STATISTICAL ANALYSIS PLAN

INCB 24360-206 / NCT02959437

A Phase 1/2 Study Exploring the Safety, Tolerability, Effect on the Tumor Microenvironment, and Efficacy of Azacitidine in Combination With Pembrolizumab and Epacadostat in Subjects With Advanced Solid Tumors and Previously Treated Stage IIIB or Stage IV Non–Small Cell Lung Cancer and Stage IV Microsatellite-Stable Colorectal Cancer

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SAP Author:	[redacted]
Date of Plan:	**18 JUL 2018**

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

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
BET	bromodomain and extra-terminal
BID	twice daily
BMI	body mass index
CI	confidence interval
CR	complete response
CRC	colorectal cancer
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
DNMT	deoxyribonucleic acid methyltransferase
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FDA	Food and Drug Administration
HNSCC	head and neck squamous cell carcinoma
IDO1	indoleamine 2,3-deoxygenase 1
IHC	immunohistochemistry
irAE	immune-related adverse event
IV	intravenously
KM	Kaplan-Meier
LSD1	lysine-specific demethylase 1A
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
mRNA	messenger ribonucleic acid
MSS	microsatellite stable
MTD	maximum tolerated dose
NCI	National Cancer Institute
NE	not evaluable
NSCLC	non–small-cell lung cancer
ORR	objective response rate
[redacted]	[redacted]

Abbreviation	Term
PAD	pharmacologically active dose
PD	progressive disease
PD-1	programmed death receptor-1
PFS	progression-free survival
PO	orally
[redacted]	[redacted]
PR	partial response
PT	preferred term
Q3W	every 3 weeks
QD	every day
QoD	every other day
QTcF	QT interval corrected by Fridericia
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	recommended Phase 2 dose
SC	subcutaneously
SD	stable disease
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOC	system organ class
TEAE	treatment-emergent adverse event
TIL	tumor-infiltrating lymphocyte
TNM	malignant tumors
Treg	T regulatory cell
UC	urothelial carcinoma
WHO	World Health Organization

1. INTRODUCTION

This is an open-label, multicenter, Phase 1/2 study evaluating the addition of 3 different epigenetic priming regimens to an immunotherapy doublet in subjects with advanced or metastatic solid tumors. This study will use a suite of tissue [redacted] technologies to evaluate the immune activity of the DNMT inhibitor, azacitidine; the BET inhibitor, INCB057643; or the LSD1 inhibitor, INCB059872, in combination with the PD-1 inhibitor pembrolizumab and the IDO1 inhibitor epacadostat. The first part of the study will consist of a dose-escalation assessment of the safety and tolerability of the treatments in subjects with advanced or metastatic solid tumors. Part 2 of the study will be an open-label Phase 2 assessment with Simon 2-stage design (Simon 1989) to evaluate ORR and TIL infiltration in previously treated NSCLC and MSS CRC. Separate treatment sequencing tumor biopsy cohorts are also included in the expansion to further evaluate epigenetic changes and changes in the tumor microenvironment in subjects with HNSCC, melanoma, UC, and MSS CRC.

The purpose of this SAP is to provide details of the statistical analyses that have been outlined in the Study INCB 24360-206 Protocol. The scope of this plan includes the final analyses that are planned and will be executed by the Department of Biostatistics or designee. [redacted]

2. STUDY INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on Study INCB 24360-206 Protocol Amendment 3 dated 20 OCT 2017 and CRFs approved 30 APR 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

- Part 1: To evaluate the safety and tolerability and to determine the MTD, maximum tested dose, or PAD of the combinations in subjects with advanced or metastatic solid tumors.
- Part 2: To evaluate the efficacy of the combinations in subjects with previously treated Stage IV or recurrent NSCLC, Stage IV MSS CRC, and select solid tumors by assessing ORR per RECIST v1.1 at the MTD, maximum tested dose, or PAD.

2.2.2. Secondary Objectives

- Part 1: To evaluate the efficacy of the combination in subjects with advanced or metastatic solid tumors by assessing ORR per RECIST v1.1 at the MTD, maximum tested dose, or PAD.
- Part 2: To evaluate the safety and tolerability of the combinations in subjects with previously treated Stage IV or recurrent NSCLC, Stage IV MSS CRC, and select solid tumors at the MTD, maximum tested dose, or PAD.
- Parts 1 and 2: To evaluate changes in T-cell infiltration in the tumor microenvironment with the combinations in subjects with advanced or metastatic solid tumors, previously treated Stage IV or recurrent NSCLC, and Stage IV MSS CRC.
- Parts 1 and 2: To evaluate the efficacy of the combinations in subjects with advanced or metastatic solid tumors, previously treated Stage IV or recurrent NSCLC, and Stage IV MSS CRC by assessing PFS.
- Parts 1 and 2: To evaluate the efficacy of the combinations in subjects with advanced or metastatic solid tumors, previously treated Stage IV or recurrent NSCLC, and Stage IV MSS CRC by assessing DOR.

