STATISTICAL ANALYSIS PLAN

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)

IND Number:	**132,309**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Protocol Version:	**Protocol Amendment 7 dated 14 FEB 2019**
CRF Approval Date:	**14 AUG 2018**
SAP Version:	**Amendment 1**
SAP Author:	[redacted], [redacted]
Date of Plan:	**12 MAR 2019**

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
AEOSI	adverse event of special interest
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
BID	twice daily
BSA	body surface area
CI	confidence interval
[redacted]	[redacted]
[redacted]	[redacted]
CR	complete response
CRC	colorectal cancer
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
ECG	electrocardiogram
eCRF	electronic case report form
ECOG	Eastern Cooperative Oncology Group
FAS	full analysis set
FDA	Food and Drug Administration
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NCI	National Cancer Institute
NE	not evaluable
NSCLC	non-small cell lung cancer
ORR	objective response rate
PAD	pharmacologically active dose
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1

Abbreviation	Term
PDAC	pancreatic ductal adenocarcinoma
[redacted]	[redacted]
PO	orally
PR	partial response
PT	preferred term
Q3W	every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	statistical analysis plan
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SI unit	International System of Units
SOC	system organ class
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
UC	urothelial carcinoma
WHO	World Health Organization

1. INTRODUCTION

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 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. Protocol Amendment 7, Section 1 provides a detailed description of the investigational product, target patient population, rationale for doses to be examined, and potential risks and benefits of treatment with the combination of epacadostat, pembrolizumab, and chemotherapy regimens.

The purpose of this SAP is to provide details of the statistical analyses that have been outlined in Study INCB 24360-207 Protocol Amendment 7 dated 14 FEB 2019. The scope of this plan includes the interim and final analyses that are planned and will be executed by the Biostatistics and Programming department or designee. [redacted]

2. STUDY INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on INCB 24360-207 Protocol Amendment 7 dated 14 FEB 2019 and CRFs approved 14 AUG 2018. Unless superseded by an amendment, this SAP will be effective for all subsequent Protocol amendments and eCRF versions.

2.2. Study Objectives

2.2.1. 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.

2.2.2. 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.

2.3. Study Endpoints

2.3.1. 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 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.

2.3.2. 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. STUDY DESIGN

3.1. Overall Study Design

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 (see Figure 1). In Phase 1, the MTD or PAD of epacadostat when given in combination with pembrolizumab and chemotherapy will be determined by a 3 + 3 + 3 design. In Phase 2, the safety, tolerability, and efficacy of the MTD or PAD of epacadostat selected in Phase 1 when given in combination with pembrolizumab and chemotherapy will be further evaluated.

3.1.1. 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.

The scenarios for de-escalation and expansion 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 are no DLTs 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 DLTs 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.

Dose interruptions and/or modifications may be implemented based on toxicity as described in Protocol Amendment 7, Section 5.5.1.1. Dose modifications should not be made during the DLT observation period without discussion with the medical monitor.

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.

Subjects will be assigned to a treatment group (see Table 2) based on the chemotherapy regimen most appropriate for the subject's 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 Days 1 and 15 • Leucovorin 400 mg/m^2 IV on Days 1 and 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 Days 1 and 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

Table 2: Treatment Groups (Continued)

Treatment Group F	**Epacadostat**	**Pembrolizumab**	**Gemcitabine and Platinum Agent**
	BID PO continuous daily dosing (see Table 1)	200 mg IV Q3W	• Gemcitabine 1000 mg/m2 IV on Days 1 and 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	• Investigators 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 to 4 Q3W

3.1.2. Phase 2: Efficacy Expansion and Mandatory Biopsy Cohorts

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) and Phase 2 mandatory biopsy Treatment Groups A, B, F, and G. Any text included in the body of this SAP that references these treatment groups and cohorts have not been deleted but should be disregarded.

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:

