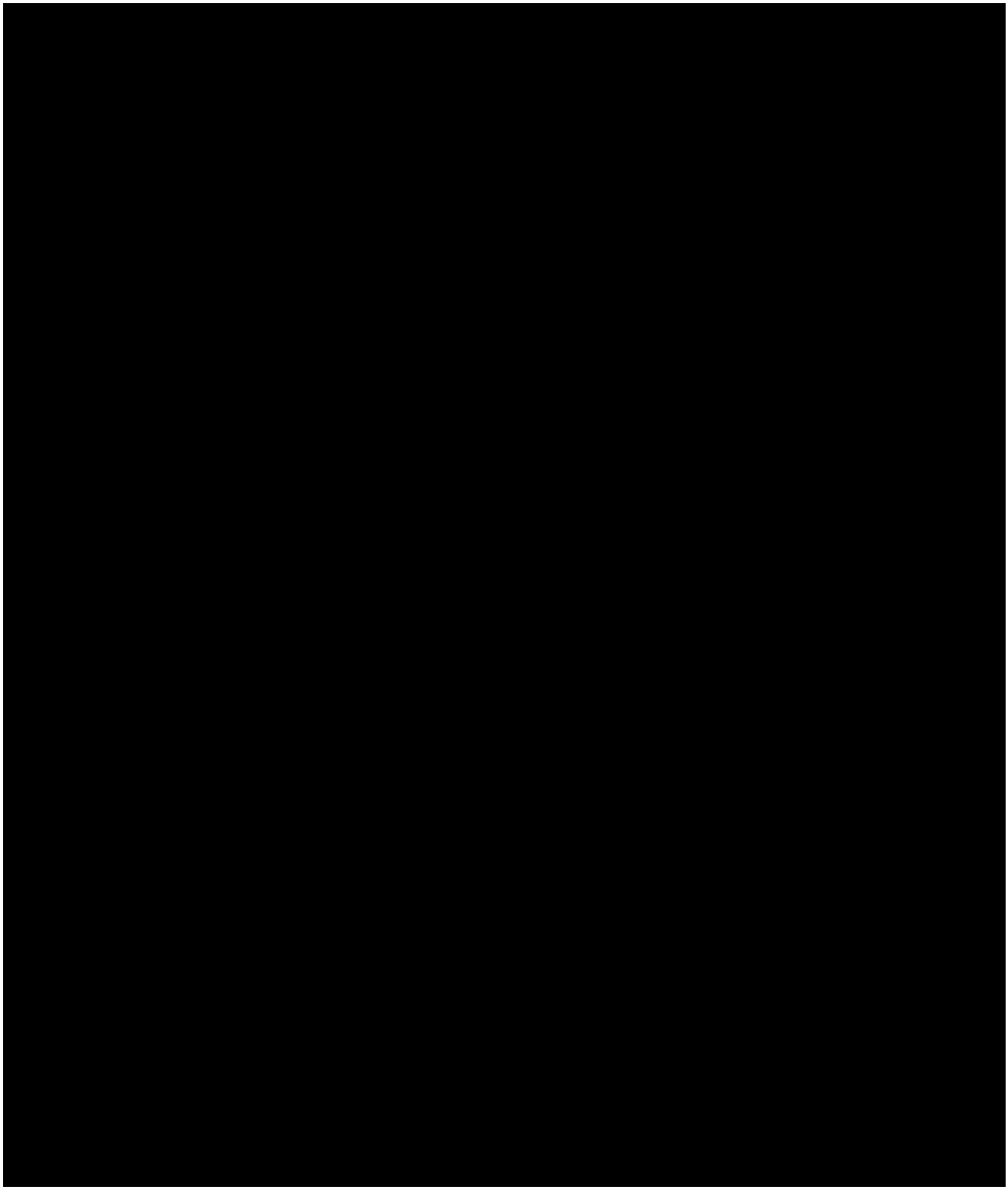
The investigator or qualified designee will assess ECOG performance status (Appendix C) at screening, before the administration of treatment on Day 1 of each cycle, and at the EOT and safety follow-up visits as specified in the schedules of assessments (Table 7, Table 9, Table 11, Table 12, and Table 14).

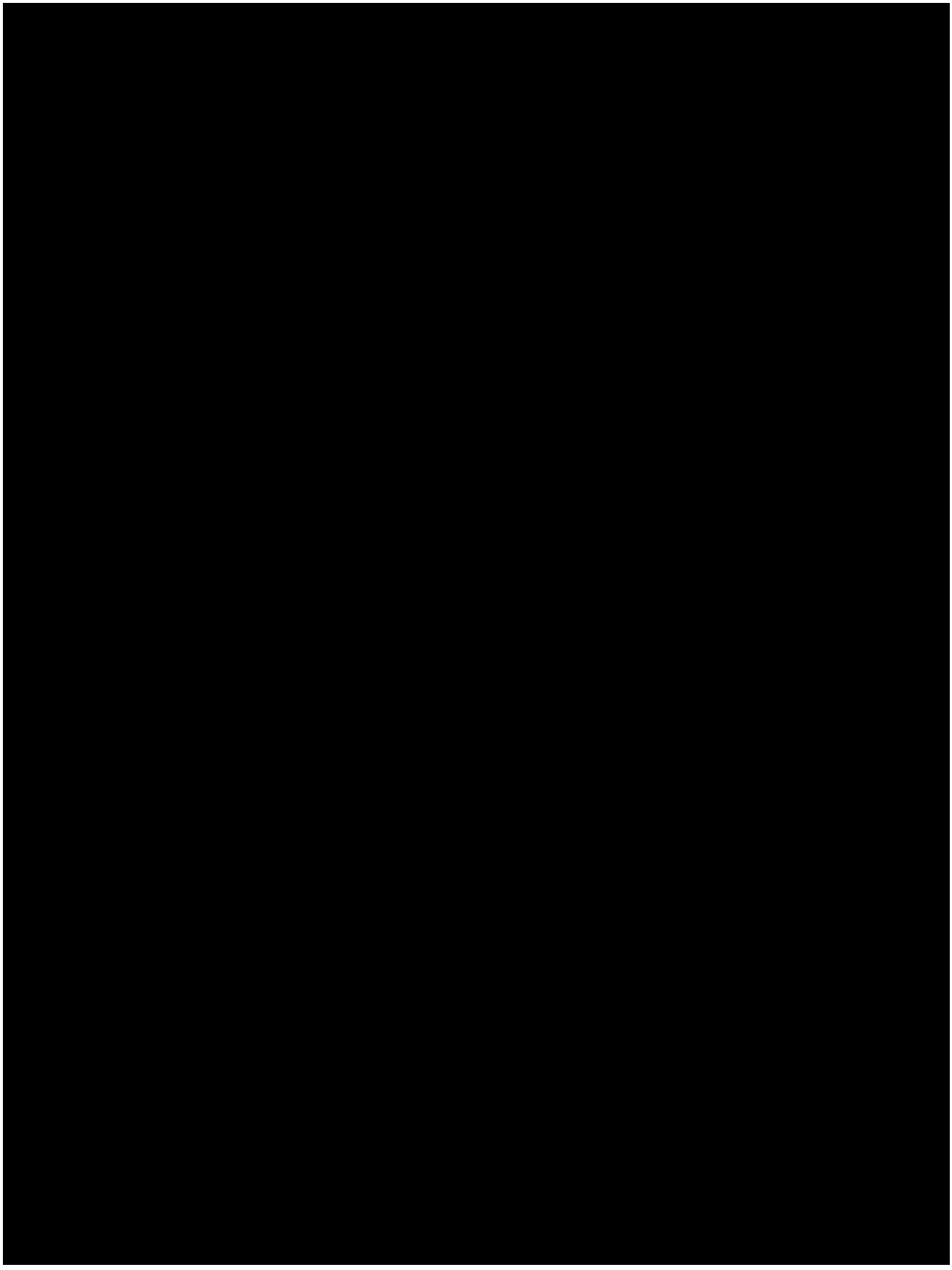


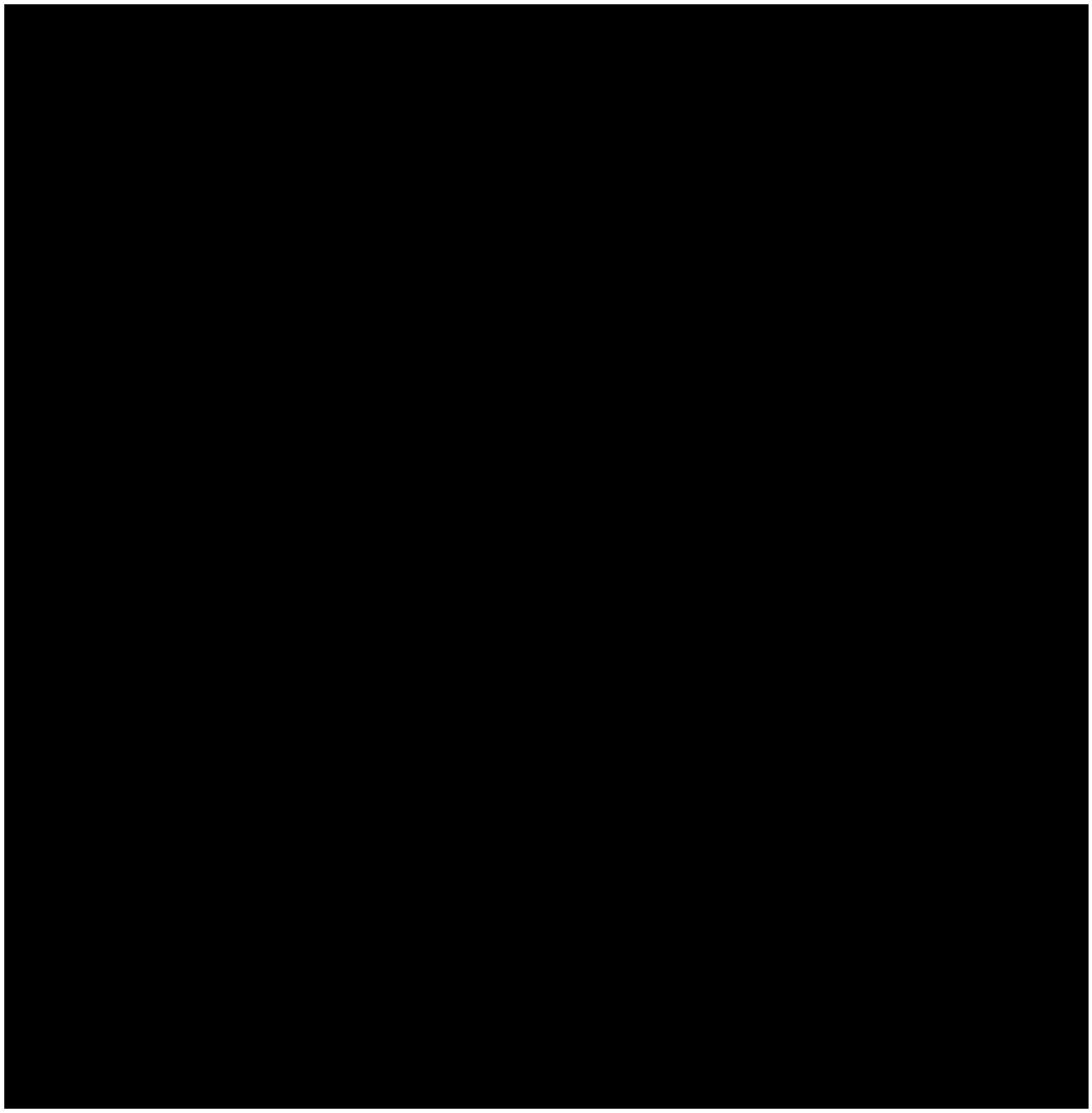












7.10. Other Study Procedures

7.10.1. Distribution of Subject Reminder Cards and Subject Diaries

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

7.10.2. Post-Treatment Anticancer Therapy Status

NOTE: As of Amendment 7, post-treatment anticancer therapy will no longer be collected.

The investigator or qualified designee will enter all new anticancer therapy initiated after the last dose of epacadostat or pembrolizumab (whichever is later) in the eCRF. If a subject initiates a new anticancer therapy before the scheduled 30-day or 90-day safety follow-up visit, the appropriate safety follow-up visit should be rescheduled so it occurs before the first dose of the new anticancer therapy.

7.10.3. Data Collection for Survival Follow-Up

NOTE: As of Amendment 7, data collection for survival follow-up visits for Phase 2 subjects are no longer required.

8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events

NOTE: As of Amendment 7, only AEs leading to discontinuation of study treatment and SAEs regardless of causality relationship will be reported in the eCRF.

8.1.1. Definitions

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

8.1.2. Reporting

Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events form of the eCRF. Conditions that were already present at the time of informed consent should be recorded on the Medical History form in the eCRF. Monitoring for the occurrence of new AEs should be continued for at least 90 days after the last dose of epacadostat or pembrolizumab, or 30 days following cessation of study treatment if the subject initiates new anticancer therapy (whichever is earlier); monitoring for pregnancy should continue for 120 days after the last dose of epacadostat or pembrolizumab (whichever is later). 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.

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

The severity of AEs will be assessed using CTCAE v4.0 Grades 1 through 4. The CTCAE v4.0 severity of Grade 5 will not be used; AEs resulting in death will be graded accordingly using Grades 1 through 4 and have the outcome noted as fatal. If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity:

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

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

- The severity grade (CTCAE Grade 1 to 4).
- Whether there is at least a reasonable possibility that the AE is related to the study treatment: suspected (yes) or not suspected (no).

NOTE: Causality assessment for epacadostat, pembrolizumab, and the chemotherapy regimen must be indicated. If appropriate, the relationship to the combination may be assessed as well.

- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to study drug.
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per serious adverse event (SAE) definition provided in Section 8.3.1.

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

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

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

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

8.2. Laboratory Test Abnormalities

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

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A Grade 3 or 4 AE does not automatically indicate an SAE unless it meets the definition of serious, as defined in Section 8.3.1. A dose modification for the laboratory abnormality may be required (see Section 5.5) and should not contribute to the designation of a laboratory test abnormality as an SAE.