2.3. Study Endpoints

2.3.1. Primary Endpoints

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

2.3.2. Secondary Endpoints

- Part 1: Objective response rate, defined as the percentage of subjects having a CR or PR, will be determined by investigator assessment of radiographic disease as per RECIST v1.1.
- Part 2: Safety and tolerability will be assessed by monitoring the frequency, duration, and severity of AEs; through physical examinations; by evaluating changes in vital signs and ECGs; and through clinical laboratory blood and urine sample evaluations.
- Parts 1 and 2: Percentage of responders, where a responder is defined as an increase in the number of TILs or the ratio of CD8+ lymphocytes to Tregs infiltrating tumor post-treatment versus pretreatment with pembrolizumab and epacadostat in combination with azacitidine, INCB057643, or INCB059872 evaluated by IHC, will be determined.

- Parts 1 and 2: Progression-free survival, defined as the time from date of first dose of study drug until the earliest date of disease progression, will be determined by investigator assessment of objective radiographic disease assessments per RECIST v1.1, or death due to any cause, if occurring sooner than progression.
- Parts 1 and 2: Duration of response determined by radiographic disease assessment, defined as the time from earliest date of disease response until the earliest date of disease progression as per RECIST v1.1, or death due to any cause, if occurring sooner than progression, will be determined.

3. STUDY DESIGN

3.1. Overall Study Design

This is an open-label, multicenter, Phase 1/2 study evaluating the addition of 3 different epigenetic priming regimens to an immunotherapy doublet in subjects with advanced or metastatic solid tumors.

Part 1 of the study will be an open-label Phase 1 assessment to evaluate the safety and tolerability and to determine the MTD, maximum tested dose, or PAD of the combinations in subjects with advanced or metastatic solid tumors.

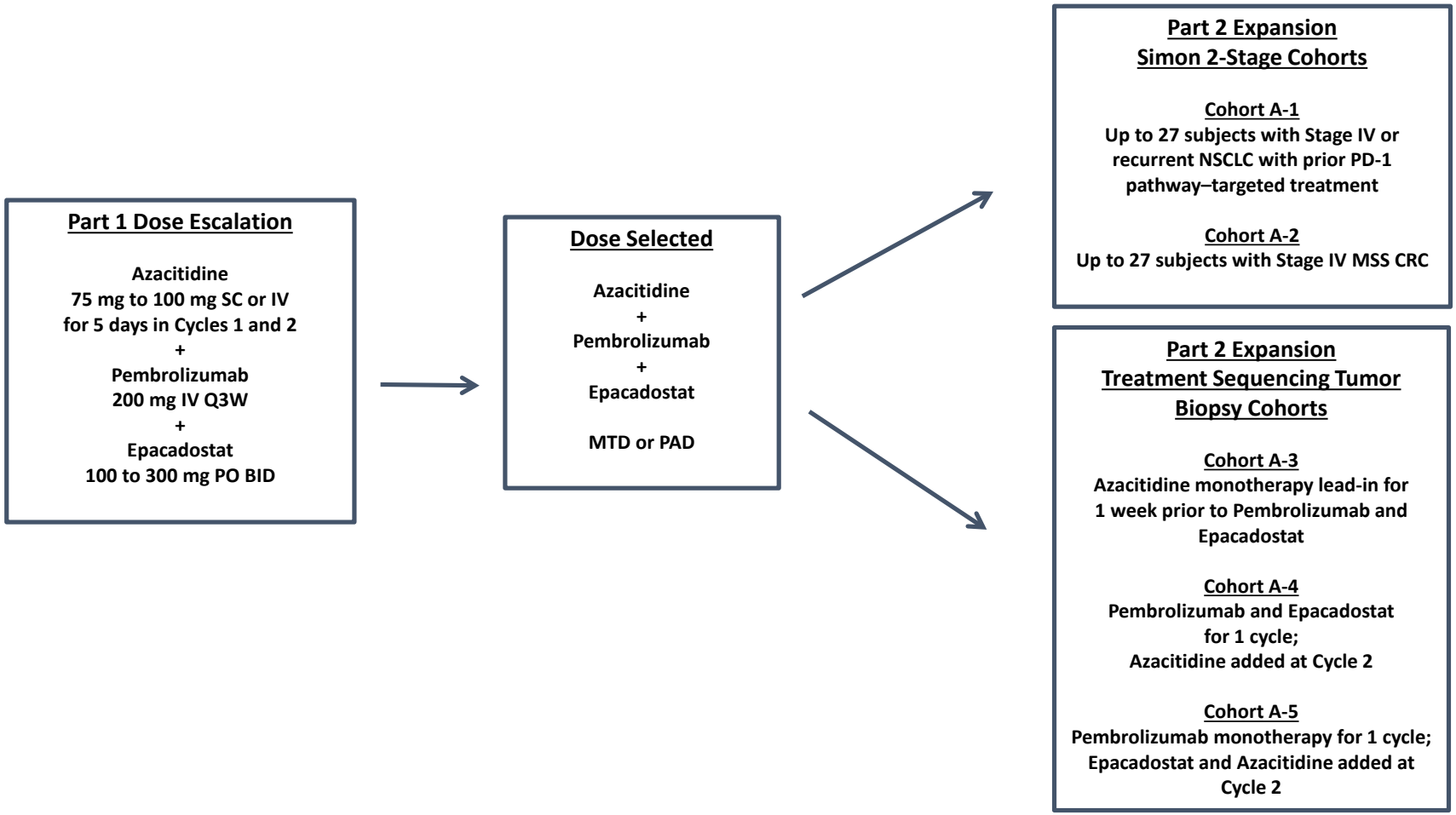
Part 2 of the study will be an open-label Phase 2 assessment with Simon 2-stage design to evaluate ORR and TIL infiltration in previously treated NSCLC and MSS CRC. Separate treatment sequencing tumor biopsy cohorts are also included in Part 2 to further evaluate epigenetic changes and changes in the tumor microenvironment in subjects with select solid tumors.