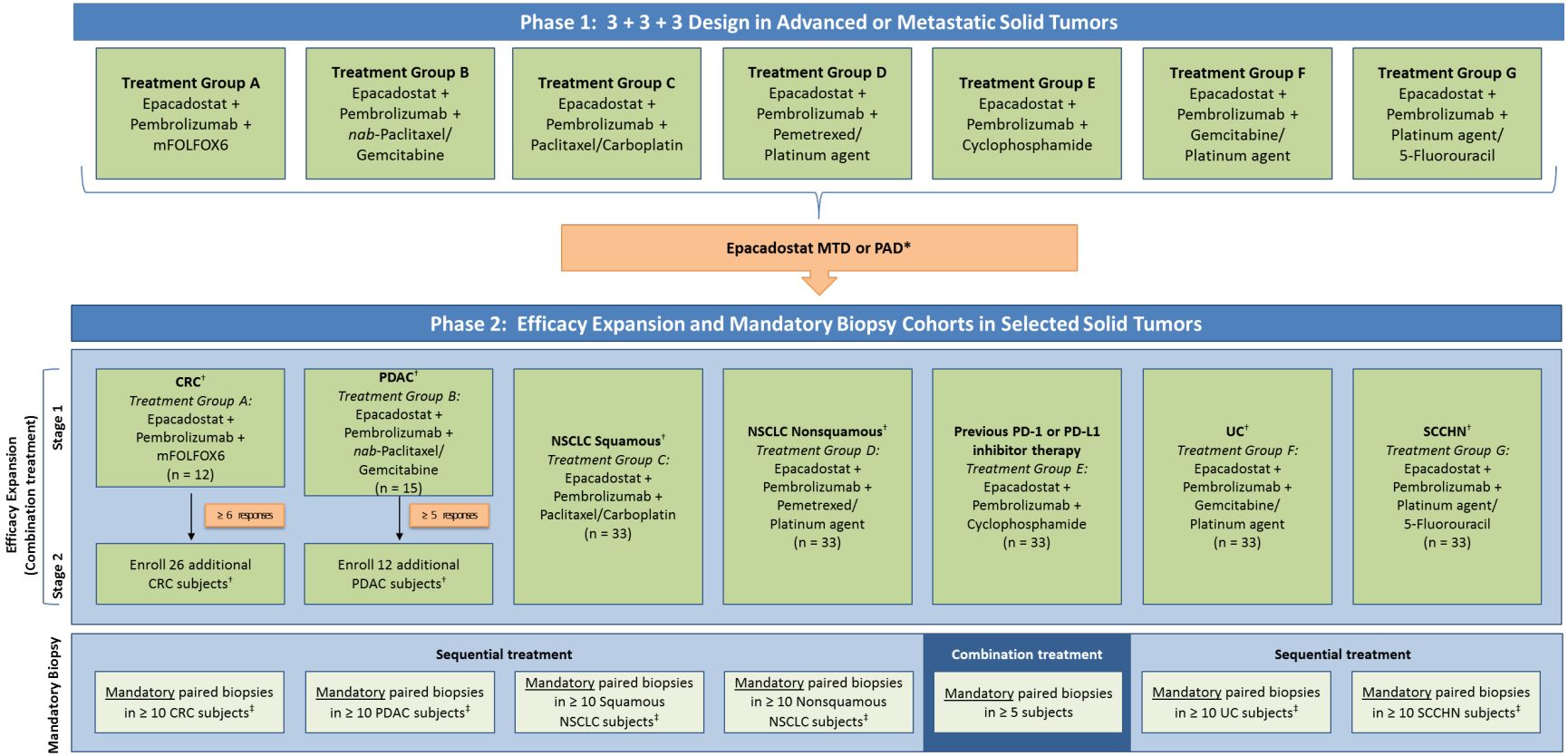
1. CRC (Treatment Group A: epacadostat + pembrolizumab + mFOLFOX6): Simon 2-Stage design
2. PDAC (Treatment Group B: epacadostat + pembrolizumab + *nab*-paclitaxel/gemcitabine): Simon 2-Stage design
3. Squamous NSCLC (Treatment Group C: epacadostat + pembrolizumab + paclitaxel/carboplatin)
4. Nonsquamous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

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.

Note: As of 25 OCT 2018, on-treatment tumor biopsies are no longer required for subjects who 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.

3.2. Control of Type I Error

For the primary efficacy endpoint in Phase 2, the 1-sided Type I error will be controlled at 0.1 for each individual treatment group. For other endpoints, CIs will be reported at a 95% confidence level. Note that this level of significance does not account for the multiple treatment groups.

3.3. Sample Size Considerations

3.3.1. 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.

3.3.2. Sample Size in Phase 2

3.3.2.1. 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 3.

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 4. The definitions of p_0, p_1, n, and r are the same as those in Table 3.

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 3: 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 4: 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

3.3.2.2. 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.

In Phase 2 mandatory biopsy cohorts, 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, non-squamous 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.

3.4. Schedule of Assessments

See Protocol Amendment 7 dated 14 FEB 2019 for a full description of all study procedures and assessment schedules for this study.

4. DATA HANDLING DEFINITIONS AND CONVENTIONS

4.1. Scheduled Study Evaluations and Study Periods

4.1.1. Day 1

Day 1 is the date that the first dose of epacadostat, pembrolizumab, or chemotherapy is administered to the subjects.

4.1.2. Study Day

If a visit/reporting date is on or after Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (Visit/Reporting Date – Day 1 date + 1).

If the visit/reporting date is before Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (Visit/Reporting Date – Day 1 date).

A study day of -1 indicates 1 day before Day 1.

4.1.3. Baseline Value

Baseline is the last nonmissing measurement obtained before the first administration of epacadostat, pembrolizumab, or chemotherapy.

When scheduled assessments and unscheduled assessments occur on the same day and time of the assessment or time of first dose is not available, use the following convention to determine baseline:

- If both a scheduled and an unscheduled visit are available on the day of the first dose and the time is missing, use the scheduled assessment as baseline.
- If all scheduled assessments are missing on the day of the first dose and an unscheduled assessment is available, use the unscheduled assessment as baseline.

4.1.4. Handling of Missing and Incomplete Data

In general, values for missing data will not be imputed unless methods for handling missing data are specified in this section or relevant sections.

Partial disease/cancer diagnosis date will be handled as follows:

- If only the day is missing, then the imputed day will be the first of the month.
- If both the month and day are missing, then the imputed day and month will be 01 JAN.
- No imputation will be done if the date is completely missing.

Missing or partial date of last dose will be handled as follows:

- If only the day is missing, then the imputed date of the last dose will be the earlier date of the first day of the month or the date that the subject discontinued treatment.
- Otherwise, the date that the subject discontinued treatment will be used as the date of the last dose.

For relevant efficacy endpoints, partial death date will be imputed as follows:

- If mmyyyy for the last contact date = mmyyyy for the death date, then the death date will be set to the day after the last contact date.
- If mmyyyy for the last contact date < mmyyyy for the death date, then the death date will be set to the first day of the death month.
- Otherwise, the partial death date will not be imputed.

For prior and concomitant medications:

The start/stop dates recorded in the eCRF by the investigator and his or her research staff will be used to identify when a concomitant medication was taken during the study. Any missing start date must be queried for resolution. Unresolved missing start dates will be handled as follows:

- If the date is completely missing, the medication will be considered both prior and concomitant.
- If only the day is missing, and the last day of the month is before the first dose date on Day 1, then the concomitant medication will be considered as starting before Day 1, and the incomplete date will be imputed as the last day of the month.
- If only the day is missing, and the first day of the month is after the first dose date on Day 1, then the concomitant medication will be considered as starting after Day 1, and the incomplete date will be imputed as the first day of the month.
- If only the day is missing, and the month is equal to the month of the first dose date on Day 1, then the incomplete date will be imputed as the first day of the month.
- If both the month and day are missing, and the last day of the year is before the first dose date on Day 1, then the concomitant medication will be considered as starting before Day 1, and the incomplete date will be imputed as if it is the last day of the year. Otherwise, the incomplete date will be imputed as if it is the first day of the year.