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

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur before 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 follows:

1. AT (ALT or AST) elevation ≥ 3 times ULN

   AND
2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum ALP)

   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 drugs known to be hepatotoxic.

8.3. Serious Adverse Events

8.3.1. Definitions

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

- Is fatal or life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is a result of:
  - A routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
  - An elective surgery or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF.
  - A treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE and not resulting in hospital admission.
  - Any social reasons and respite care, in the absence of any deterioration in the subject's general condition.
- Results in persistent or significant disability, incapacity, or a substantial disruption of a person's ability to conduct normal life functions.
- Constitutes a congenital anomaly or birth defect.
- Is considered to be an important medical event or a medically significant event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above.

8.3.2. Reporting

Every SAE, regardless of suspected causality (eg, relationship to study drug[s] or study procedure or disease progression), occurring after the subject has signed the ICF through 90 days (120 days for pregnancy) after the last dose of epacadostat or pembrolizumab, or 30 days following cessation of study treatment if the subject initiates new anticancer therapy (whichever is earlier) must be reported to the sponsor (or designee) within **24 hours** of learning of its occurrence, unless otherwise specified by the Protocol. Any SAEs occurring more than 90 days (120 days for pregnancy) after the last dose of epacadostat or pembrolizumab (whichever is later) should be reported to the sponsor or its designee only if the investigator suspects a causal relationship to the study drug.

Information about all SAEs is collected and recorded on the Adverse Event form of the eCRF. The investigator must assess and record the causal relationship of each SAE to the study treatment. NOTE: Causality assessment for epacadostat, pembrolizumab, and the chemotherapy regimen must be indicated. If appropriate, the relationship to the combination may be assessed as well.

The investigator must also complete the Incyte Serious Adverse Event Report Form, in English, and send the completed and signed form to the sponsor or designee within 24 hours of becoming aware of the SAE. The investigator must provide a causality assessment, that is, assess whether there is at least a reasonable possibility that the SAE is related to the study treatment: suspected (yes) or not suspected (no). Causality assessment for epacadostat, pembrolizumab, and each chemotherapy agent administered must be indicated. If appropriate, the relationship to the combination may be assessed as well. Refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.

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

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

If the SAE (new occurrence) is not documented in the IBs for epacadostat or pembrolizumab or in the US prescribing information or EMA Summary of Product Characteristics for the chemotherapy agents and is thought to be related to epacadostat, pembrolizumab, or chemotherapy agent, then the sponsor or its designee may urgently require further information from the investigator for reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC, or as per national regulatory requirements in participating countries.

NOTE: As of Amendment 7, all SAEs regardless of causality relationship will be submitted to the sponsor as described above and entered in the eCRF.

8.4. Emergency Unblinding of Treatment Assignment

Not applicable.

8.5. Pregnancy

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

- The study drug must be discontinued immediately (female subjects only; see Section 5.5.2 for the maximum permitted duration of study drug interruption).
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

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

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

8.6. Events of Clinical Interest

Events of clinical interest (ECIs) must be recorded as such in the eCRF as an ECI.

For this study, ECIs include:

1. Potential drug-induced liver injury (or Hy's Law) – an elevated AST or ALT laboratory value that is ≥ 3 × the ULN and an elevated total bilirubin laboratory value that is ≥ 2 × the ULN and, at the same time, an ALP laboratory value that is < 2 × the ULN, as determined by way of Protocol-specified laboratory testing or unscheduled laboratory testing.

   Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow-up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

2. An overdose of epacadostat or pembrolizumab that is not associated with clinical symptoms or abnormal laboratory results. For this study, an overdose will be defined as ≥ 1000 mg of epacadostat or ≥ 1000 mg (5 times the dose) of pembrolizumab. No specific information is available on the treatment of overdose of epacadostat or pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.
3. Serotonin syndrome (see Section 5.5.6 for further details).
4. Any of the following AEs:
   a. ≥ Grade 3 diarrhea
   b. ≥ Grade 3 colitis
   c. ≥ Grade 2 pneumonitis
   d. ≥ Grade 3 rash or dermatitis
   e. Grade 4 laboratory abnormality

Events of clinical interest that occur in any subject from the date of first dose of treatment through 90 days after EOT or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to epacadostat or pembrolizumab, must be recorded in the eCRF. A detailed narrative of the event should be reported to the sponsor within 24 hours of the event.

8.7. Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

For purposes of this study, an overdose is defined as an overdose will be defined as ≥ 1000 mg of epacadostat or ≥ 1000 mg (5 times the dose) of pembrolizumab. All occurrences of overdose must be reported as an SAE (see Section 8.3.2 for reporting details).

8.8. Warnings and Precautions

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

8.9. Safety Monitoring Committee

Due to the complexity of the study, an SMC will review safety data at regular intervals throughout the study. The frequency of meetings will be contingent upon enrollment and availability of safety data for analysis and review. Details regarding membership, roles, and responsibilities of the committee are specified in the SMC charter.

8.10. Product Complaints

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

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

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

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

9. STATISTICS

9.1. Study Populations

The safety population includes all subjects enrolled in the study who received at least 1 dose of epacadostat. All safety analyses will be based on the safety population.

The full analysis set includes all subjects enrolled in the study who received at least 1 dose of epacadostat and have at least 1 postbaseline assessment or who discontinued epacadostat. All efficacy analyses will be based on the full analysis set.

[redacted]

9.2. Selection of Sample Size

9.2.1. Sample Size in Phase 1

A 3 + 3 + 3 design will be used in Phase 1 to determine the MTD or PAD and DLT of epacadostat when given in combination with pembrolizumab and 7 chemotherapy regimens. The total number of subjects will depend on the frequency of DLTs and number of dose levels tested before MTD or PAD is established. Based on 3 + 3 + 3 design algorithm, within each treatment group, a minimum of 6 subjects and up to 9 subjects will be enrolled at each dose level.

9.2.2. Sample Size in Phase 2

9.2.2.1. Efficacy Expansion

NOTE: As of 25 OCT 2018, this study is closed to enrollment. As of this date, no subjects were enrolled in Phase 2 efficacy expansion (all treatment groups) or Phase 2 mandatory biopsy Treatment Groups A, B, F, and G; therefore, disregard this section.

Phase 2 consists of expansion cohorts (efficacy and mandatory biopsy) in specific tumor types (advanced or metastatic CRC, PDAC, squamous or nonsquamous NSCLC, UC, SCCHN, or any advanced or metastatic solid tumor that progressed on previous therapy with a PD-1 or PD-L1 inhibitor). A Simon 2-stage design will be used for the CRC and PDAC efficacy expansion cohorts. The response rates for the historical control (p_0), desired response rates for the combination (p_1), number of subjects needed in Stage 1 (n_1) and Stage 2 (n_2), total number of subjects (n), first-stage threshold declaring cohort undesirable (r_1), and the upper limit of the number of responses in n subjects such that futility of the drug is concluded (r) are provided for each expansion cohort in Table 21.

In addition, a single-stage Phase 2 expansion will be used for all other efficacy expansion cohorts. The sample sizes and decision rules are summarized in Table 22. The definitions of p_0, p_1, n, and r are the same as those in Table 21.

The calculation is based on a 1-sided Type I error of 0.1 and power of 80%, with the exception of the cohort enrolling solid tumors that progressed on previous treatment with a PD-1 or PD-L1 inhibitor, which is based on a 1-sided Type I error of 0.1 and power of approximately 98%.

Table 21: Sample Size and Decision Rule for Simon 2-Stage Design Phase 2 Efficacy Expansion Cohorts

Tumor Type	p_0	p_1	n_1	n_2	n	r_1	r
CRC	40%	60%	12	26	38	5	18
PDAC	25%	45%	15	12	27	4	9

Table 22: Sample Size and Decision Rule for Single-Stage Design Phase 2 Efficacy Expansion Cohorts

Tumor Type	p_0	p_1	n	r
Squamous NSCLC	30%	50%	33	13
Nonsquamous NSCLC	50%	70%	33	20
Solid tumors that progressed on previous therapy with a PD-1 or PD-L1 inhibitor	5%	25%	33	3
UC	60%	80%	33	23
SCCHN	50%	70%	33	20

9.2.2.2. Phase 2 Mandatory Biopsy Cohorts

NOTE: As of 25 OCT 2018, this study is closed to enrollment. As of this date, only Phase 2 mandatory biopsy Treatment Groups C, D, and E enrolled subjects, and the minimum number of subjects was not enrolled; therefore, disregard this section.

- A minimum of 10 subjects will be enrolled in the CRC, PDAC, squamous NSCLC, nonsquamous NSCLC, UC, and SCCHN Phase 2 mandatory biopsy cohorts.
- A minimum of 5 subjects will be enrolled in any advanced or metastatic solid tumor that progressed on previous therapy with a PD-1 or PD-L1 inhibitor mandatory biopsy cohorts.

[redacted]

9.3. Level of Significance

For the primary efficacy endpoints, the 1-sided Type I error will be controlled at 0.1 for each individual cohort expansion. For other endpoints, CIs will be reported at a 95% confidence level. Note that this level of significance does not account for the multiple expansion cohorts.

9.4. Statistical Analyses

9.4.1. Primary Analyses

- Phase 1: The clinical safety data (AEs, vital signs, ECGs, routine laboratory tests) will be summarized using descriptive statistics (eg, mean, frequency) based on the safety population. The analyses of safety data are described in Section 9.4.4.
- Phase 2: ORR, defined as the percentage of subjects having a CR or PR, per RECIST v1.1 will be estimated with a 95% CI.

9.4.2. Secondary Analyses

- Phase 1: ORR, defined as the percentage of subjects having a CR or PR, per RECIST v1.1 will be estimated with 95% CI.
- Phase 2: The clinical safety data (AEs, vital signs, ECGs, routine laboratory tests) will be summarized using descriptive statistics (eg, mean, frequency) based on the safety population. The analyses of safety data are detailed in Section 9.4.4.

9.4.4. Safety Analyses

9.4.4.1. Adverse Events

A treatment-emergent AE is any AE either reported for the first time or worsening of a pre-existing event after the first dose of epacadostat, pembrolizumab, or chemotherapy. Analysis of AEs will be limited to treatment-emergent AEs, but data listings will include all AEs regardless of their timing to treatment administration. Adverse events will be tabulated by the MedDRA preferred term and system organ class. Severity of AEs will be based on the NCI CTCAE v4.0 using Grades 1 through 4.

The subset of AEs considered by the investigator to have a relationship to epacadostat will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to epacadostat, the AE will be considered treatment-related. The incidence of AEs and treatment-related AEs will be tabulated.

9.4.4.2. Clinical Laboratory Tests

Laboratory test values outside the normal range will be assessed for severity based on the normal ranges for the clinical reference laboratory. The incidence of abnormal laboratory values and shift tables relative to baseline will be tabulated.

Laboratory data will be classified into Grades 1 through 4 using CTCAE v4.0. The following summaries will be produced for the laboratory data:

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

9.4.4.3. Vital Signs

Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, pulse, respiratory rate, and body temperature) at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities (see Table 23), and subjects exhibiting clinically notable vital sign abnormalities will be listed. A value will be considered an "alert" value if it is outside the established range and shows a > 25% change from baseline.

Table 23: Criteria for Clinically Notable Vital Sign Abnormalities

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

9.4.4.4. Electrocardiograms

Descriptive statistics and mean change from baseline will be determined for each ECG parameter at each assessment time. Electrocardiogram results will be reviewed for clinically notable abnormalities according to predefined criteria (Table 24). Subjects exhibiting clinically notable ECG abnormalities will be listed.

Table 24: Criteria for Clinically Notable Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold
QTcF	> 480 msec	< 295 msec
PR	> 220 msec	< 75 msec
QRS	> 120 msec	< 50 msec
QT	> 500 msec	< 300 msec
RR	> 1330 msec	< 600 msec

QTcF = Fridericia correction.

9.4.4.5. Events of Clinical Interest

Events of clinical interest include potential drug-induced liver injury (or Hy's Law), an overdose of epacadostat or pembrolizumab that is not associated with clinical symptoms or abnormal laboratory results, SS, and any of the following AEs: ≥ Grade 3 diarrhea, ≥ Grade 3 colitis, ≥ Grade 2 pneumonitis, ≥ Grade 3 rash or dermatitis, Grade 4 laboratory abnormality. See Section 8.6 for further details.

A summary of ECIs including the number (%) of subjects reporting any ECIs will be provided.

[redacted]

9.5. Analyses for the Safety Monitoring Committee

Details regarding safety data to be evaluated by the SMC will be addressed in the SMC charter.

9.6. Interim Analysis

Note: As of 25 OCT 2018, this study is closed to enrollment. As of this date, no subjects were enrolled in Phase 2 efficacy expansion (all treatment groups) or Phase 2 mandatory biopsy Treatment Groups A, B, F, and G; therefore, the interim analysis is no longer applicable.

In Phase 2, there will be a planned interim analysis for futility in the CRC and PDAC expansion cohorts. The Simon 2-stage design will be applied to each expansion cohort independently. According to Table 21, during Stage 1, n_1 subjects with specific tumor types (advanced or

metastatic CRC or PDAC) will be enrolled in each cohort. If $\leq r_1$ responses are observed, the cohort will be terminated for futility. If more than r_1 responses are observed within each cohort, additional n_2 subjects will be enrolled for Stage 2 evaluation.

Based on this early termination rule, the probabilities of early termination under the assumption of historical control response rates (H_0) and desired response rates (H_A) are shown in Table 25.

Table 25: Probabilities of Early Termination for Simon 2-Stage Design

Tumor Type	p_0	p_1	Probability of Early Termination	
			Under H_0	Under H_A
CRC	40%	60%	0.6652	0.1582
PDAC	25%	45%	0.6865	0.1204

The interim analysis for each expansion cohort will be conducted once the first postbaseline radiologic tumor assessments for Stage 1 subjects within the cohort are available. Enrollment will be held at that time unless a sufficient number of responders have been observed before that time.

10. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

10.1. Investigator Responsibilities

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

The investigator will be responsible for:

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

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

10.2. Accountability, Handling, and Disposal of Study Drug

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

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

The investigational product must be used only in accordance with the Protocol. The investigator will also maintain records adequately documenting that the subjects were provided the specified study treatment. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the investigational product and study subjects.