3.1.1. Treatment Groups

3.1.1.1. Treatment Group A

In Treatment Group A, subjects will receive the DNMT inhibitor azacitidine in combination with the PD-1 inhibitor pembrolizumab and the IDO1 inhibitor epacadostat. Part 1 of Treatment Group A will consist of a dose-escalation assessment of the safety and tolerability of the treatments in subjects with advanced or metastatic solid tumors. In Part 1 of Treatment Group A, pembrolizumab and epacadostat will be administered in 21-day cycles from Cycle 1 Day 1 in combination with azacitidine. Subjects in Treatment Group A will receive up to 6 cycles of azacitidine as long as the subject is receiving benefit from treatment and has not met any criteria for study withdrawal (except for Expansion Cohorts A-4 and A-5, which will receive up to 5 cycles). In Part 2 of Treatment Group A will consist of Simon 2-Stage cohorts in previously treated NSCLC and MSS CRC. Separate treatment sequencing tumor biopsy cohorts are also included in Part 2 to further evaluate epigenetic changes and changes in the tumor microenvironment in subjects with select solid tumors. In Treatment Group A, subjects who have an initial response or SD for greater than 6 months but later relapse while receiving pembrolizumab and epacadostat will have the opportunity to repeat the epigenetic priming regimen to which they were originally assigned. Study treatment may continue as long as the subject is receiving benefit and has not met any criteria for study withdrawal or until the subject has received 35 administrations of pembrolizumab (approximately 2 years), whichever occurs first. See Figure 1 for study design illustration.

Figure 1: Study Design: Treatment Group A



3.1.1.2. Treatment Groups B and C

In Treatment Group B, subjects will receive the BET inhibitor INCB057643 as a monotherapy priming regimen in Cycle 1 and then will add pembrolizumab and epacadostat on Cycle 2 Day 1. In Treatment Group C, subjects will receive the LSD1 inhibitor INCB059872 as a monotherapy priming regimen in Cycle 1 and then will add pembrolizumab and epacadostat on Cycle 2 Day 1. Part 1 of Treatment Groups B and C will consist of a dose-escalation assessment of the safety and tolerability of the treatments in subjects with advanced or metastatic solid tumors. Part 1 will also contain dose-expansion cohorts in previously treated NSCLC and MSS CRC. Following enrollment of Part 1, there will be an optional study hold for evaluation of safety, efficacy [redacted] to facilitate a go/no-go decision regarding enrollment of Part 2. Part 2 of Treatment Groups B and C will consist of Simon 2-stage cohorts in previously treated NSCLC and MSS CRC. Separate treatment sequencing tumor biopsy cohorts are also included in Part 2 to further evaluate epigenetic changes and changes in the tumor microenvironment in subjects with select solid tumors. Enrollment of the treatment sequencing tumor biopsy cohorts is contingent upon passing Stage 1 in 1 of the 2 cohorts, for each respective treatment group. Study treatment may continue as long as the subject is receiving benefit and has not met any criteria for study withdrawal or until the subject has received 35 administrations of pembrolizumab (approximately 2 years), whichever occurs first. See Figure 2 and Figure 3 for study design illustration for Treatment Groups B and C, respectively.