4.1.5. Cycle Length and Duration

Cycle 1 Day 1 is the day that the first dose of epacadostat, pembrolizumab, or chemotherapy is administered. Scheduled cycle length is 21 or 28 days depending on the chemotherapy administered. For mFOLFOX6 and *nab*-paclitaxel/gemcitabine regimens, the scheduled cycle length is 28 days. For all other chemotherapy regimens, the scheduled cycle length is 21 days.

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 Protocol Amendment 7, Section 5.6.1).

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 Protocol Amendment 7, Section 5.6.1).

Actual Day 1 of subsequent cycles will correspond with the first day of administration of epacadostat, pembrolizumab, or chemotherapy in that cycle; thus, treatment cycles may become out of sync with the originally planned schedule and cycle length may be different from 21 or 28 days. The date of Day 1 of subsequent cycles recorded on the eCRF will be used as Day 1 of the subsequent cycles.

4.2. Variable Definitions

The following variables will only be calculated if not reported on the eCRF.

4.2.1. Age

Subject age will be calculated as the integer part of the number of years from date of birth to the date of signing the IC, using the following formula:

Age = integer part of (date of informed consent – date of birth + 1) / 365.25.

When date of birth was not collected for a subject and the age of the subject was reported on the eCRF, the reported age will substitute for the calculated age.

4.2.2. Body Surface Area

Body surface area will be calculated based on the Mosteller (1987) formula as follows:

$$BSA\ (m^2) = \{[weight\ (kg) \times height\ (cm)] / 3600\}^{1/2}$$

Sites will also record the BSA calculated per institutional standards.

4.2.3. Prior and Concomitant Medication

Prior medication is defined as any nonstudy medication started before the first dose of epacadostat, pembrolizumab, or the assigned chemotherapy regimen.

Concomitant medication is defined as any nonstudy medication that is started accordingly:

- Before the date of first administration of epacadostat, pembrolizumab, or the assigned chemotherapy regimen and is ongoing throughout the study or ends on/after the date of first study drug administration.
- On/after the date of first administration of epacadostat, pembrolizumab, or the assigned chemotherapy regimen and is ongoing or ends during the course of study drug.

A prior medication could also be classified as "both prior and concomitant medication" if the end date is on or after first dose of epacadostat, pembrolizumab, or chemotherapy regimen. In the listing, it will be indicated whether a medication is prior-only, concomitant-only, or both prior and concomitant medication.

For the purposes of analysis, all medications will be considered concomitant medications unless the medications can unequivocally be defined as not concomitant.

5. STATISTICAL METHODOLOGY

5.1. General Methodology

Unless otherwise noted, SAS® software (SAS Institute Inc, Cary, NC; v9.4 or later) will be used for the generation of all tables, graphs, and statistical analyses. Descriptive summaries for continuous variables will include, but not be limited to, the number of observations, mean, standard deviation, median, minimum, and maximum. Descriptive summaries for categorical variables will include the number and percentage of subjects in each category.

Interim analyses are planned for this study as defined in Section 9.

5.2. Treatment Groups

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 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.

In Phase 1, subjects will be enrolled into 7 treatment groups. Subjects will be assigned to a treatment group (see Table 2) based on the chemotherapy regimen most appropriate for their tumor type. The initial dose level for epacadostat in each treatment group will be 100 mg BID. The doses of epacadostat to be evaluated and the scenarios for dose de-escalation are summarized in Table 1.

In Phase 2, the efficacy expansion + cohorts and the mandatory biopsy cohorts will be limited to the following advanced or metastatic tumor types:

1. CRC (Treatment Group A: epacadostat + pembrolizumab+ mFOLFOX6)
2. PDAC (Treatment Group B: epacadostat + pembrolizumab+ *nab*-paclitaxel/gemcitabine)
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)

Data will be summarized by treatment group for Phase 1 and Phase 2 combined.

5.3. Analysis Populations

5.3.1. Full Analysis Set

The FAS includes subjects enrolled in the study who received at least 1 dose of epacadostat, pembrolizumab, or applicable chemotherapy agent and have at least 1 postbaseline assessment or who discontinued treatment.

The FAS population will be used for the summary of all efficacy data.

5.3.2. Safety Population

The safety population includes all subjects enrolled in the study who received at least 1 dose of epacadostat, pembrolizumab, or applicable chemotherapy agent.

Specific safety analysis populations to be used for drug-specific tables include the following subgroups:

- epacadostat safety population
- pembrolizumab safety population
- mFOLFOX6 safety population
- *nab*-paclitaxel and gemcitabine safety population
- paclitaxel and carboplatin safety population
- pemetrexed and platinum agent safety population
- cyclophosphamide safety population
- gemcitabine and platinum agent safety population
- 5-fluorouracil and platinum agent safety population

All of the chemotherapy safety populations are defined as all subjects enrolled in the study who received at least 1 dose of any chemotherapy agent. For example, the mFOLFOX6 safety population includes all subjects enrolled in the study who received at least 1 dose of oxaliplatin, leucovorin, or fluorouracil.

The safety population will be used for the summary of safety analyses.