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

10.3. Data Management

Note: As of Amendment 7, only SAEs, AEs leading to discontinuation, EOT disposition (reason for discontinuation), drug accountability, dosing information, EOS disposition (end of study form), informed consent, and death (if it occurs within the safety reporting period) will be collected in the eCRF.

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

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

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

10.4. Data Privacy and Confidentiality of Study Records

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

Subject names will not be supplied to the sponsor or its designee, if applicable. Only the subject number will be recorded in the eCRF; if the subject's name appears on any other document (eg, laboratory report), it must be redacted from the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed that representatives of the sponsor or its designee, IRB or IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

10.5. Financial Disclosure

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

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

10.6. Publication Policy

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

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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] Vasectomised partner is a highly effective method of avoiding pregnancy provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
[4] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Source: CTFG 2014.

APPENDIX C. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Grade	Performance Status
0	Fully active, able to carry on all predisease 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 self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken et al 1982.

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

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

APPENDIX E. COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V4.0

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be used for adverse event reporting (http://ctep.cancer.gov/reporting/ctc.html).

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

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

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

Source: Eisenhauer et al 2009.

In addition, volumetric analysis will be explored by central review for response assessment.

APPENDIX G. DOSE MODIFICATIONS FOR EPACADOSTAT AND PEMBROLIZUMAB

G.1. Dose Modifications for Epacadostat and Pembrolizumab for Immune-Related Adverse Events

Adverse events (AEs) associated with epacadostat and/or pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of epacadostat and/or pembrolizumab treatment and may affect more than 1 body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of epacadostat and/or pembrolizumab, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue epacadostat and/or pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab and/or epacadostat are provided in Table G-1.

Table G-1: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated With Epacadostat and/or Pembrolizumab

irAEs	Toxicity Grade or Conditions (CTCAE v4.0)	Study Treatment	Action Taken with Study Treatment	irAE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-Up
Pneumonitis	Grade 2	Pembrolizumab	Withhold until Grade 0-1	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of pneumonitis. • Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment. • Add prophylactic antibiotics for opportunistic infections.
		Epacadostat	Withhold until Grade 0-1		
	Grade 3 or 4, or recurrent Grade 2	Pembrolizumab	Permanently discontinue		
		Epacadostat	Permanently discontinue		
Diarrhea/colitis	Grade 2 or 3	Pembrolizumab	Withhold until Grade 0-1	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of enterocolitis (ie diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie peritoneal signs and ileus). • Subjects with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Subjects with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
		Epacadostat	Withhold until Grade 0-1		
	Grade 4 or recurrent Grade 3	Pembrolizumab	Permanently discontinue		
		Epacadostat	Permanently discontinue		

Table G-1: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated With Epacadostat and/or Pembrolizumab (Continued)

irAEs	Toxicity Grade or Conditions (CTCAE v4.0)	Study Treatment	Action Taken with Study Treatment	irAE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-Up
AST/ALT Elevation or Increased Bilirubin	Grade 2	Pembrolizumab	Withhold until Grade 0-1	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returns to baseline or is stable).
		Epacadostat	Withhold until Grade 0-1		
	Grade 3 or 4	Pembrolizumab	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
		Epacadostat	Permanently discontinue		
Type 1 diabetes mellitus (T1DM) or Hyperglycemia[b]	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Pembrolizumab	Withhold until Grade 0-1	• Initiate insulin replacement therapy for subjects with T1DM • Administer anti-hyperglycemic in subjects with hyperglycemia	• Monitor subjects for hyperglycemia or other signs and symptoms of diabetes.
		Epacadostat	Withhold until Grade 0-1		

Table G-1: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated With Epacadostat and/or Pembrolizumab (Continued)

irAEs	Toxicity Grade or Conditions (CTCAE v4.0)	Study Treatment	Action Taken with Study Treatment	irAE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-Up
Hypophysitis	Grade 2	Pembrolizumab	Withhold until Grade 0-1	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency).
		Epacadostat	Withhold until Grade 0-1		
	Grade 3 or 4	Pembrolizumab	Withhold until Grade 0-1 or permanently discontinue[a]		
		Epacadostat	Withhold until Grade 0-1 or permanently discontinue[a]		
Hyperthyroidism[b]	Grade 2	Pembrolizumab	Continue	• Treat with non-selective beta-blockers (eg propranolol) or thioamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
		Epacadostat	Continue		
	Grade 3 or 4	Pembrolizumab	Withhold until Grade 0-1 or permanently discontinue[a]		
		Epacadostat	Withhold until Grade 0-1 or permanently discontinue[a]		
Hypothyroidism[b]	Grade 2-4	Pembrolizumab	Continue	• Initiate thyroid replacement hormones (eg levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
		Epacadostat	Continue		
Nephritis and Renal Dysfunction	Grade 2	Pembrolizumab	Withhold until Grade 0-1	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
		Epacadostat	Withhold until Grade 0-1		
	Grade 3 or 4	Pembrolizumab	Permanently discontinue		
		Epacadostat	Permanently discontinue		

Table G-1: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated With Epacadostat and/or Pembrolizumab (Continued)

irAEs	Toxicity Grade or Conditions (CTCAE v4.0)	Study Treatment	Action Taken with Study Treatment	irAE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-Up
Myocarditis	Grade 1 or 2	Pembrolizumab	Withhold until Grade 0	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes.
		Epacadostat	Withhold until Grade 0		
	Grade 3 or 4	Pembrolizumab	Permanently discontinue		
		Epacadostat	Permanently discontinue		
Rash	Grade 1 or 2	Pembrolizumab	Continue	• Manage with topical steroids with or without drug interruption.	
		Epacadostat	Continue		
	Grade 3[c]	Pembrolizumab	Withhold until Grade 0-1	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	• Restart epacadostat at same dose if rash is mild and assessed as Grade 3 based only on body surface area and resolves without oral steroids. If oral steroids are required, or rash is severe, decrease by 1 dose level once resolved to Grade 0-1.
		Epacadostat	Withhold until Grade 0-1		
	Grade 4	Pembrolizumab	Permanently discontinue		
		Epacadostat	Permanently discontinue		

Table G-1: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated With Epacadostat and/or Pembrolizumab (Continued)

irAEs	Toxicity Grade or Conditions (CTCAE v4.0)	Study Treatment	Action Taken with Study Treatment	irAE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-Up
Asymptomatic Amylase or Lipase Increased	3	Pembrolizumab	May continue treatment with medical monitor approval		• Permanently discontinue if clinical signs and symptoms of pancreatitis develop (abdominal pain, nausea, vomiting). • If toxicity does not resolve within 12 weeks of last dose after an interruption, must permanently discontinue unless approved by the medical monitor to continue. • If Grade 4 lipase/amylase elevation is asymptomatic and abdominal imaging suggests no pathology, study drug administration dosing may continue with medical monitor approval.
		Epacadostat	May continue treatment with medical monitor approval		
	4	Pembrolizumab	Withhold until toxicity resolves to Grade 0-1		
		Epacadostat	Withhold until toxicity resolves to Grade 0-1		

Table G-1: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated With Epacadostat and/or Pembrolizumab (Continued)

irAEs	Toxicity Grade or Conditions (CTCAE v4.0)	Study Treatment	Action Taken with Study Treatment	irAE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-Up
All Other irAEs	Intolerable/ persistent Grade 2	Pembrolizumab	Withhold until Grade 0-1	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes.
		Epacadostat	Withhold until Grade 0-1		
	Grade 3	Pembrolizumab	Withhold until Grade 0-1, or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
		Epacadostat	Withhold until Grade 0-1 Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Pembrolizumab	Permanently discontinue		
		Epacadostat	Permanently discontinue		

AEs = adverse events; ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CTCAE = Common Terminology Criteria for Adverse Events; GI = gastrointestinal; irAE = immune-related adverse events; IV = intravenous; T1DM = Type 1 diabetes mellitus.

General Instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab and epacadostat have been withheld, pembrolizumab and epacadostat can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab and epacadostat should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

NOTES:

a. Withhold OR permanently discontinue pembrolizumab or epacadostat at the discretion of the investigator.

b. For subjects with Grade 3 or 4 immune-related endocrinopathy where withholding of pembrolizumab and epacadostat is required, pembrolizumab and epacadostat may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

c. Subjects with Grade 3 rash in the absence of desquamation, no mucosal involvement, does not require systemic steroids, and resolves to Grade 1 within 14 days does not have to hold study treatment.

G.2. Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion reactions, including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab-associated infusion reaction are provided in Table G-2.

Table G-2: Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None.
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	**Stop Infusion.** Additional appropriate medical therapy may include, but is not limited to, the following: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/h to 50 mL/h). Otherwise, dosing will be held until symptoms resolve, and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment.	Subject may be premedicated 1.5 hours (± 30 minutes) before infusion of pembrolizumab with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).

Table G-2: Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines (Continued)

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms after initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include, but is not limited, to the following: • Epinephrine* *In cases of anaphylaxis, epinephrine should be used immediately. • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. Subject should be permanently discontinued from further study drug treatment.	No subsequent dosing.
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the CTCAE v4.0 at http://ctep.cancer.gov.		

NCI = National Cancer Institute; NSAID = nonsteroidal anti-inflammatory drug; PO = orally.

G.3. Other Allowed Dose Interruption for Epacadostat and/or Pembrolizumab

Epacadostat and/or pembrolizumab may be interrupted for situations other than treatment-related AEs, such as medical/surgical events or logistical reasons not related to study therapy. Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the sponsor. The reason for interruption should be documented in the eCRF.

APPENDIX H. DOSE MODIFICATIONS FOR MFOLFOX6

H.1. Criteria for Start of Cycle (Criteria for Administration on Day 1 of Each Cycle)

After confirmation that each subject meets criteria for the start of each cycle described in Table H-1, mFOLFOX6 will be administered. If any criteria are not met, administration of therapy will be postponed. From the second cycle onwards, all treatments will be discontinued if therapy has not been initiated by 14 days after the estimated Day 1.

Table H-1: Criteria for Administration of mFOLFOX6 on Day 1 of Each Cycle

Parameter		Criterion for Start
WBC		$\geq 3.0 \times 10^9$/L
Neutrophil count		$\geq 1.5 \times 10^9$/L
Platelet count		$\geq 75 \times 10^9$/L
Infection		No fever (> 38.0°C or 100.4°F) suspect for infection
Nonhematologic toxicities	Diarrhea	No watery diarrhea
	Others	< Grade 2 (except for nausea, vomiting, anorexia, and fatigue)

If mFOLFOX6 is held for any of the reasons noted in Table H-1 above, both epacadostat and pembrolizumab should be held as well, and the subject will be evaluated at least weekly until the toxicity has resolved. The dose of each agent selected for use in the new cycle will follow the guidelines shown in Table H-2 and Table H-3 for hematologic toxicities, taking tolerability of the most recent dose into account.

H.2. Management Guidelines for Hematologic Toxicities

Table H-2 provides guidance for dose reductions for the first appearance of the hematologic toxicities. Toxicities must be resolved to Grade 0 or 1 before resuming treatment. When the dose of 5-FU is reduced, the dose of leucovorin will remain the same.

Table H-2: Criteria for Dose Reductions for the First Appearance of Hematologic Toxicities

Criteria	Oxaliplatin	5-FU Bolus	5-FU Continuous
Grade 3 leukopenia or neutropenia	20% dose reduction	Stop treatment	No dose reduction
Grade 4 leukopenia or neutropenia			
Grade 2 or 3 thrombocytopenia			
Grade 4 thrombocytopenia			

Note: The dose of leucovorin remains the same.

Table H-3 provides guidance for dose reductions for the second appearance of the specified hematologic toxicities.

Table H-3: Criteria for Dose Reductions for Recurrent Hematologic Toxicities

Criteria	Oxaliplatin	5-FU Bolus	5-FU Continuous
Grade 3 leukopenia or neutropenia	20% dose reduction	N/A	No dose reduction
Grade 4 leukopenia or neutropenia			
Grade 2 or 3 thrombocytopenia			
Grade 4 thrombocytopenia			

Note: The dose of leucovorin remains the same.

After a second dose reduction, if any hematologic toxicities reoccur (third occurrence) and are clearly associated with chemotherapy, chemotherapy may be discontinued, and epacadostat and pembrolizumab may be continued at the same dose at the discretion of the investigator and approval of the medical monitor.

H.3. Management Guidelines for Nonhematologic Toxicities

Table H-4 provides guidance for dose reductions for the appearance of nonhematologic toxicities. Toxicities must be resolved to Grade 0 or 1 before resuming treatment. When the dose of 5-FU is reduced, the dose of leucovorin will remain the same.

It is important to note that some chemotherapy-related AEs will overlap with potential irAEs (including but not limited to gastrointestinal toxicity, including diarrhea; renal insufficiency; high-grade laboratory abnormalities; rash/hypersensitivity). In these cases, both the chemotherapy-related AE and irAE management guidance (Appendix G) should be reviewed to determine the most appropriate management of therapy.