6. BASELINE, EXPOSURE, AND DISPOSITION VARIABLES AND ANALYSES

Appendix A provides a list of planned tables and listings. Sample data displays are provided in a separate document. The list of tables and listings and the shells are to be used as a guideline. Modifications of the list or shells that do not otherwise affect the nature of the analysis will not warrant an amendment to the SAP.

6.1. Baseline and Demographics, Physical Characteristics, and Disease History

6.1.1. Demographics

The following demographics will be summarized for all subjects in the safety population by treatment group: age, sex, race, and ethnicity.

6.1.2. Baseline Disease Characteristics and Disease History

The baseline disease characteristics include tumor types, current stage, current number of metastatic organ/tissue sites, current sites of disease, and types prior therapies for cancer (eg, radiotherapy, surgery, systemic therapy or prior PD1/L1 therapy), will be summarized by treatment group.

ECOG performance status will be summarized for all subjects in the safety population by treatment group.

6.1.3. Prior Therapy

Number of subjects who received prior systemic cancer therapy regimens will be summarized for all subjects in the safety population by treatment group. Regimen name, component drugs, start and stop date, purpose of the regimen, best response, reason for discontinuation, and date of relapse/progression will be listed.

Number of subjects who received prior radiation will be summarized for all subjects in the safety population by treatment group. Radiotherapy type, body site, start and stop date, reason for regimen, number of fractions, total dose, and best response will be listed.

Number of subjects who had prior surgery or surgical procedure for the malignancies under study will be summarized for all subjects in the safety population by treatment group. Date and description of the surgery/procedure will be listed.

6.1.4. Medical History

Medical history will be summarized by assigned treatment group for all subjects in the safety population by treatment group. This summation will include the number and percentage of subjects with significant medical history for each body system/organ class as documented on the eCRF.

6.2. Disposition of Subjects

The number and percentage of subjects who were enrolled, treated, completed the study, discontinued study treatment with a primary reason for discontinuation, and discontinued from the study with a primary reason for withdrawal will be summarized for all subjects in the safety population by treatment group. The number of subjects enrolled by site will also be provided by treatment group.

6.3. Protocol Deviations

Protocol deviations recorded on the eCRF will be presented in the subject data listings. If data warrant, protocol deviations will be summarized for all subjects in the safety population by treatment group.

6.4. Exposure

6.4.1. Exposure for Epacadostat

The following variables will be summarized for epacadostat:

- **Duration of treatment (days):** Date of last dose of epacadostat – date of first dose of epacadostat + 1.
- **Total dose administered (mg):** Total dose administered (mg) for each subject will be the sum of epacadostat administered (mg) across cycles.
- **Average Daily Dose (mg/day):** Total dose administered (mg) divided by the duration of treatment in days.

6.4.2. Exposure for Pembrolizumab

The following variables will be summarized for pembrolizumab:

- **Total number of infusions:** Total number of infusions per subject will be the total number of infusions per subject with a nonzero dose of pembrolizumab.
- **Dose administered per cycle (mg):** The actual dose administered (mg) per cycle.
- **Total dose administered (mg):** Total dose (mg) administered is the sum of the cumulative dose of pembrolizumab that has been administered to the subject.

  For an infusion i, let C_i be the concentration (mg/mL) of pembrolizumab and V_i be the total volume administered (in mL) reported on the pembrolizumab dosing eCRF; let N be the total number of infusions:

  Total dose administered (mg) = $\sum_{i=1}^{N} C_i \times V_i$.

- **Average dose (mg):** The average dose (mg) will be the total dose administered (mg) divided by the total number of infusions.
- **Duration of treatment (days):** Date of last dose of pembrolizumab – date of first dose of pembrolizumab + 1.

6.4.3. Exposure for Cyclophosphamide

The exposure for cyclophosphamide will be summarized the same as that for epacadostat in Section 6.4.1.

6.4.4. Exposure for Intravenous Chemotherapies

6.4.4.1. Exposure for Carboplatin

The following variables will be summarized for the exposure for carboplatin at AUC5, AUC6, and other dose levels separately:

- **Total number of infusions:** Total number of infusions per subject will be the total number of infusions per subject with a nonzero dose of carboplatin.
- **Dose administered per cycle (mg):** The actual dose administered (mg) per cycle.
- **Total dose administered (mg):** Total dose (mg) administered is the sum of the BSA-adjusted cumulative dose of carboplatin that has been administered to the subject.

  For an infusion i, let C_i be the concentration (mg/mL) of carboplatin and Vi be the total volume administered (in mL) reported on carboplatin dosing eCRF and let N be the total number of infusions:

  Total dose administered (mg) = $\sum_{i=1}^{N} C_i \times V_i$.
- **Average dose (mg):** The average dose (mg) will be the total dose administered (mg) divided by the total number of infusions.
- **Duration of treatment (days):** Date of last dose of carboplatin – date of first dose of carboplatin + 1.

6.4.4.2. Exposure for Other Intravenous Chemotherapies

The following variables will be summarized for each component of all other IV chemotherapies:

- **Total number of infusions:** Total number of infusions per subject will be the total number of infusions per subject with a nonzero dose of each IV chemotherapy agent.
- **Dose administered per cycle (mg/m^2):** The actual dose administered (mg/m^2) per cycle.
- **Total dose administered (mg/m^2):** Total dose (mg/m^2) administered is the sum of the BSA-adjusted cumulative dose of each IV chemotherapy agent that has been administered to the subject.

For an infusion *i*, let C_i be the concentration (mg/mL) of each IV chemotherapy agent and V_i be the total volume administered (in mL) reported on each IV chemotherapy agent dosing eCRF; let *B* be the subject's baseline BSA (m^2), and let *N* be the total number of infusions:

Total dose administered (mg/m^2) = $\sum_{i=1}^{N} \frac{C_i \times V_i}{B}$.