Table H-4: Criteria for Dose Reductions for Nonhematologic Toxicities

Criteria		Oxaliplatin	5-FU Bolus	5-FU Continuous
Allergic reaction to oxaliplatin		Stop treatment	No dose reduction	No dose reduction
AST/ALT	Grade 1 (< 3 × ULN)	No dose reduction	No dose reduction	No dose reduction
	Grade 2 (3 × to < 5 × ULN)	No dose reduction	No dose reduction	No dose reduction
	Grade 3 or 4 (> 5× ULN)	20% dose reduction	Stop treatment	No dose reduction
Bilirubin	Grade 2 (> 1.5 × to 3 × ULN)	No dose reduction	No dose reduction	No dose reduction
	Grade 3 (> 3 × to 10 × ULN)	20% dose reduction	Stop treatment	No dose reduction
	Grade 4 (> 10 × ULN)	Stop treatment	Stop treatment	Stop treatment
Hy's Law[a]		Stop treatment	Stop treatment	Stop treatment
Diarrhea	Grade 1	No dose reduction	No dose reduction	No dose reduction
	Grade 2	No dose reduction	No dose reduction	No dose reduction
	Grade 3 or 4	20% dose reduction	Stop treatment	No dose reduction
Neurologic toxicities	Grade 2	20% dose reduction	No dose reduction. Stop treatment for hyperammonemic encephalopathy, acute cerebellar syndrome, confusion, disorientation, ataxia or visual disturbances	
	Grade 3	Stop treatment		
Respiratory symptoms indicative of pulmonary fibrosis due to oxaliplatin		Stop treatment	No dose reduction	No dose reduction
Other nonhematologic toxicity	Grade 3	20% dose reduction	Stop treatment	No dose reduction
	Grade 4	Stop treatment	Stop treatment	Stop treatment

[a] Hy's law is defined as follows: 1) Aminotransferase elevation (ALT or AST) ≥ 3 × ULN; 2) Total bilirubin > 2 × ULN, without initial findings of cholestasis (elevated serum ALP); 3) No other immediately apparent possible cause of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, liver metastases, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic. Permanently discontinue study therapy at the first occurrence of liver enzyme elevations meeting the criteria for Hy's law.

APPENDIX I. DOSE MODIFICATIONS FOR GEMCITABINE/*NAB*-PACLITAXEL

I.1. Criteria for Start of Cycle (Criteria for Administration on Day 1 of Each Cycle)

A cycle of therapy may begin on a scheduled Day 1 if the following conditions are met:

- ANC $\geq 1.5 \times 10^9$/L.
- Platelet count $\geq 100 \times 10^9$/L.
- Sensory neuropathy has improved to $\leq$ Grade 1.
- Any other AE that occurred has resolved to $\leq$ Grade 1 severity or returned to baseline.

The dose of each agent selected for use in the new cycle will follow the guidelines shown in Table I-1, taking tolerability of the most recent dose into account.

If new cycle starting requirements are not met, regardless of dose modification, all treatments (epacadostat, pembrolizumab, gemcitabine, and *nab*-paclitaxel) will be held, and the subject will be evaluated at least weekly until the toxicity has resolved.

From the second cycle onwards, all treatments will be discontinued if therapy has not been initiated within the 14 days after the scheduled Day 1.

I.2. *nab*-Paclitaxel and Gemcitabine Dose Modifications

Gemcitabine treatment cycles and those including *nab*-paclitaxel may be delayed or the dose may be reduced for laboratory parameters or AEs that are judged to be related to gemcitabine or *nab*-paclitaxel. A maximum of 2 dose reductions are allowed: for gemcitabine from 1000 mg/m^2 to 800 mg/m^2 and 600 mg/m^2, and for *nab*-paclitaxel from 125 mg/m^2 to 100 mg/m^2 and 75 mg/m^2 (Table I-1).

Day 1 of each study cycle will correspond with the first day of chemotherapy administration. Thus, study cycles may become out of sync with the originally planned schedule. All assessments will shift to coincide with the revised treatment (cycle) schedule.

Table I-1: *nab*-Paclitaxel and Gemcitabine Dose Level Reductions

Dose Reduction	Gemcitabine	*nab*-Paclitaxel
Full dose	1000 mg/m^2	125 mg/m^2
First dose reduction	800 mg/m^2	100 mg/m^2
Second dose reduction	600 mg/m^2	75 mg/m^2
If additional dose reduction required	Discontinue	Discontinue

After a second dose reduction, if neutropenia or thrombocytopenia reoccur (third occurrence) and are clearly associated with chemotherapy, *nab*-paclitaxel and gemcitabine may be discontinued, and pembrolizumab and epacadostat may be continued at the discretion of the investigator and approval of the medical monitor.

I.3. Changes to Treatment Regimen During a Cycle for Hematologic Toxicities

Mandatory dose interruptions and modifications of *nab*-paclitaxel and gemcitabine on Days 1, 8, and 15 of a cycle for hematologic toxicity are shown in Table I-2.

Table I-2: Modifications for Neutropenia and/or Thrombocytopenia at the Start of a Cycle or Within a Cycle

Cycle Day	ANC ($\times 10^9$/L)		Platelet Count ($\times 10^9$/L)	*nab*-Paclitaxel and Gemcitabine
Day 1	< 1.5	OR	< 100	Delay dose until recovery
Day 8	0.5 to < 1.0	OR	50 to < 75	Reduce 1 dose level
	< 0.5	OR	< 50	Withhold doses
Day 15: If Day 8 doses were reduced or given without modification	0.5 to < 1.0	OR	50 to < 75	Reduce 1 dose level from Day 8
	< 0.5	OR	< 50	Withhold doses
Day 15: If Day 8 doses were withheld	≥ 1.0	OR	≥ 75	Reduce 1 dose level from Day 1
	0.5 to < 1.0	OR	50 to < 75	Reduce 2 dose levels from Day 1
	< 0.5	OR	< 50	Withhold doses

I.4. Other Adverse Drug Reactions in Subjects With *nab*-Paclitaxel and Gemcitabine

Dose interruptions and modifications for *nab*-paclitaxel and gemcitabine for other adverse drug reactions are described in Table I-3.

Table I-3: Dose Modifications for *nab*-Paclitaxel and Gemcitabine Adverse Drug Reactions

	Gemcitabine	*nab*-Paclitaxel
Febrile neutropenia: Grade 3 or 4	Withhold until fever resolved and ANC ≥ 1.5 × 10^9/L; resume at next lower dose level.	
Peripheral neuropathy: Grade 3 or 4	No dose reduction.	Withhold until improves to ≤ Grade 1; resume at next lower dose level.
Cutaneous toxicity: Grade 2 or 3	Reduce to next lower dose level; discontinue treatment if toxicity persists.	
Gastrointestinal toxicity: Grade 3 mucositis or diarrhea	Withhold until improves to ≤ Grade 1; resume at next lower dose level.	

Note: If the subject meets more than 1 of the criteria listed, dose modifications should always be based on the system showing the greatest degree of toxicity. Dose interruptions and modifications will be made at the discretion of the investigator.

If the toxicities listed in Table I-3 persist or reoccur despite 2 dose reductions and are clearly associated with chemotherapy, *nab*-paclitaxel/gemcitabine may be discontinued, and pembrolizumab and epacadostat may be continued at the discretion of the investigator and approval of the medical monitor. If *nab*-paclitaxel must be discontinued for peripheral neuropathy, gemcitabine, pembrolizumab, and epacadostat may be continued at the discretion of the investigator and approval of the medical monitor.

I.4.1 *nab*-Paclitaxel Hypersensitivity Reactions

Hypersensitivity reactions are not expected with *nab*-paclitaxel. If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, hypotension, or tachycardia may require

temporary interruption of the infusion. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria, require immediate discontinuation of *nab*-paclitaxel and aggressive symptomatic therapy. Subjects who experience a ≥ Grade 3 allergic reaction or anaphylaxis events will not be rechallenged with *nab*-paclitaxel. Subjects with < Grade 3 infusion reactions can be rechallenged following premedication (per institutional guidelines). If *nab*-paclitaxel is discontinued due to a hypersensitivity reaction, gemcitabine, pembrolizumab, and epacadostat may be continued at the discretion of the investigator and approval of the medical monitor.

I.4.2. Management Guidelines for Nonhematologic Toxicities

Table I-4 provides guidance for dose reductions for the appearance of nonhematologic toxicities. Toxicities must be resolved to Grade 0 or 1 before resuming treatment.

It is important to note that some chemotherapy-related AEs will overlap with potential irAEs (including but not limited to gastrointestinal toxicity, including diarrhea; renal insufficiency; high-grade laboratory abnormalities; rash/hypersensitivity). In these cases, both the chemotherapy-related AE and irAE management guidance (Appendix G) should be reviewed to determine the most appropriate management of therapy.

Table I-4: Criteria for Dose Reductions for Nonhematologic Toxicities

Criteria		Gemcitabine	*nab*-Paclitaxel
Hypersensitivity reaction to *nab*-paclitaxel	≤ Grade 2	No dose reduction	Rechallenge following premedication allowed
	≥ Grade 3	No dose reduction	Stop treatment
AST/ALT	Grade 1 (< 3 × ULN)	No dose reduction	No dose reduction
	Grade 2 (3 × to < 5 × ULN)	No dose reduction	Consider dose reduction
	Grade 3 or 4 (> 5 × ULN)	No dose reduction	Dose reduce 1 level
Bilirubin	Grade 2 (> 1.5 × to 3 × ULN)	No dose reduction	No dose reduction
	Grade 3 (> 3 × to 10 × ULN)	No dose reduction	Reduce dose 1 level
	Grade 4 (> 10 × ULN)	Stop treatment	Stop treatment
Hy's Law[a]		Stop treatment	Stop treatment
Diarrhea	Grade 1	No dose reduction	No dose reduction
	Grade 2	No dose reduction	No dose reduction
	Grade 3 or 4	Reduce dose 1 level	Reduce dose 1 level
Neurologic toxicities	Grade 2	No dose reduction	No dose reduction
	Grade 3	No dose reduction	Reduce dose 1 level
Other nonhematologic toxicity	Grade 3	Reduce dose 1 level	Reduce dose 1 level
	Grade 4	Stop treatment	Stop treatment

[a] Hy's law is defined as follows: 1) Aminotransferase elevation (ALT or AST) ≥ 3 × ULN; 2) Total bilirubin > 2 × ULN, without initial findings of cholestasis (elevated serum ALP); 3) No other immediately apparent possible cause of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, liver metastases, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic. Permanently discontinue study therapy at the first occurrence of liver enzyme elevations meeting the criteria for Hy's law.

APPENDIX J. DOSE MODIFICATIONS FOR PACLITAXEL/CARBOPLATIN

J.1. Criteria for Start of Cycle (Criteria for Administration on Day 1 of Each Cycle)

After confirmation that each subject satisfies criteria for the start of each cycle described in Table J-1, paclitaxel will be administered first, followed by carboplatin. If any criteria are not met, administration of therapy (ie, epacadostat, pembrolizumab, carboplatin, paclitaxel) will be postponed. From the second cycle onwards, all treatments will be discontinued if administration of therapy has not been initiated by 14 days after the estimated Day 1.

Table J-1: Criteria for Administration of Paclitaxel and Carboplatin on Day 1 of Each Cycle

Parameter		Criterion for Start
WBC		$\geq 2.5 \times 10^9$/L
Neutrophil count		$\geq 1.0 \times 10^9$/L
Platelet count		$\geq 100 \times 10^9$/L
Renal function		> 30 mL/min AND < 10% change in GFR from previous cycle
Nonhematologic toxicities	Bilirubin	≤ ULN
	AST/ALT	< 2.5 × ULN

If carboplatin and/or paclitaxel are held for any of the reasons noted in Table J-1 above, both epacadostat and pembrolizumab should be held as well, and the subject will be evaluated at least weekly until the toxicity has resolved. The dose of each agent selected for use in the new cycle will follow the guidelines shown in Table J-2 and Table J-3, taking tolerability of the most recent dose into account.

J.2. Paclitaxel and Carboplatin Dose Modifications

Table J-2 provides guidance for dose reductions for the first appearance of specified toxicities, and Table J-3 provides guidance for dose reductions for elevations of AST, ALT, and/or bilirubin.

It is important to note that some chemotherapy-related AEs will overlap with potential irAEs (including but not limited to gastrointestinal toxicity, including diarrhea; renal insufficiency; high-grade laboratory abnormalities; rash/hypersensitivity). In these cases, both the chemotherapy-related AE and irAE management guidance (Appendix G) should be reviewed to determine the most appropriate management of therapy.

Table J-2: Criteria for Dose Reductions for Specified Toxicities

Hematologic toxicity	Dose modifications based on neutrophil and/or platelet count on day of treatment (Day 1).					
	ANC		**Platelet Count**	**Action**	**Dose Modification After Recovery**	
					Paclitaxel	**Carboplatin**
	$\geq 1.0 \times 10^9$/L	AND	$\geq 100 \times 10^9$/L	Dose as scheduled	Full dose	Full dose
	$< 1.0 \times 10^9$/L	OR	$< 100 \times 10^9$/L	Delay 1 week until recovery	No dose reduction	Reduce by 1 AUC
	$< 1.0 \times 10^9$/L	AND	$< 100 \times 10^9$/L	Delay 1 week until recovery	25% dose reduction	Reduce by 1 AUC
Renal impairment	If the calculated GFR falls by more than10% from the previous cycle, then consider a dose modification.					
	GFR	**Carboplatin Dose**				
	≥ 30 mL/min	Use AUC as per protocol.				
	20-30 mL/min	EDTA then use AUC as per protocol or consider discontinuing carboplatin.				
	< 20 mL/min	Discontinue carboplatin, continue paclitaxel.				
Additional toxicities	**Toxicity**	**Definition**		**Dose Modification**		
	Febrile neutropenia	ANC $< 0.5 \times 10^9$/L with fever requiring IV antibiotics ± hospitalization		20% reduction for carboplatin and dose paclitaxel at 135 mg/m^2.		
	Fatigue	Grade 3		First occurrence give 25% dose reduction; if persistent, 50% reduction or omit paclitaxel only.		
	Neuropathy	Grade 2		Reduce paclitaxel to 135 mg/m^2 in all subsequent cycles. If persistent, reduce paclitaxel to 90 mg/m^2 or omit.		
		Grade 3		Withhold paclitaxel until < Grade 1; restart at 90 mg/m^2. Discontinue if no recovery.		
	Arthralgia and/or myalgia	≥ Grade 2 toxicity		If not contraindicated, consider giving diclofenac 50 mg TID for 5 days. Alternatively, consider prednisone 10 mg BID for 5 days starting 24 hours after paclitaxel. If arthralgia and/or myalgia persists reduce subsequent paclitaxel doses to 135 mg/m^2.		
	Other toxicities	Grade 3 toxicity (except alopecia, nausea, and vomiting)		Continue with 20% dose reduction of carboplatin and/or paclitaxel at 135 mg/m^2 provided toxicity has resolved to ≤ Grade 1. If further toxicity occurs, an additional reduction may be made after discussion with medical monitor.		
		Grade 4 toxicity (except alopecia, nausea, and vomiting)		Withhold treatment and discuss with medical monitor		

Table J-3: Management Guidelines for Hepatic Toxicity

AST/ALT	Bilirubin	Carboplatin	Paclitaxel
Grade 1 (< 3 × ULN)	≤ ULN	Continue same dose	Continue same dose
Grade 2 (3 × to < 5 × ULN)	≤ ULN	Continue same dose	Continue same dose
Grade 2 (3 × to < 5 × ULN)	Grade 1 (ULN to 1.5 × ULN)	Continue same dose	Reduce dose to 135 mg/m^2
Grade 2 (3 × to < 5 × ULN)	Grade 2 (1.5 × to 3 × ULN) *Note: If > 2 × ULN, meets Hy's Law[a]	Continue same dose	Reduce dose to 75 mg/m^2
ANY Grade 3 or Grade 4		Permanently discontinue treatment	
Hy's Law[a]		Permanently discontinue treatment	

[a] Hy's law is defined as follows: 1) Aminotransferase elevation (ALT or AST) ≥ 3 × ULN; 2) Total bilirubin > 2 × ULN, without initial findings of cholestasis (elevated serum ALP); 3) No other immediately apparent possible cause of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, liver metastases, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic. Permanently discontinue study therapy at the first occurrence of liver enzyme elevations meeting the criteria for Hy's law.

APPENDIX K. DOSE MODIFICATIONS FOR PEMETREXED/PLATINUM AGENT

K.1. Criteria for Start of Cycle (Criteria for Administration on Day 1 of Each Cycle)

After confirmation that each subject satisfies criteria for the start of each cycle described in Table K-1, pemetrexed and platinum agent (ie, carboplatin or cisplatin) may be administered. If any criteria are not met, administration of therapy will be postponed. From the second cycle onwards, the all treatments will be discontinued if administration of therapy has not been initiated by 14 days after the estimated Day 1.

Table K-1: Criteria for Administration of Pemetrexed and Platinum Agent on Day 1 of Each Cycle

Parameter	Criterion for Start
WBC	$\geq 2.5 \times 10^9$/L
Neutrophil count	$\geq 1.0 \times 10^9$/L
Platelet count	$\geq 100 \times 10^9$/L
Renal function	> 20 mL/min for carboplatin or > 50 mL/min for cisplatin AND < 10% change in GFR from previous cycle

If pemetrexed/platinum agent are held for any of the reasons noted in Table K-1 above, both epacadostat and pembrolizumab should be held as well, and the subject will be evaluated at least weekly until the toxicity has resolved. The dose of each agent selected for use in the new cycle will follow the guidelines shown in Table K-2, taking tolerability of the most recent dose into account.

K.2. Pemetrexed and Platinum Agent Dose Modifications

Table K-2 provides guidance for dose reductions for hematologic toxicities, and Table K-3 provides guidance for nonhematologic toxicities.

It is important to note that some chemotherapy-related AEs will overlap with potential irAEs (including but not limited to gastrointestinal toxicity, including diarrhea; renal insufficiency; high-grade laboratory abnormalities; rash/hypersensitivity). In these cases, both the chemotherapy-related AE and irAE management guidance (Appendix G) should be reviewed to determine the most appropriate management of therapy.

Table K-2: Criteria for Dose Reductions for Hematologic Toxicities

Hematologic toxicity	Dose modifications based on neutrophil and/or platelet count on day of treatment (Day 1).				
	Nadir ANC ($\times 10^9$/L)		**Nadir Platelet Count ($\times 10^9$/L)**	**Dose Modification After Recovery**	
				Pemetrexed	**Platinum Agent (Carboplatin or Cisplatin)**
	≥ 500	AND	≥ 50	Full dose	Full dose
	< 500	AND	≥ 50	75% of previous dose	75% of previous dose
	Any	AND	≤ 50 without bleeding	75% of previous dose	75% of previous dose
	Any	AND	≤ 50 with bleeding	50% of previous dose	50% of previous dose
	Febrile neutropenia			75% of previous dose	75% of previous dose

Table K-3: Criteria for Dose Reductions for Nonhematologic Toxicities

Criteria		**Pemetrexed**	**Platinum Agent (Carboplatin or Cisplatin)**
AST/ALT	Grade 1 (< 3 × ULN)	No dose reduction	No dose reduction
	Grade 2 (3 × to < 5 × ULN)	No dose reduction	No dose reduction
	Grade 3 or 4 (> 5 × ULN)	75% of previous dose	75% of previous dose
Bilirubin	Grade 2 (> 1.5 × to 3 × ULN)	No dose reduction	No dose reduction
	Grade 3 (> 3 × to 10 × ULN)	75% of previous dose	75% of previous dose
	Grade 4 (> 10 × ULN)	Stop treatment	Stop treatment
Hy's Law[a]		Stop treatment	Stop treatment
Diarrhea	Any Grade requiring hospitalization OR Grade 3 or 4	75% of previous dose	75% of previous dose
Neurotoxicity	Grade 2	No dose reduction	50% of previous dose
	Grade 3 or 4	Stop treatment	Stop treatment
Mucositis Grade 3 or 4		50% of previous dose	No dose reduction
Other nonhematologic toxicity	Grade 3	75% of previous dose	75% of previous dose
	Grade 4	Stop treatment	Stop treatment

[a] Hy's law is defined as follows: 1) Aminotransferase elevation (ALT or AST) ≥ 3 × ULN; 2) Total bilirubin > 2 × ULN, without initial findings of cholestasis (elevated serum ALP); 3) No other immediately apparent possible cause of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, liver metastases, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic. Permanently discontinue study therapy at the first occurrence of liver enzyme elevations meeting the criteria for Hy's law.

APPENDIX L. DOSE MODIFICATIONS FOR CYCLOPHOSPHAMIDE

L.1. Criteria for Start of Cycle (Criteria for Administration on Day 1 of Each Cycle)

After confirmation that each subject satisfies criteria for the start of each cycle described in Table L-1, cyclophosphamide may be administered. If any criteria are not satisfied, administration of the cycle will be postponed. From the second cycle onwards, all treatments will be discontinued if administration of the cycle has not been initiated by 14 days after the estimated Day 1.

Table L-1: Criteria for Administration of Cyclophosphamide on Day 1 of Each Cycle

Parameter	Criterion for Start
Neutrophil count	$\geq 1.0 \times 10^9$/L
Platelet count	$\geq 75 \times 10^9$/L
Nonhematologic toxicities	No ≥ Grade 2 anorexia, nausea, vomiting, diarrhea, stomatitis, and dryness of the mouth, epigastric pain or increase in bilirubin or transaminases

If cyclophosphamide is held for any of the reasons noted in Table L-1, both epacadostat and pembrolizumab should be delayed as well. The dose of each agent selected for use in the new cycle will follow the guidelines shown in Table L-2, taking tolerability of the most recent dose into account.

L.2. Management Guidelines for Hematologic Toxicities

Table L-2 provides guidance for dose reductions for the first appearance of specified hematologic toxicities.

Table L-2: Criteria for Dose Reductions for the Hematologic Toxicities

Criteria	Cyclophosphamide
Grade 3 leukopenia or neutropenia	Reduce dose 50% OR change to every other day dosing if reduced dosage strength is unavailable
Grade 4 leukopenia or neutropenia	Reduce dose 50% OR change to every other day dosing if reduced dosage strength is unavailable
Grade 2 or 3 thrombocytopenia	Reduce dose 50% OR change to every other day dosing if reduced dosage strength is unavailable
Grade 4 thrombocytopenia	Reduce dose 50% OR change to every other day dosing if reduced dosage strength is unavailable

Table L-3 provides guidance for dose reductions for recurrent specified hematologic toxicities.

Table L-3: Criteria for Dose Reductions for Recurrent Hematologic Toxicities

Criteria	Cyclophosphamide
Grade 3 leukopenia or neutropenia	Stop treatment
Grade 4 leukopenia or neutropenia	Stop treatment
Grade 2 or 3 thrombocytopenia	Stop treatment
Grade 4 thrombocytopenia	Stop treatment

L.3. Management Guidelines for Nonhematologic Toxicities

Table L-4 provides guidance for dose reductions for the appearance of nonhematologic toxicities for subjects who receive cyclophosphamide. Toxicities must be resolved to Grade 0 or 1 before resuming treatment.

It is important to note that some chemotherapy-related AEs will overlap with potential irAEs (including but not limited to gastrointestinal toxicity, including diarrhea; renal insufficiency; high-grade laboratory abnormalities; rash/hypersensitivity). In these cases, both the chemotherapy-related AE and irAE management guidance (Appendix G) should be reviewed to determine the most appropriate management of therapy.

Table L-4: Criteria for Dose Reductions for Nonhematologic Toxicities

Criteria		Cyclophosphamide
AST/ALT	Grade 1 (< 3 × ULN)	No dose reduction
	Grade 2 (3 × to < 5 × ULN)	No dose reduction
	Grade 3 or 4 (> 5 × ULN)	50% dose reduction
Bilirubin	Grade 2 (> 1.5 × to 3 × ULN)	No dose reduction
	Grade 3 (> 3 × to 10 × ULN)	50% dose reduction
	Grade 4 (> 10 × ULN)	Stop treatment
Hy's Law[a]		Stop treatment
Diarrhea	Grade 1	No dose reduction
	Grade 2	No dose reduction
	Grade 3 or 4	50% dose reduction
Neurologic toxicities	Grade 2	No dose reduction
	Grade 3	50% dose reduction
Other nonhematologic toxicity	Grade 3	50% dose reduction
	Grade 4	Stop treatment

[a] Hy's law is defined as follows: 1) Aminotransferase elevation (ALT or AST) ≥ 3 × ULN; 2) Total bilirubin > 2 × ULN, without initial findings of cholestasis (elevated serum ALP); 3) No other immediately apparent possible cause of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, liver metastases, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic. Permanently discontinue study therapy at the first occurrence of liver enzyme elevations meeting the criteria for Hy's law.

APPENDIX M. DOSE MODIFICATIONS FOR GEMCITABINE/PLATINUM AGENT

M.1. Criteria for Start of Cycle (Criteria for Administration on Day 1 of Each Cycle)

After confirmation that each subject satisfies criteria for the start of each cycle described in Table M-1, gemcitabine and platinum agent (ie, carboplatin or cisplatin) may be administered. If any criteria are not met, administration of therapy will be postponed. From the second cycle onwards, the study treatment will be discontinued if administration of therapy has not been initiated by 14 days after the estimated Day 1.

Table M-1: Criteria for Administration of Gemcitabine and Platinum Agent on Day 1 of Each Cycle

Parameter	Criterion for Start
WBC	$\geq 2.5 \times 10^9$/L
Neutrophil count	$\geq 1.0 \times 10^9$/L
Platelet count	$\geq 100 \times 10^9$/L
Infection	No fever (> 38.0°C or 100.4°F) suspect for infection
Renal function	> 20 mL/min for carboplatin or > 50 mL/min for cisplatin AND < 10% change in GFR from previous cycle

If gemcitabine/platinum agent is held for any of the reasons noted in Table M-1 above, both epacadostat and pembrolizumab should be held as well, and the subject will be evaluated at least weekly until the toxicity has resolved. The dose of each agent selected for use in the new cycle will follow the guidelines shown in Table M-2 and Table M-3 for hematologic toxicities, taking tolerability of the most recent dose into account.

M.2. Management Guidelines for Hematologic Toxicities

Table M-2 provides guidance for dose reductions for the first appearance of the hematologic toxicities. Toxicities must be resolved to Grade 0 or 1 before resuming treatment.

Table M-2: Criteria for Dose Reductions for the First Appearance of Hematologic Toxicities

Hematologic toxicity	Dose modifications based on neutrophil and/or platelet count on day of treatment (Day 1).					
					Dose Modification After Recovery	
	ANC		Platelet Count	Action	Gemcitabine	Platinum Agent (Carboplatin or Cisplatin)
	$\geq 1.0 \times 10^9$/L	AND	$\geq 100 \times 10^9$/L	Dose as scheduled	Full dose	Full dose
	$< 1.0 \times 10^9$/L	OR	$\leq 100 \times 10^9$/L	Delay 1 week until recovery	Reduce 1 dose level	75% dose
	$< 1.0 \times 10^9$/L	AND	$\leq 100 \times 10^9$/L	Delay 1 week until recovery	Reduce 2 dose levels	75% dose

Table M-3 provides guidance for dose reductions for the recurrent specified hematologic toxicities. A maximum of 2 dose reductions for gemcitabine is allowed (Table M-4). After a second dose reduction, if any hematologic toxicities reoccur (third occurrence) and are clearly associated with chemotherapy, chemotherapy may be discontinued, and epacadostat and pembrolizumab may be continued at the same dose at the discretion of the investigator and approval of the medical monitor.

Table M-3: Criteria for Dose Reductions for Recurrent Hematologic Toxicities

Hematologic toxicity	Dose modifications based on neutrophil and/or platelet count on day of treatment (Day 1).					
					Dose Modification After Recovery	
	ANC		Platelet Count	Action	Gemcitabine	Platinum Agent (Carboplatin or Cisplatin)
	$\geq 1.0 \times 10^9$/L	AND	$\geq 100 \times 10^9$/L	Dose as scheduled	Full dose	Full dose
	$< 1.0 \times 10^9$/L	OR	$\leq 100 \times 10^9$/L	Delay 1 week until recovery	Reduce 1 dose level	75% dose
	$< 1.0 \times 10^9$/L	AND	$\leq 100 \times 10^9$/L	Delay 1 week until recovery	Reduce 2 dose levels	75% dose

Table M-4: Gemcitabine Dose Level Reductions

Dose Reduction	Gemcitabine
Full dose	1000 mg/m^2
First dose reduction	800 mg/m^2
Second dose reduction	600 mg/m^2
If additional dose reduction required	Discontinue

M.3. Management Guidelines for Nonhematologic Toxicities

Table M-5 provides guidance for dose reductions for the appearance of nonhematologic toxicities. Toxicities must be resolved to Grade 0 or 1 before resuming treatment.