- **Average dose (mg/m^2):** The average dose (mg/m^2) will be the total dose administered (mg/m^2) divided by the total number of infusions.
- **Duration of treatment (days):** Date of last dose – date of first dose + 1.

Other IV chemotherapies in this study include the following: 5-fluorouracil, leucovorin, oxaliplatin, gemcitabine, *nab*-paclitaxel, paclitaxel, pemetrexed, and cisplatin.

6.5. Prior and Concomitant Medication

For subjects in the safety population, prior medications and concomitant medications will be coded using the WHO Drug Dictionary and summarized by WHO drug class and WHO drug term. Results will be summarized as number and percentage of subjects with prior and concomitant medications by preferred term and WHO drug class.

7. EFFICACY

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); therefore, no efficacy tables or listings will be provided.

7.1. General Considerations

The efficacy endpoint of this study is ORR by investigator assessment based on RECIST v1.1. The primary efficacy assessment is based on RECIST v1.1. Listings of response assessment at each visit will be provided.

7.2. Efficacy Hypotheses

A Simon 2-stage design (Simon 1989) will be applied to Phase 2 efficacy expansion subjects in Treatment Groups A and B in testing the null hypothesis that the true ORR is less than or equal to the clinically insignificant response rates of p_0 against the alternative hypothesis that the true ORR is equal to the target ORR of p_1. The values of p_0 and p_1 for each tumor type are displayed in Table 3.

7.3. Analysis of the Efficacy Parameters

7.3.1. Response Criteria

Overall disease status will be categorized using RECIST v1.1. Subjects will have their overall response evaluated as CR, PR, SD, PD, or NE at each postbaseline radiological assessment based on changes in target lesions, nontarget lesions, and appearance of new lesions.

7.3.2. Objective Response Rates and Best Overall Response

A subject is defined as an objective responder if the subject has an overall response of CR or PR at any postbaseline visit prior to first PD. Objective responders will be assessed based on RECIST v1.1.

Objective response rate is defined as the proportion of subjects with objective responses. Objective response rate will be estimated with 95% CIs overall by cohort-specific tumor type. Confidence intervals will be calculated based on the method for Simon-2-Stage CIs of response rates outlined in Koyama and Chen (2008). Subjects who do not have sufficient baseline information will be included in the denominators in the calculation of ORR.

In general, best overall response is the best response recorded postbaseline prior to and including the first PD, in the order of CR, PR, SD, PD, and NE. In the case of SD, measurements must meet the SD criteria at least once after the date of first dose at a minimum interval of 56 (63-7) days. Subjects that fail to meet this criterion will have best overall response of PD if the next available assessment indicates PD or NE if there is no additional assessment available. Under RECIST v1.1, if radiologic imaging shows CR or PR, a tumor assessment should be repeated at a minimum of 4 weeks to confirm the response in order to claim the CR or PR as the best overall response. If there is no second CR or PR tumor assessment in the minimum 21 (28-7)-day follow-up time, the CR or PR will be unconfirmed. Table 5 lists the scenarios of

responses that can occur after an unconfirmed CR or PR in the 4-week follow-up time and provides a rule for determining the best overall response in each scenario.

Table 5: Best Overall Response When Confirmation of CR and PR is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE[b]	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE[b]	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

[a] If a CR is truly met at the first timepoint, then any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best overall response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present, and in fact, the subject had a PR, not a CR at the first timepoint. Under these circumstances, the original CR should be changed to a PR and the best overall response is PR.

[b] In cases where confirmatory scans with NEs are subsequently followed by another scan confirming the response, for example, a subject with timepoint responses of PR-NE-PR, it is reasonable to consider PR as a confirmed response.

7.3.2.1. Objective Response Rate Under RECIST v1.1

Under RECIST v1.1, the best response is determined by subject using the highest overall response achieved postbaseline prior to and including the first PD, in the order of CR, PR, SD, PD, and NE. Responses of CR, PR, or SD after a response of PD will not be considered in determining best response by RECIST v1.1 criteria. In the case of SD, measurements must meet the SD criteria at least after the date of first dose at a minimum of 56 (63-7) days. Subjects who fail to meet this criterion will have best overall response of PD if the next available assessment indicated PD or NE if there is no additional assessment available.

For subjects with measurable disease at baseline, the RECIST v1.1 assessment criteria presented in Table 6 can be used to determine the overall disease status at a given timepoint based on the target lesion, nontarget lesion, and new lesion assessment.

Table 6: RECIST Evaluation Criteria for Overall Response: Measurable Disease at Baseline

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

7.3.3. Largest Percentage Reduction in Sum of Diameters of Target Lesions

For each subject in the FAS population with target lesions at baseline, target lesion sizes will be measured by sum of diameters. The best percent change from baseline, defined as the largest decrease in target lesion size for each subject, will be summarized descriptively, and a waterfall plot of the best percent change will be generated.

Per RECIST criteria, target lesions considered "too small to measure" will be assigned a default value of 5 mm for purposes of this analysis. Likewise, target lesions identified as "not present" at postbaseline assessments will be assigned 0 mm for this analysis. In the event a target lesion is unaccounted for in a particular postbaseline timepoint (ie, assessment missing or NE), then the overall sum of diameters for target lesions will not be evaluable for that postbaseline timepoint.

8. SAFETY AND TOLERABILITY

Appendix A provides a list of planned tables and listings. Sample data displays are provided in a separate document. The list of tables and listings and the shells are to be used as a guideline. Modifications of the list or shells that do not otherwise affect the nature of the analysis will not warrant an amendment to the SAP.

8.1. General Considerations

Summary tables may be replaced with listings when appropriate. For instance, an AE frequency table may be replaced with a listing if it only contains a few unique PTs reported on relatively few subjects.