It is important to note that some chemotherapy-related AEs will overlap with potential irAEs (including but not limited to gastrointestinal toxicity, including diarrhea; renal insufficiency;

high-grade laboratory abnormalities; rash/hypersensitivity). In these cases, both the chemotherapy-related AE and irAE management guidance (Appendix G) should be reviewed to determine the most appropriate management of therapy.

Table M-5: Criteria for Dose Reductions for Nonhematologic Toxicities

Criteria		Gemcitabine	Platinum Agent (Carboplatin or Cisplatin)
Diarrhea	Grade 1	No dose reduction	No dose reduction
	Grade 2	Reduce 1 dose level	No dose reduction
	Grade 3 or 4	Reduce 2 dose levels	75% dose
Neurologic toxicities	Grade 2	No dose reduction	75% dose
	Grade 3		Stop treatment
Other nonhematologic toxicity	Grade 3	Reduce 1 dose level	75% dose
	Grade 4	Stop treatment	Stop treatment

Table M-6 provides guidance for dose reductions for platinum agent in the event of renal impairment. If the calculated GFR falls by more than 10% from the previous cycle, consider dose reduction.

Table M-6: Criteria for Dose Reductions of Platinum Agent for Renal Impairment

GFR	Cisplatin Dose	GFR	Carboplatin Dose
≥ 50 mL/min	Full dose per protocol	≥ 30 mL/min	Use AUC as per protocol
≥ 30 to < 50 mL/min	Reduce cisplatin dose 50% or switch to carboplatin AUC 5 (discuss with medical monitor prior to switching)	20-30 mL/min	EDTA, then use AUC as per protocol or consider discontinuing carboplatin
< 30 mL/min	Discontinue cisplatin, continue paclitaxel	< 20 mL/min	Discontinue carboplatin, continue paclitaxel

Table M-7 provides guidance for dose reductions for elevations of AST, ALT, and/or bilirubin.

Table M-7: Criteria for Dose Reductions for Hepatic Toxicity

AST/ALT	Bilirubin	Gemcitabine	Platinum Agent
Grade 1 (< 3× ULN)	≤ ULN	No dose reduction	Continue same dose
Grade 2 (3 × to < 5 × ULN)	≤ ULN	No dose reduction	Continue same dose
Grade 2 (3 × to < 5 × ULN)	Grade 1 (ULN to 1.5 × ULN)	No dose reduction	Continue same dose
Grade 2 (3 × to < 5 × ULN)	Grade 2 (1.5 × to 3 × ULN) *Note: If > 2 × ULN, meets Hy's Law[a]	No dose reduction	Continue same dose
ANY Grade 3 or Grade 4		Permanently discontinue treatment	
Hy's Law[a]		Permanently discontinue treatment	

[a] Hy's law is defined as follows: 1) Aminotransferase elevation (ALT or AST) ≥ 3 × ULN; 2) Total bilirubin > 2 × ULN, without initial findings of cholestasis (elevated serum ALP); 3) No other immediately apparent possible cause of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, liver metastases, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic. Permanently discontinue study therapy at the first occurrence of liver enzyme elevations meeting the criteria for Hy's law.

APPENDIX N. DOSE MODIFICATIONS FOR PLATINUM AGENT/5-FLUOROURACIL

N.1. Criteria for Start of Cycle (Criteria for Administration on Day 1 of Each Cycle)

After confirmation that each subject satisfies criteria for the start of each cycle described in Table N-1, platinum agent (ie, carboplatin or cisplatin) and 5-fluorouracil may be administered. If any criteria are not met, administration of therapy will be postponed. From the second cycle onwards, the study treatment will be discontinued if administration of therapy has not been initiated by 14 days after the estimated Day 1.

Table N-1: Criteria for Administration of Platinum Agent and 5-Fluorouracil on Day 1 of Each Cycle

Parameter		Criterion for Start
WBC		$\geq 2.5 \times 10^9$/L
Neutrophil count		$\geq 1.0 \times 10^9$/L
Platelet count		$\geq 100 \times 10^9$/L
Infection		No fever (> 38.0°C or 100.4°F) suspect for infection
Nonhematologic toxicities	Diarrhea	No watery diarrhea
	Renal function	> 20 mL/min for carboplatin or > 50 mL/min for cisplatin AND < 10% change in GFR from previous cycle
	Others	< Grade 2 (except for nausea, vomiting, anorexia, and fatigue)

If platinum agent/5-fluorouracil is held for any of the reasons noted in Table N-1 above, both epacadostat and pembrolizumab should be held as well, and the subject will be evaluated at least weekly until the toxicity has resolved. The dose of each agent selected for use in the new cycle will follow the guidelines shown in Table N-2 and Table N-3 for hematologic toxicities, taking tolerability of the most recent dose into account.

N.2. Management Guidelines for Hematologic Toxicities

Table N-2 provides guidance for dose reductions for the first appearance of the hematologic toxicities. Toxicities must be resolved to Grade 0 or 1 before resuming treatment.

Table N-2: Criteria for Dose Reductions for the First Appearance of Hematologic Toxicities

Hematologic toxicity	Dose modifications based on neutrophil and/or platelet count on day of treatment (Day 1).					
					Dose Modification Following Recovery	
	ANC		**Platelet Count**	**Action**	**Platinum Agent (Carboplatin or Cisplatin)**	**5-Fluorouracil**
	$\geq 1.0 \times 10^9$/L	AND	$\geq 100 \times 10^9$/L	Dose as scheduled	Full dose	Full dose
	$< 1.0 \times 10^9$/L	OR	$\leq 100 \times 10^9$/L	Delay 1 week until recovery	75% dose	75%-100% dose
	$< 1.0 \times 10^9$/L	AND	$\leq 100 \times 10^9$/L	Delay 1 week until recovery	75% dose	75% dose

Table N-3 provides guidance for dose reductions for the specified recurrent hematologic toxicities. After a second dose reduction, if any hematologic toxicities reoccur (third occurrence) and are clearly associated with chemotherapy, chemotherapy may be discontinued, and epacadostat and pembrolizumab may be continued at the same dose at the discretion of the investigator and approval of the medical monitor.

Table N-3: Criteria for Dose Reductions for Recurrent Hematologic Toxicities

Hematologic toxicity	Dose modifications based on neutrophil and/or platelet count on day of treatment (Day 1).					
					Dose Modification Following Recovery	
	ANC		**Platelet Count**	**Action**	**Platinum Agent (Carboplatin or Cisplatin)**	**5-Fluorouracil**
	$\geq 1.0 \times 10^9$/L	AND	$\geq 100 \times 10^9$/L	Dose as scheduled	Full dose	Full dose
	$< 1.0 \times 10^9$/L	OR	$\leq 100 \times 10^9$/L	Delay 1 week until recovery	75% dose	75%-100% dose
	$< 1.0 \times 10^9$/L	AND	$\leq 100 \times 10^9$/L	Delay 1 week until recovery	75% dose	75% dose

N.3. Management Guidelines for Nonhematologic Toxicities

Table N-4 provides guidance for dose reductions for the appearance of nonhematologic toxicities. Toxicities must be resolved to Grade 0 or 1 before resuming treatment.

It is important to note that some chemotherapy-related AEs will overlap with potential irAEs (including but not limited to gastrointestinal toxicity, including diarrhea; renal insufficiency; high-grade laboratory abnormalities; rash/hypersensitivity). In these cases, both the chemotherapy-related AE and irAE management guidance (Appendix G) should be reviewed to determine the most appropriate management of therapy.

Table N-4: Criteria for Dose Reductions for Nonhematologic Toxicities

Criteria		Platinum Agent (Carboplatin or Cisplatin)	5-Fluorouracil
Diarrhea	Grade 1	No dose reduction	No dose reduction
	Grade 2	No dose reduction	No dose reduction
	Grade 3 or 4	75% dose	75% dose
Neurologic toxicities	Grade 2	No dose reduction. Stop treatment for hyperammonemic encephalopathy, acute cerebellar syndrome, confusion, disorientation, ataxia, or visual disturbances	75% dose
	Grade 3		Stop treatment
Other nonhematologic toxicity	Grade 3	75% dose	75% dose
	Grade 4	Stop treatment	Stop treatment

Table N-5 provides guidance for dose reductions for platinum agent in the event of renal impairment. If the calculated GFR falls by more than 10% from the previous cycle, consider dose reduction.

Table N-5: Criteria for Dose Reductions of Platinum Agent for Renal Impairment

GFR	Cisplatin Dose	GFR	Carboplatin Dose
≥ 50 mL/min	Full dose per protocol	≥ 30 mL/min	Use AUC as per protocol
≥ 30 to < 50 mL/min	Reduce cisplatin dose 50% or switch to carboplatin AUC 5 (discuss with medical monitor prior to switching)	20-30 mL/min	EDTA then use AUC as per protocol, or consider discontinuing carboplatin
< 30 mL/min	Discontinue cisplatin, continue paclitaxel.	< 20 mL/min	Discontinue carboplatin, continue paclitaxel

Table N-6 provides guidance for dose reductions for elevations of AST, ALT, and/or bilirubin.

Table N-6: Criteria for Dose Reductions for Hepatic Toxicity

AST/ALT	Bilirubin	5-Fluorouracil	Platinum Agent (Carboplatin or Cisplatin)
Grade 1 (< 3× ULN)	≤ ULN	Continue same dose	Continue same dose
Grade 2 (3 × to < 5 × ULN)	≤ ULN	Continue same dose	Continue same dose
Grade 2 (3 × to < 5 × ULN)	Grade 1 (ULN to 1.5 × ULN)	Continue same dose	Continue same dose
Grade 2 (3 × to < 5 × ULN)	Grade 2 (1.5 × to 3 × ULN) *Note: If > 2 × ULN, meets Hy's Law[a]	Continue same dose	Continue same dose
ANY Grade 3 or Grade 4		Permanently discontinue treatment	
Hy's Law[a]		Permanently discontinue treatment	

[a] Hy's law is defined as follows: 1) Aminotransferase elevation (ALT or AST) ≥ 3 × ULN; 2) Total bilirubin > 2 × ULN, without initial findings of cholestasis (elevated serum ALP); 3) No other immediately apparent possible cause of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, liver metastases, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic. Permanently discontinue study therapy at the first occurrence of liver enzyme elevations meeting the criteria for Hy's law.

APPENDIX O. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment (Version) 1:	10 JAN 2017
Amendment (Version) 2:	28 MAR 2017
Amendment (Version) 3:	18 MAY 2017
Amendment (Version) 4:	31 JUL 2017
Amendment (Version) 5:	02 FEB 2018
Amendment (Version) 6:	31 AUG 2018
Amendment (Version) 7:	14 FEB 2019

Amendment 7 (14 FEB 2019)

Overall Rationale for the Amendment: The primary purpose of this amendment is to provide guidance for the management of ongoing subjects as enrollment has been terminated for the study as of 25 OCT 2018.

1. **Synopsis; Section 2, Study Objectives and Endpoints; Section 4.1, Overall Study Design; Section 9.2.2, Sample Size in Phase 2; Section 9.4, Statistical Analyses; Section 9.6, Interim Analysis**

   Description of changes:

   - Removed text describing secondary objectives/endpoints for DOR and PFS by RECIST 1.1 and irRECIST for Phase 1 and Phase 2.
   - [redacted]

   Rationale for changes: Update based on sponsor decision to terminate enrollment, not all cohorts have been fully enrolled, and Phase 2 efficacy expansion cohorts, where overall survival was to be collected, will not be open for enrollment. Therefore, it will not be possible to adequately complete analysis for some objectives.

2. **Synopsis; Section 4.1.2, Phase 2: Efficacy Expansion and Mandatory Biopsy Cohorts; Section 7.9.4.1, Tumor Biopsy in the Phase 2 Mandatory Biopsy Subjects Section 7.9.4.2, Tumor Biopsy in the Phase 2 Efficacy Expansion Subjects**

   Description of changes:

   - Removed text regarding optional on-treatment biopsies in Phase 2 efficacy expansion subjects.
   - Added text indicating that on-treatment biopsies are no longer required for subjects enrolled in Phase 2 mandatory biopsy cohorts.

   Rationale for changes: Update to study assessments based on enrollment termination.

3. **Synopsis; Section 4.3.1, Planned Number of Subjects**

   Description of change: The number of subjects enrolled has been updated.

   Rationale for change: Enrollment has been terminated by the sponsor; therefore, the number of subjects planned and enrolled has been updated.

4. **Section 4.4, Duration of Treatment and Subject Participation**

   Description of change: Clarification was added for the required length of contraception after chemotherapy.

   Rationale for change: For consistency with Inclusion Criterion #5.

5. **Section 4.5, Overall Study Duration**

   Description of change: The text in this section was revised to clearly define an end of the study for subject management and data analysis.

   Rationale for change: Given enrollment has been terminated by the sponsor and all subjects have been followed for at least 18 weeks (2 imaging assessments), the sponsor is considering this the end of the study for the purpose of database lock and study analysis. Subjects will continue receive study treatment if none of the discontinuation criteria are met.

6. **Section 5.2.1.2, Supply, Packaging, and Labeling; Section 5.5.1, Dose Modifications; Section 5.5.2, Criteria and Procedures for Dose Reductions or Interruptions of Epacadostat and/or Pembrolizumab; Section 5.6.1, Discontinuation Criteria; Appendix G, Dose Modifications for Epacadostat and Pembrolizumab (Table G-1: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated With Epacadostat and/or Pembrolizumab)**

   Description of change: Dose reductions of epacadostat will no longer be permitted and the 25-mg tablet has been removed. If the subject has a toxicity and it resolves to Grade 0-1, treatment may resume at the starting dose of epacadostat. If they cannot restart at that dose then they must discontinue treatment.

   Rationale for change: Sponsor decision to require therapy to be resumed at current dose to maintain target inhibition. No dose reductions are permitted and all subjects are currently using the 100-mg tablets.