8.2. Adverse Events

8.2.1. Adverse Event Definitions

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first dose of study drug. Analysis of AEs (as discussed below) will be limited to TEAEs, but data listings will include all AEs regardless of their timing in relation to study drug administration.

Adverse events will be tabulated by MedDRA PT and SOC. Severity of AEs will be graded using the NCI CTCAE. The CTCAE v4.03 is used for this study. The CTCAE reporting guidelines and grading details are available on the Cancer Therapy Evaluation Program website.

The subset of AEs considered by the investigator to be related to study treatment will be considered to be treatment-related AEs. The incidence of AEs and treatment-related AEs will be tabulated. In addition, serious TEAEs will also be tabulated.

Any missing onset date, causality, or severity must be queried for resolution. Unresolved missing causality and severity will be handled according to the following rules:

- An unresolved missing causality will be considered treatment-related.
- An unresolved missing severity will be identified as an unknown severity.

For purposes of analysis, all AEs will be considered TEAEs unless the AE can unequivocally be defined as not treatment emergent.

8.2.2. Dose-Limiting Toxicities

The number of subjects with DLTs and the type of DLT will be listed by dose level.

8.2.3. Maximum Tolerated Dose

In Phase 1, the MTD is defined as the highest dose level at which $\leq 1/6$ or $\leq 2/9$ subjects experience a DLT.

8.2.4. Events of Clinical Interest and Adverse Events of Special Interest

Events of clinical interest must be recorded as such on the eCRF.

For this study, events of clinical interests include:

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

An overall summary of sponsor-determined AEOSIs will include number (%) of subjects reporting any immune-related AEs.

Subjects meeting the criteria of Hy's Law will be listed with study visit and assigned treatment group.

8.2.5. Adverse Event Summaries

An overall summary of AEs by treatment group will include:

- Number (%) of subjects reporting any TEAEs
- Number (%) of subjects reporting any DLTs
- Number (%) of subjects reporting any serious TEAEs
- Number (%) of subjects reporting any Grade 3 or 4 TEAEs
- Number (%) of subjects reporting any TEAEs related to any study drug
- Number (%) of subjects who temporarily interrupted epacadostat and/or pembrolizumab because of TEAEs
- Number (%) of subjects who permanently discontinued epacadostat and/or pembrolizumab because of TEAEs
- Number (%) of subjects with epacadostat dose reductions because of TEAEs
- Number (%) of subjects who had a fatal TEAE

The following summaries will be produced by MedDRA term (if 10 or fewer subjects appear in a table, a listing may be appropriate):

- Summary of TEAEs by SOC and PT
- Summary of TEAEs by PT in decreasing order of frequency
- Summary of Grade 3 or 4 TEAEs by SOC and PT
- Summary of Grade 3 or 4 TEAEs by PT in decreasing order of frequency
- Summary of any treatment-related TEAEs by SOC and PT
- Summary of any treatment-related TEAEs by PT in decreasing order of frequency
- Summary of TEAEs with a fatal outcome by SOC and PT
- Summary of serious TEAEs by SOC and PT

- Summary of serious TEAEs by PT in decreasing order of frequency
- Summary of TEAEs leading to any dose reduction by SOC and PT
- Summary of TEAEs leading to any dose interruption by SOC and PT
- Summary of TEAEs leading to discontinuation of study drug by SOC and PT
- Summary of sponsor-determined AEOSIs by category and PT

8.3. Clinical Laboratory Tests

8.3.1. Laboratory Value Definitions

Laboratory values and change from baseline values will be summarized descriptively by visit. The baseline value will be determined according to Section 4.1.3 using the nonmissing values collected before the first dose, prioritizing scheduled assessments for baseline identification over unscheduled visits. The last record before administration in the highest priority will be considered the baseline record. For baseline laboratory candidates with the same date and time in the same priority category, additional rules may be provided after consultation with the medical monitor to delineate which value will be defined as baseline.

Laboratory test values outside the normal range will be assessed for severity based on CTCAE grade or similar criteria where clinical intervention is required for CTCAE grading. The incidence of abnormal laboratory values and shift tables relative to baseline will be tabulated.

8.3.2. Laboratory Value Summaries

All test results and associated normal ranges from central laboratories will be reported in SI units. All tests with numeric values will have a unique unit per test. Any laboratory test results and associated normal ranges from local laboratories will be converted to SI units. For the limited number of cases where the associated normal ranges from a local laboratory cannot be obtained despite due diligence, associated central laboratory normal ranges will be applied. In the event that central laboratory normal ranges are not available, a set of standard normal ranges based on documented reference ranges will be applied to facilitate reporting the test results.

When there are multiple laboratory nonmissing values for a subject's particular test at a scheduled visit, the laboratory value with the smallest laboratory sequence number will be used in by-visit summaries.

Numeric laboratory values will be summarized descriptively in SI units, and non-numeric test values will be tabulated when necessary.

For test results that will be summarized with available normal ranges, the number and percentage of subjects with the laboratory values being low (but never high), normal, high (but never low), and both low and high will be calculated for each test. This shift summary will be produced for each test for the safety population. The denominator for the percentage calculation will use the number of subjects in the baseline category (ie, low, high, normal, and missing) as the denominator for the percentage in each of the categories during the treatment period.

Shift tables will be presented showing change in CTCAE grade from baseline to worst grade postbaseline. Separate summaries for abnormally high and abnormally low laboratory values

will be provided when the laboratory parameter has both high and low grading criteria. The denominator for the percentage calculation will be the number of subjects in the baseline category.

In cases where differentials of hematology parameters are obtained without corresponding absolute count data, efforts will be made to investigate if the conversion to an absolute value will lead to additional abnormalities. This will be discussed with the clinical team regarding appropriate documentation and action.