7. **Synopsis; Section 5.6.1, Discontinuation Criteria; Section 5.6.2, Discontinuation Procedures; Section 5.7, Procedures for Withdrawal From Study; Section 6, Study Assessments; Section 7.4, Prior and Concomitant Medications and Procedures; Section 7.5, Safety Assessments; Section 7.6, Efficacy Assessments; Section 7.6.2, Tumor Imaging During the Study; Section 7.7, Performance and Quality-of-Life Assessments; Section 7.8.1, Blood Sample Collection; Section 7.10.2, Post-Treatment Anticancer Therapy Status; Section 7.10.3, Data Collection for Survival Follow-Up; Section 8.1, Adverse Events; Section 8.3.2, Reporting; Section 10.3 Data Management**

   Description of change: Study procedures for all subjects remaining on study treatment have been limited to standard of care for the subject's condition via local labs and disease status should continue to be monitored by CT, MRI, or PET-CT scan as appropriate at a frequency consistent with the standard of care for the subject's disease. Data will only be collected for informed consent, SAEs, AEs leading to discontinuation, EOT disposition (reason for discontinuation), drug accountability, dosing information only, EOS disposition (end of study form), and death if it occurs within the safety reporting period.

   Rationale for change: Update to study assessments based on enrollment termination, and all on-going subjects have met the updated definition of EOS as defined in Section 4.5.

8. **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 (31 AUG 2018)

Overall Rationale for the Amendment: The primary purpose of this amendment is to update the study design based on recent developments in the epacadostat clinical development program.

1. **Synopsis; Section 4.1.2, Phase 2: Efficacy Expansion and Mandatory Biopsy Cohorts (Figure 1: Study Design); Section 7.9.4.1, Tumor Biopsy in the Phase 2 Mandatory Biopsy Subjects; Section 9.2.2.2, Phase 2 Mandatory Biopsy Cohorts**

   Description of change: Removed text regarding the opening of the Phase 2 mandatory biopsy cohorts for squamous and nonsquamous NSCLC cohorts being at the discretion of the sponsor. Figure 1 was updated accordingly.

   Rationale for change: Based on the Study INCB 24360-301 results, the sponsor believes obtaining translational data from tumor tissue samples of subjects with NSCLC will allow for a better understanding of mechanisms of action for epacadostat, pembrolizumab, and chemotherapy in the tumor microenvironment.

2. **Synopsis; Section 3.1, Inclusion Criteria**

   Description of change: Updated inclusion criterion #24 for subjects enrolling in the Phase 2 mandatory biopsy cohort who have any solid tumor that progressed on previous therapy with a PD-1 or PD-L1 inhibitor.

   Rationale for change: To provide additional clarity for primary refractory versus secondary relapsed subjects.

3. **Synopsis; Section 3.2, Exclusion Criteria**

   Description of changes:

   - Updated exception to exclusion criterion #4 for subjects who have known active CNS and/or carcinomatous meningitis.
   - Added history of allogeneic stem cell transplant to exclusion criterion #10.
   - Updated heading for exclusion criterion #24 to include subjects in Treatment Groups A and G in Phase 1 and 2.

   Rationale for changes:

   - To provide additional clarity.
   - Subjects with a history of allogeneic stem cell transplant are immunocompromised and should be excluded from the study.
   - 5-Fluorouracil is administered as a prolonged infusion in both Treatment Groups A and G; therefore, subjects with a known dihydropyrimidine dehydrogenase deficiency in these treatment groups are at a greater risk of experiencing toxicities.

4. **Synopsis; Section 6, Study Assessments (Tables 7, 11, and 12); Section 7.5.4, Electrocardiograms**

   Description of change: Removed requirement for ECG measurement on Cycle 1 Day 1 and Cycle 1 Day 8 for all Phase 1 subjects and Phase 2 efficacy expansion subjects.

Rationale for change: To update the schedule of ECG assessments, as Study INCB 24360-103 met the requirements for a negative QT study, and the FDA agreed that extensive ECG monitoring in ongoing clinical studies with epacadostat is no longer needed.

5. **Synopsis; Section 6.4.2, Disease Status Follow-Up; Section 7.6.2, Tumor Imaging During the Study**

   Description of change: Updated text describing imaging frequency for subjects who are on study treatment and for subjects who discontinued treatment for a reason other than disease progression.

   Rationale for change: To provide clarity on imaging schedule.

6. **Section 1.2, Overview of Epacadostat; Section 1.11.12, Risks From Combining Epacadostat and Pembrolizumab**

   Description of change: Added information about Study INCB 24360-301.

   Rationale for change: To provide updated information on efficacy and safety of the combination of epacadostat and pembrolizumab based on recent published data.

7. **Section 5.3.1.2, Supply Packaging, and Labeling**

   Description of change: Updated text regarding pembrolizumab supply.

   Rationale for change: To reflect use of only investigational supply of pembrolizumab.

8. **Section 5.10, Prohibited Medications/Treatment**

   Description of change: Removed mefenamic acid from the list of UGT1A9 inhibitors.

   Rationale for change: To align with current clinical information from the epacadostat IB.

9. **Section 5.10.1, Supportive Care Guidelines**

   Description of change: Removed guidance on the management of diarrhea.

   Rationale for change: To avoid conflict with guidance for managing diarrhea/colitis that is included in Appendix G, Table G-1.

10. **Section 7.5.5.4, Coagulation Panel; Section 7.5.5.5, Endocrine Function; Section 7.5.5.6, Urinalysis**

    Description of change: Added a statement indicating that more frequent monitoring may be performed for these analytes if clinically indicated.

    Rationale for change: For consistency with other laboratory monitoring.

11. **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 (02 FEB 2018)

Overall Rationale for the Amendment: The primary purpose of this amendment is to update the dose modification guidance for epacadostat and pembrolizumab for the management of immune-related adverse events.

1. **Synopsis**

   Description of change: Revised text regarding the timing of laboratory [redacted]

   Rationale for change: To more accurately describe the Protocol-defined assessments.

2. **Synopsis; Section 3.1, Subject Inclusion Criteria**

   Description of change: Revised inclusion criterion 5 to clarify that contraception methods should continue for 120 days from the last dose of epacadostat and pembrolizumab and that if a subject continues on chemotherapy after discontinuation of epacadostat and pembrolizumab, contraception methods should continue for 180 days after the last dose of chemotherapy.

   Rationale for change: To make consistent with other studies that are investigating epacadostat and pembrolizumab in combination.

3. **Synopsis; Section 3.2, Subject Exclusion Criteria**

   Description of change: Updated exclusion criterion 18 to state that subjects who have feeding tubes are eligible.

   Rationale for change: To reflect that medical monitor approval is no longer needed, given submission of appropriate regulatory documents outside of the United States.

4. **Synopsis; Section 4.1.1, Phase 1**

   Description of change: Revised the first rule for cohort expansion in the event of a DLT from no DLTs to ≤ 1 DLT.

   Rationale for change: To make consistent with Section 4.1.2.

5. **Section 1.3, Overview of Pembrolizumab; Section 1.11.2, Risks From Pembrolizumab**

   Description of change: Removed text for approved pembrolizumab indications in the United States and the European Union. Updated text describing risks of pembrolizumab to reflect information from the pembrolizumab Investigator's Brochure. Updated references to pembrolizumab prescribing information and summary of product characteristics to the pembrolizumab Investigator's Brochure.

   Rationale for change: To ensure that the most up-to-date information is referenced in the pembrolizumab Investigator's Brochure, given that approvals and risk language may change during the course of this study and because approvals may have regional differences.

6. **Section 1.11.1, Risks From Epacadostat; Section 5.5.6, Procedure for Subjects Exhibiting Serotonin Syndrome**

   Description of change: Updated text on SS.

   Rationale for change: To reflect revised text on SS included in Version 10 of the epacadostat Investigator's Brochure and to update the management procedure of subjects, study treatments, and concomitant medications in the event of SS.

7. **Section 4.5, Overall Study Duration**

   Description of change: Added text to allow for data analysis of individual treatment groups, provided the treatment group has been completed.

   Rationale for change: To allow for flexibility with data analysis of individual treatment groups, should enrollment times differ among the groups.

8. **Section 5.3.1.2, Supply, Packaging, and Labeling**

   Description of change: Updated text regarding pembrolizumab supply.

   Rationale for change: To reflect use of investigational supply of pembrolizumab.

9. **Section 5.6.1, Discontinuation Criteria**

   Description of change: Added unacceptable adverse events as described in Appendix G, Table G-1 with a requirement to permanently discontinue.

   Rationale for change: To update discontinuation criteria for accuracy.

10. **Section 5.9, Restricted Medications**

    Description of change: Updated text on use of coumarin-based anticoagulants and removed Table 7, Recommendations for Warfarin Dose Modifications.

    Rationale for change: To clarify, as Table 7 was redundant; both target international normalized ratio regimens require only close monitoring when given with epacadostat 100 mg twice daily.

11. **Section 5.10, Prohibited Medications/Treatment**

    Description of change: Removed restriction on the use of melatonin supplements and certain UGT1A9 inhibitors while on study treatment.

    Rationale for change: To align with recent literature or evidence indicating 1) a lack of a confirmed association between melatonin use and SS and 2) that certain UGT1A9 inhibitors may not interfere with the metabolism of epacadostat.

12. **Section 6, Study Assessments (Table 7 through Table 15)**

    Description of change: Updated Schedule of Assessment and Laboratory Assessment tables.

    Rationale for change: To correct inconsistencies and provide additional clarity with corresponding sections within the Protocol.

13. **Section 6, Study Assessments (Table 11); Section 7.5.4, Electrocardiograms**

    Description of change: Revised Table 11 and updated text in Section 7.5.4 on ECG requirements for subjects in Phase 2 efficacy expansion Treatment Groups C and D.

    Rationale for change: To provide additional clarity that 1) ECGs are not required on Cycle 1 Day 1 for Phase 2 efficacy expansion subjects in Treatment Groups C and D, as these subjects do not receive the first dose of epacadostat in the clinic and 2) ECGs are not required for any Phase 2 mandatory biopsy subject, as these subjects do not receive epacadostat during Cycle 1.

14. **Section 8.6, Events of Clinical Interest; Section 9.4.4.5, Events of Clinical Interest**

    Description of change: Revised to reflect ECIs only.

    Rationale for change: To refine the list of ECIs to provide clarity for investigative sites.

15. **Appendix G, Dose Modifications for Epacadostat and Pembrolizumab (Table G-1)**

    Description of change: Updated Table G-1.

    Rationale for change: To provide updated dose management guidance for epacadostat and pembrolizumab in the event of immune-related adverse events.

16. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment, including the addition of all summary of changes to Appendix O.

Amendment 4 (31 JUL 2017)

Overall Rationale for the Amendment: The primary purpose of this amendment is to update the study design.

1. **Title; Synopsis; Section 1, Introduction; Section 2.1, Study Objectives; Section 4, Investigational Plan; Section 5, Treatment; Section 6, Study Assessments; Section 7.6, Efficacy Assessments**

   Description of change: Replaced nivolumab/programmed cell death protein 1 (PD-1) inhibitor in Treatment Groups A and B with pembrolizumab.

   Rationale for change: Change in study design.

2. **Title; Synopsis; Section 1.10.1, Justification for Treatment Regimen; Section 4.1, Overall Study Design; Section 4.3.1, Planned Number of Subjects; Section 5.9, Restricted Medications**

   Description of change: Modified Phase 1 study design to remove dose-escalation and to allow for the start of Phase 2 if a minimum of 6 subjects have been treated with epacadostat 100 mg twice daily and there are ≤ 1 of 6 dose-limiting toxicities in all treatment groups (previously limited to only Treatment Groups C and D).

   Rationale for change: Change in study design.

3. **Synopsis; Section 1.8, Overview of Gemcitabine/Platinum Agent in Urothelial Carcinoma; Section 1.9, Overview of Platinum Agent/5-Fluorouracil in Squamous Cell Carcinoma of the Head and Neck; Section 1.11.8, Risks From Gemcitabine/Platinum Agent; Section 1.11.9, Risks From Platinum Agent/5-Fluorouracil; Section 2.1, Study Objectives; Section 3, Subject Eligibility; Section 4, Investigational Plan; Section 5.3.7, Gemcitabine and Platinum Agent; Section 5.3.8, Platinum Agent and 5-Fluorouracil; Section 6, Study Assessments; Section 9.2, Selection of Sample Size; Appendix M, Dose Modifications for Gemcitabine/Platinum Agent; Appendix N, Dose Modifications for Platinum Agent/5-Fluoroucil**

   Description of change: Added 2 new chemotherapy regimens to evaluate in combination with epacadostat and pembrolizumab in Phase 1, which will be limited to 2 tumor-specific cohorts in Phase 2.

   Rationale for change: Update to study design.

5. **Synopsis; Section 2, Study Objectives and Endpoints; Section 4.2, Measures Taken to Avoid Bias; Section 9.4, Statistical Analyses**

   Description of change: Clarified that primary and secondary efficacy measurements are per RECIST v1.1 and that efficacy by immune-related RECIST (irRECIST) [redacted]

   Rationale for change: Update to study design.

6. **Synopsis; Section 5.5.5, Treatment After Initial Radiologic Evidence of Disease Progression; Section 5.6.1, Discontinuation Criteria; Section 6, Study Assessments; Section 7.6.2.1, Assessment of Progressive Disease According to Immune-Related RECIST Criteria**

   Description of change: Edited text to show that the adaptation of RECIST v1.1 is known as irRECIST and that irRECIST should be used to guide treatment decisions for discontinuation of therapy.

   Rationale for change: To provide additional clarification.

7. **Synopsis; Section 3, Subject Eligibility**

   Description of change: Updated to provide a clear definition on eligibility criteria for the Phase 2 subjects who received previous treatment with a PD-1 or programmed cell death ligand 1 inhibitor, and provided clarifications for other criterion.

   Rationale for change: To provide additional guidance on eligibility criteria.

8. **Synopsis; Section 3.1, Subject Inclusion Criterion; Section 4.1.2, Phase 2: Efficacy Expansion and Mandatory Biopsy Cohorts; Section 6, Study Assessments; Section 7.9.4, Tumor Biopsy**

   Description of change: Added requirement that all Phase 2 efficacy expansion subjects are required to provide a biopsy at screening and updated timing of collection of on-treatment biopsies in the Phase 2 mandatory biopsy subjects.

   Rationale for change: Update to study design.

9. **Synopsis; Section 4.4, Duration of Treatment and Subject Participation; Section 5.6.1, Discontinuation Criteria; Section 6.2, Treatment**

   Description of change: Updated the duration of treatment of with pembrolizumab to be 35 infusions of pembrolizumab and duration of treatment with epacadostat to be the end of the cycle in which the 35th infusion of pembrolizumab is administered.

   Rationale for change: Update to study design.

10. **Synopsis; Section 5.3, Background Therapies**

    Description of change: Updated text on order of administration of background therapies.

    Rationale for change: To provide additional clarification on order of administration of pembrolizumab and individual agents of the chemotherapy regimen.

11. **Synopsis; Section 6, Study Assessments**

    Description of change: Updated timing of collection of [redacted] assessments.

    Rationale for change: To provide additional alignment with frequency of study visits as a subject progresses through the study.

12. **Synopsis; Section 6.4.2, Disease Status Follow-Up; Section 7.6.2.1, Assessment of Progressive Disease According to Immune-Related RECIST Criteria**

    Description of change: Updated text on timeframe for when disease status follow-up should continue and when scan frequency can change to longer intervals.

    Rationale for change: To provide additional clarification.

13. **Section 1.11.1, Risks From Epacadostat; Section 5.5.6, Procedure for Subjects Exhibiting Serotonin Syndrome**

    Description of change: Included updated information on serotonin syndrome events in epacadostat studies and updated the table describing signs/symptoms that may be indicative of serotonin syndrome

    Rationale for change: To provide the most recent information on serotonin syndrome with epacadostat treatment and provide additional guidance on signs and symptoms.

14. **Section 5.5.3, Management of Immune-Related Adverse Events; Section 5.5.4, Management of Chemotherapy-Related Adverse Events; Appendices G through M**

    Description of change: Revised protocol sections and appendices so that dose modifications for epacadostat and pembrolizumab for immune-related adverse events are described in 1 appendix and dose modifications for individual components of the chemotherapy regimen are described in the corresponding appendices.

    Rationale for change: To provide simplified guidance for the management of adverse events.

15. **Section 5.10.1, Supportive Care Guidelines**

    Description of change: Added text on the management of diarrhea and reference to management of infusion reactions with pembrolizumab in Appendix G**.**

    Rationale for change: To provide additional clarification.

16. **Section 8.6, Events of Clinical Interest and Adverse Events of Special Interest; Section 8.7, Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor**

    Description of change: Updated to include the definition of an overdose for epacadostat and pembrolizumab.

    Rationale for change: To provide clear guidance on overdose thresholds.

17. **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 3 (18 MAY 2017)

Overall Rationale for the Amendment: The primary purpose of this amendment is to update the study design of Phase 1 and provide flexibility in DLT determination in Phase 1.

1. **Synopsis; Section 3.1, Subject Inclusion Criteria; Section 4.1, Overall Study Design (including Figure 1, Study Design); Section 4.1.1, Phase 1: Dose Escalation in Selected Chemotherapy Regimens; Section 4.3.1, Planned Number of Subjects; Section 9.2.1.2, Safety Expansion**

   Description of change: Removed text related to the 2 safety expansion cohorts in Phase 1 and added text to indicate that for Treatment Groups C and D, at least 6 subjects must be treated at epacadostat 100 mg BID before opening Phase 2 at that dose.

   Rationale for change: Change in study design after further assessment following feedback from the FDA.

2. **Synopsis; Section 4.1.1, Phase 1: Dose Escalation in Selected Chemotherapy Regimens**

   Description of change: Text has been added to allow for determination of a dose-limiting toxicity (DLT) by the Data Monitoring Committee in certain cases where chemotherapy toxicities are indistinguishable from immune-related toxicities.

   Rationale for change: To allow for flexibility with determining a DLT in situations where there are overlapping toxicities between chemotherapy and immunotherapy and the subject has received < 80% dose intensity.

Amendment 2 (28 MAR 2017)

Overall Rationale for the Amendment: The primary purpose of this amendment is to update the study design of both Phase 1 and Phase 2 and provide clarity within the Protocol with respect to definition of study drug.

1. **Synopsis, Overall Study Design; Section 4.1, Overall Study Design; Section 5.5.1.1, Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose**

   Description of change: Text has been added to 1) address the inclusion of 2 safety expansion cohorts of subjects with NSCLC at epacadostat 100 mg BID for Treatment Group C and Treatment Group D in Phase 1; 2) clarify the criteria for determining evaluability for dose tolerability, 3) clarify the rules for dose escalation or de-escalation, and 4) address the change in Phase 2 from a Simon 2-stage design to a single stage for all cohorts treated with pembrolizumab, and 5) include the cumulative incidence of treatment-related serious adverse events (SAEs) within a Phase 2 cohort as part of the threshold for evaluating toxicity in Phase 2.

   Rationale for change: To address changes in study design in Phase 1 and Phase 2 and provide clarification on evaluation of tolerability in Phase 1 and Phase 2.

2. **Synopsis, Study Population (Key Inclusion Criteria); Section 3.1, Subject Inclusion Criteria**

   Description of change: Text has been added to provide details on inclusion criterion for the Phase 1 safety expansion NSCLC subjects (criterion 21).

   Rationale for change: To provide clarification on prior immunotherapies that are allowed and not allowed for the Phase 1 safety expansion NSCLC subjects.

3. **Section 3.1, Subject Inclusion Criteria; Section 4.4, Duration of Treatment and Subject Participation; Section 6.2, Treatment**

   Description of change: Updated to indicate that if a subject continues on a PD-1 inhibitor or chemotherapy after discontinuing epacadostat, contraception methods should continue according to guidance outlined in the prescribing information of each therapy (criterion 5).

   Rationale for change: To inform investigators and site staff that appropriate contraception measures must continue after subject is discontinued from epacadostat but continues on background therapy.

4. **Synopsis, Study Population (Key Exclusion Criteria); Section 3.2, Subject Exclusion Criteria**

   Description of change: Text has been added to (1) allow for the use of partial thromboplastin time (PTT) in place of activated PTT (aPTT) results to determine eligibility (criterion 1g), (2) clarify windows for meeting exclusion criteria must be within various thresholds of Cycle 1 Day 1 (criteria 2-4 and 15), and (3) provide details on gastrointestinal conditions that affect drug absorption that would qualify as exclusionary and that subjects with feeding tubes would require medical monitor approval (criterion 18).

   Rationale for change: To allow for flexibility for coagulation tests per institutional standards, clarify the window for thresholds is within Cycle 1 Day 1 so that criteria apply to all subjects enrolled in the study (including the Phase 2 mandatory biopsy cohorts who start epacadostat on Cycle 2 Day 1), and provide guidance on types of subjects with gastrointestinal conditions that may or may not be included in the study.

5. **Synopsis, Combination Therapy, Dosage, and Mode of Administration; Section 5.3, Background Therapies**

   Description of change: The PD-1 inhibitors have been reclassified as background therapies. Additionally, text has been added to clarify the start date of the PD-1 inhibitor and timing of administration after epacadostat and before premedications or chemotherapy, and to provide additional clarity on timing of administration of chemotherapy regimens. Text has been added to the carboplatin/paclitaxel and carboplatin/pemetrexed sections to allow for sites to have the option to use equivalent alternatives for the listed premedications as per institutional guidelines, investigator practice, or availability of similar medications on the investigative site's formulary.

   Rationale for change: To clarify timing of administration of PD-1 inhibitors and chemotherapy regimens, and to allow for alternatives to required premedications if those that are described in the Protocol are not available.

6. **Synopsis, Study Schedule/Procedures; Section 6.3, End of Treatment; Section 6.4, Follow-Up**

   Description of change: Revised to clarify that the end of treatment is defined as the end of epacadostat treatment and that follow-up assessments (safety, disease status, survival) will occur from the end of treatment date of epacadostat based on the respective windows defined in the Protocol.

   Rationale for change: To clearly define the end of treatment for purposes of subject entry in to the follow-up portion of the study.

7. **Synopsis, Estimated Number of Subjects and Statistical Methods; Section 4.3.1, Planned Number of Subjects; Section 9, Statistics**

   Description of change: Updated the anticipated total number of subjects and selection of sample sizes/statistical methods.

   Rationale for change: To account for changes in study design.

8. **Section 1.3, Overview of Nivolumab; Section 1.4, Overview of Pembrolizumab; Section 1.10.1, Risks from Epacadostat; Section 1.10.2, Risks from Nivolumab; Section 1.10.3, Risks From Pembrolizumab**

   Description of change: Updated preclinical data for epacadostat and to reflect recent approvals and risk language in US prescribing information for nivolumab and pembrolizumab.

   Rationale for change: To provide the most updated information.

9. **Section 5.7, Procedures for Withdrawal From Study**

   Description of change: New section added detailing procedures for subject withdrawal from the study.

   Rationale for change: To clarify that subjects have the option to discontinue treatment and/or study assessments but allow collection of information in the follow-up period of the study or discontinue.

10. **Section 5.10, Prohibited Medications/Treatment**

    Description of change: Section revised to update criteria for allowed steroid use and radiation therapy, to prohibit melatonin supplements, and to remove redundancy with exception for immunologic treatment.

    Rationale for change: To provide additional information on exceptions to prohibited medications while on study.

11. **Section 6, Study Assessments (Table 8 and Table 10)**

    Description of change: Additional evaluations of concomitant medications, targeted physical examination, and vital signs and weight have been added for the cohorts where nivolumab is administered.

    Rationale for change: To provide consistency with frequency of assessments in the cohorts where pembrolizumab is administered.

12. **Section 6, Study Assessments (Tables 9, 11, 14, 16, 17)**

    Description of change: Urine pregnancy test is now required in all women of childbearing potential at the intervals noted within the tables and not just per country-specific requirements.

    Rationale for change: To ensure appropriate monitoring for pregnancy while on study.

13. **Section 5.5.5.1, Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose (Table 3); Section 6, Study Assessments (Tables 9, 11, 14, 16); Section 7.5.5.5, Lipid Panel**

    Description of change: Lipid panel testing has been removed.

    Rationale for change: Alterations in lipids is not common with epacadostat, and routine monitoring is not necessary.

14. **Section 6, Study Assessments (Tables 10, 13, and 15); Section 7.5.4, Electrocardiograms; Section [redacted], [redacted]**

    Description of change: ECGs on Cycle 1 Day 1 and Cycle 1 Day 8, [redacted] should only be collected for Phase 1 and the Phase 2 efficacy expansion subjects. ECGs on Cycle 1 Day 1 and Cycle 1 Day 8 do not need to be conducted in subjects enrolled in the Phase 2 mandatory biopsy cohorts.

    Rationale for change: To clarify ambiguity in Protocol text.

15. **Section 6, Study Assessments (Table 17: Clinical Laboratory Analytes)**

    Description of change: Under Serum Chemistries, magnesium has been added to the list of analytes and phosphorus has been corrected to phosphate. Collection of reticulocytes has been removed from Hematology. The header for liver enzyme analytes has been updated to "Liver Chemistry Tests."

    Rationale for change: To update recommended analytes that are needed to monitor safety in this study.

16. **Clarification of study drug.** Wherever possible throughout the Protocol, epacadostat replaced "study drug" to provide clarity. All changes are noted in the redline version of the amendment.

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

Amendment 1 (10 JAN 2017)

Overall Rationale for the Amendment: The primary purpose of this amendment is to address FDA's correspondence from 03 JAN 2017.

1. **Synopsis, Key Inclusion Criteria; Section 3.1, Subject Inclusion Criteria (Criterion #20)**

   Description of change: Text describing inclusion criterion for Phase 2 subjects with non–small cell lung cancer (NSCLC) who have driver mutations (EGFR, ALK fusion oncogene, or ROS1) was clarified to indicate these subjects must have received prior treatment with an approved tyrosine kinase inhibitor.

   Rationale for change: FDA request.

2. **Section 5.5.1.1, Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose (Table 3, Definition of Dose-Limiting Toxicity)**

   Description of change: Two new criteria for dose-limiting toxicities (DLTs) were added: Grade 4 (life-threatening) immune-related adverse event (irAE) and Grade 4 (life-threatening) electrolyte abnormality. Additionally, the criterion for DLT exceptions related to nausea, vomiting, and diarrhea adequately controlled with medical therapy within 48 hours was limited to Grade 3 events.

   Rationale for change: FDA request.

3. **Synopsis, Data Monitoring Committee; Section 8.9, Data Monitoring Committee; Section 9.5, Analyses for the Data Monitoring Committee**

   Description of change: Text describing the establishment of a Data Monitoring Committee to monitor patient safety was added.

   Rationale for change: FDA request.

4. **Synopsis, Estimated Number of Subjects; Section 4.3.1, Planned Number of Subjects**

   Description of change: Text added to Phase 2 Expansion to clarify that this will include subjects from the Simon 2-stage and Biopsy cohorts.

   Rationale for change: FDA request.

5. **Section 4.4, Duration of Treatment and Subject Participation; Section 5.2.1.1, Description and Administration; Section 5.2.2.1, Description and Administration; Section 5.2.3.1, Description and Administration; Section 6.2, Treatment**

   Description of change: Text on the maximum duration of treatment with epacadostat and applicable PD-1 inhibitor was revised.

   Rationale for change: To correct inconsistencies within various Protocol sections.

6. **Synopsis, Overall Study Design; Section 4.1.2, Phase 2: Expansion Cohorts; Section 7.9.4, Tumor Biopsy**

   Description of change: Text on optional biopsies for subjects enrolled in the Simon 2-stage portion of Phase 2 was revised. Additional text indicating that subjects who provide a biopsy that does not meet minimum standards for evaluation (as outlined in the Laboratory Manual) may still enroll in the study but may be replaced in order to enroll sufficient numbers of biopsy evaluable subjects.

   Rationale for change: To provide guidance on the collection and timing of optional biopsies for subjects enrolled in the Simon 2-stage portion of Phase 2 who receive IV chemotherapy, and flexibility to replace nonevaluable biopsy samples.

7. **Section 9.6, Interim Analysis**

   Description of change: Text describing interim analyses for futility in the Simon 2-stage portion of Phase 2 was added.

   Rationale for change: To provide guidance on assumptions, probabilities, and timing of interim analyses.

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

Signature Manifest

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INCB 24360-207 Protocol AM7

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