8.4. Vital Signs

Values at each scheduled visit, change, and percent change from baseline for vital signs, including systolic blood pressure, diastolic blood pressure, pulse, respiration rate, body temperature, and weight will be summarized descriptively.

Criteria for clinically notable vital sign abnormalities are defined in Table 7. The abnormal values for subjects exhibiting clinically notable vital sign abnormalities will be listed along with their assigned treatment group. Alert vital signs are defined as an absolute value outside the defined range and percentage change greater than 25%. The abnormal values for subjects exhibiting alert vital sign abnormalities will be listed.

Table 7: 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 breaths/min	< 8 breaths/min

8.5. Electrocardiograms

Twelve-lead ECGs including heart rate, PR, QRS, QT, QTc (QTcF or QTcB), and JTc (if applicable) intervals will be obtained for each subject during the study.

Criteria for clinically notable ECG abnormalities are defined in Table 8. The number of subjects with clinically significant ECGs will be summarized by treatment group. Subjects exhibiting clinically notable ECG abnormalities will also be listed with study visit and assigned treatment group. Abnormal values for subjects with alert ECG values, defined as both the absolute value and the percentage change from baseline being outside normal ranges, will be identified and listed.

Table 8: Criteria for Clinically Notable Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold
QTcF	> 450 ms	< 295 ms
PR	> 220 ms	< 75 ms
QRS	> 120 ms	< 50 ms
QT	> 500 ms	< 300 ms
RR	> 1330 ms	< 600 ms
Heart rate	> 100 bpm	< 45 bpm

QTcF = Fridericia correction.

Twelve-lead ECGs will be obtained for each subject during the study. Electrocardiogram abnormalities, both at baseline and postbaseline visits, will be tabulated by treatment group. Incidences of abnormalities will be listed with study visit, assigned treatment group, and a description of the abnormality.

9. INTERIM ANALYSES

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, interim analysis is no longer applicable.

There are no planned, formal interim analyses for Phase 1. Periodic review of accrued clinical data will be conducted by Incyte and provided to study investigators via teleconferences at the end of each part. Based on review of the most current safety data, the sponsor (in consultation with the study investigators) will determine if and at what dose additional subjects should be treated in the study.

In Phase 2, there will be 2 interim analyses for futility in the CRC and PDAC efficacy expansion cohorts. The Simon 2-stage design (Simon 1989) will be applied to each efficacy expansion cohort independently. During Stage 1, 12 CRC subjects and 15 PDAC subjects will be enrolled. If ≤ 5 responses are observed in CRC efficacy expansion cohort, the cohort will be terminated for futility. If ≥ 6 responses are observed in the CRC efficacy expansion cohort, an additional 26 CRC subjects will be enrolled for Stage 2 evaluation. Similarly, if ≤ 4 responses are observed in the PDAC efficacy expansion cohort, the cohort will be terminated for futility. If ≥ 5 responses are observed in PDAC expansion cohort, an additional 12 PDAC 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 9.

Table 9: Probability 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 probability of early termination for Stage 1 is summarized in Table 10.

Table 10: Probability of Early Termination at Stage 1 for Simon 2-Stage Design

True Response Rate	Probability of Early Termination at Stage 1	
	CRC	PDAC
25%	0.9456	0.6865
30%	0.8822	0.5155
35%	0.7873	0.3519
40%	0.6652	0.2173
45%	0.5269	0.1204
50%	0.3872	0.0592
55%	0.2607	0.0255
60%	0.1582	0.0093
65%	0.0846	0.0028
70%	0.0386	0.0007

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. CHANGES AND MODIFICATIONS TO THE ANALYSIS PLAN

All versions of the SAP are listed in Table 11.

Table 11: Statistical Analysis Plan Versions

SAP Version	Date
Original	14 NOV 2017
Amendment 1	12 MAR 2019

10.1. Changes to Protocol-Defined Analyses

Not applicable.

10.2. Changes to the Statistical Analysis Plan

10.2.1. Amendment 1

The primary purpose of this amendment is to update the statistical analyses as enrollment has been terminated for the study as of 25 OCT 2018.

- Secondary [redacted] efficacy objectives and endpoints including duration of response, progression-free survival, and overall survival per RECIST v1.1 and all efficacy objectives and endpoints per irRECIST were removed. Corresponding statistical analyses were removed.
- Safety analyses were simplified to meet the requirement of abbreviated Clinical Study Report.

11. REFERENCES

Koyama T, Chen H. Proper inference from Simon's two-stage designs. Stat Med 2008;27:3145-154.

Mosteller RD. Simplified calculation of body-surface area. N Engl J Med 1987;317:1098.

Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials 1989;10:1-10.

APPENDIX A. PLANNED TABLES AND LISTINGS

This appendix provides a list of the planned tables and listings for the Clinical Study Report. Standard tables will follow the conventions in the Standard Safety Tables v1.1. Shells are provided for nonstandard tables in a separate document. In-text tables are identical in structure and content as appendix tables, but follow a Rich Text Format.

The lists of tables and listings are to be used as guidelines. Modifications of the lists that do not otherwise affect the nature of the analysis will not warrant an amendment to the SAP.

Tables

Table No.	Title	Population
Baseline and Demographic Characteristics		
1.1 Disposition		
1.1.1	Analysis Populations	Safety
1.1.2	Summary of Subject Disposition	Safety
1.1.3	Summary of Number of Subjects Enrolled By Site	Safety
1.2 Demography		
1.2.1	Summary of Demographics	Safety
1.3 Baseline Characteristics		
1.3.1	Summary of Cancer History and Baseline Disease Characteristics	Safety
1.4 Prior Medication and Concomitant Medication		
1.4.1	Summary of Prior Systemic Cancer Therapy	Safety
1.4.2	Summary of Prior Medications	Safety
1.4.3	Summary of Concomitant Medications	Safety
1.5 Others		
1.5.1	Summary of General Medical History	Safety
1.5.2	Summary of Protocol Deviations	Safety
Safety		
3.1 Dose Exposure		
3.1.1.1	Summary of Exposure to Epacadostat	Epacadostat Safety
3.1.1.2	Summary of Exposure to Pembrolizumab	Pembrolizumab Safety
3.1.1.3	Summary of Exposure to Components of mFOLFOX6	mFOLFOX6 Safety
3.1.1.4	Summary of Exposure to *nab*-Paclitaxel and Gemcitabine	*nab*-Paclitaxel and Gemcitabine Safety
3.1.1.5	Summary of Exposure to Paclitaxel and Carboplatin	Paclitaxel and Carboplatin Safety
3.1.1.6	Summary of Exposure to Pemetrexed and Platinum Agent	Pemetrexed and Platinum Agent Safety
3.1.1.7	Summary of Exposure to Cyclophosphamide	Cyclophosphamide Safety
3.1.1.8	Summary of Exposure to Gemcitabine and Platinum Agent	Gemcitabine and Platinum Agent Safety
3.1.1.9	Summary of Exposure to 5-Fluorouracil and Platinum Agent	5-Fluorouracil and Platinum Agent Safety

Table No.	Title	Population
3.2 Adverse Events		
3.2.1	Overall Summary of Treatment-Emergent Adverse Events	Safety
3.2.2.1	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
3.2.2.2	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety
3.2.3.1	Summary of Grade 3 or 4 Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
3.2.3.2	Summary of Grade 3 or 4 Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety
3.2.4.1	Summary of any Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
3.2.4.2	Summary of any Treatment-Related Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety
3.2.5	Summary of Treatment-Emergent Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term	Safety
3.2.6	Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
3.2.7	Summary of Serious Treatment-Emergent Adverse Events by Preferred Term in Decreasing Order of Frequency	Safety
3.2.8.1	Summary of Treatment-Emergent Adverse Events Leading to any Dose Reduction By MedDRA System Organ Class and Preferred Term	Safety
3.2.8.2	Summary of Treatment-Emergent Adverse Events Leading to any Dose Interruption by MedDRA System Organ Class and Preferred Term	Safety
3.2.8.3	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug by MedDRA System Organ Class and Preferred Term	Safety
3.2.9	Summary of Sponsor-Determined Adverse Events of Special Interest by Category and MedDRA Preferred Term	Safety
3.3 Laboratory		
3.3.1	Summary of Laboratory Values - Hematology	Safety
3.3.2	Shift Summary of Hematology Laboratory Values in CTC Grade - to the Worst Abnormal Value	Safety
3.3.3	Summary of Laboratory Values - Chemistry	Safety
3.3.4	Shift Summary of Chemistry Laboratory Values in CTC Grade - to the Worst Abnormal Value	Safety
3.4 Vital Signs		
3.4.1	Summary of Pulse	Safety
3.4.2	Summary of Systolic Blood Pressure	Safety
3.4.3	Summary of Diastolic Blood Pressure	Safety
3.4.4	Summary of Respiration Rate	Safety
3.4.5	Summary of Body Temperature	Safety
3.4.6	Summary of Weight	Safety
3.5 ECG		
3.5.9	Summary of Clinically Significant ECGs	Safety

Listings

Listing No.	Title
2.1 Discontinued Subjects (Subject Disposition)	
2.1.1	Subject Enrollment and Disposition Status
2.2 Protocol Deviation	
2.2	Protocol Deviations
2.3 Data Excluded From [redacted] Efficacy, and/or Safety Analyses	
2.3	Analysis Population
2.4 Demography and Baseline (Including Prior and Concomitant Medications)	
2.4.1	Demographic and Baseline Disease Characteristics
2.4.2	Disease History
2.4.3	Prior Radiation Treatment
2.4.4	Prior Systemic Therapy
2.4.5	Prior Surgery or Surgical Procedure
2.4.6	Medical History
2.4.7	Prior and Concomitant Medication
2.5 Exposure	
2.5	Study Drug Administration
2.7 Adverse Events (and Exposure)	
2.7.1	Treatment-Emergent Adverse Events
2.7.2	Dose-Limiting Toxicities
2.7.3	Serious Treatment-Emergent Adverse Events
2.7.4	Fatal Treatment-Emergent Adverse Events
2.7.5	Treatment-Emergent Adverse Events Leading to Discontinuation of Epacadostat/Pembrolizumab
2.7.6	Treatment-Emergent Adverse Events Leading to Interruption of Epacadostat/Pembrolizumab
2.7.7	Treatment-Emergent Adverse Events Leading to Dose Reduction of Epacadostat
2.8 Laboratory Data	
2.8.1	Clinical Laboratory Values - Hematology
2.8.2	Clinical Laboratory Values - Chemistry
2.8.4	Clinical Laboratory Values - Coagulation
2.8.7	Abnormal Clinical Laboratory Values
2.8.8	Hy's Law
2.9 Vital Signs	
2.9.1	Vital Signs
2.10 ECG	
2.10.1	12-Lead ECG Values

Signature Manifest

Document Number: IC-STS-SAP-0130 **Revision:** 0

Title: INCB 24360-207 SAP Amendment 1

All dates and times are in Eastern Standard Time.

INCB 24360-207 SAP Amendment 1

Approval

Name/Signature	Title	Date	Meaning/Reason
[redacted]	[redacted]	19 Mar 2019, 02:36:01 PM	Approved
[redacted]	[redacted]	19 Mar 2019, 02:49:48 PM	Approved
[redacted]	[redacted]	22 Mar 2019, 04:02:02 PM	Approved
[redacted]	[redacted]	22 Mar 2019, 04:14:14 PM	Approved