Figure 2: Study Design: Treatment Group B

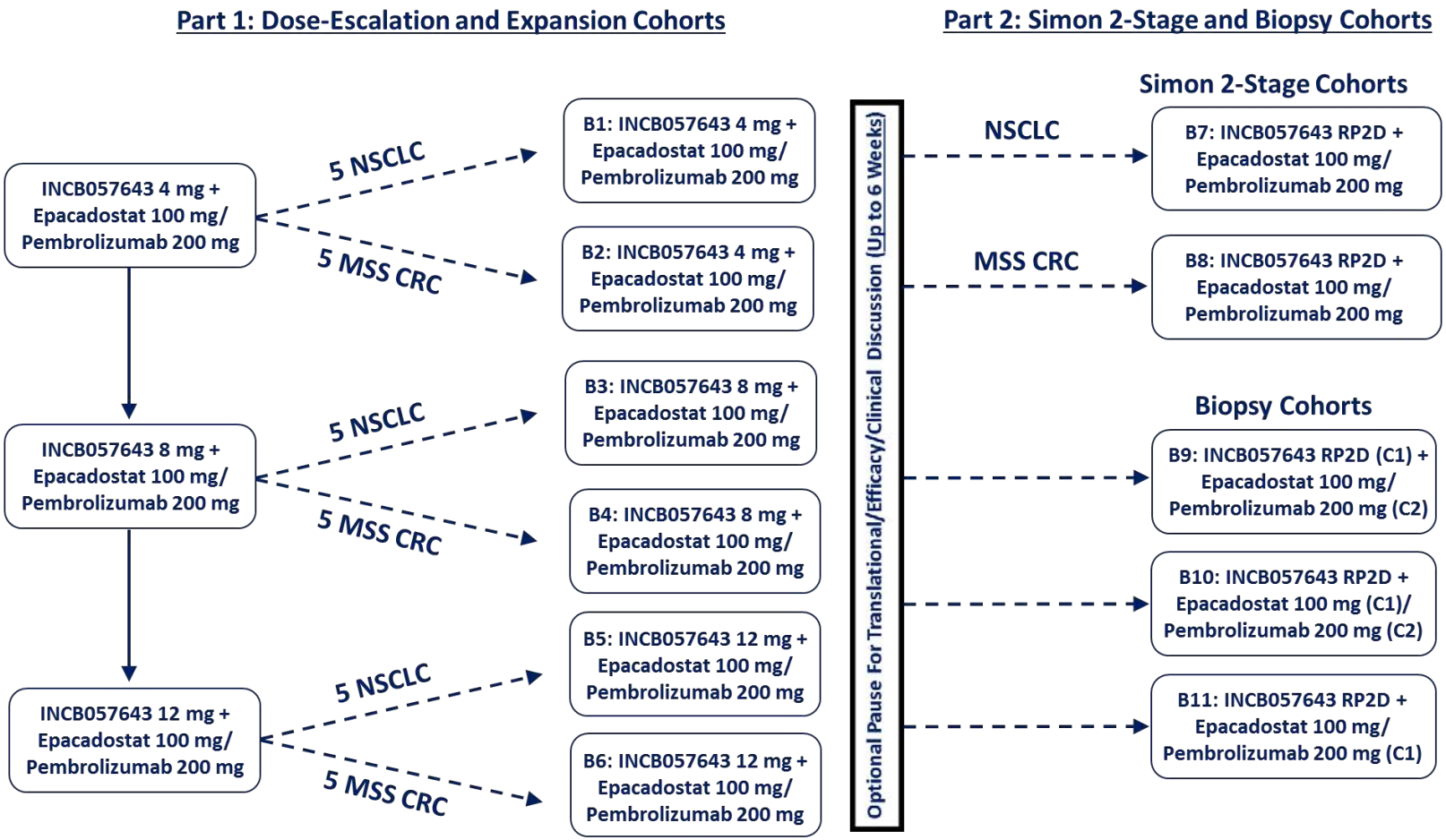
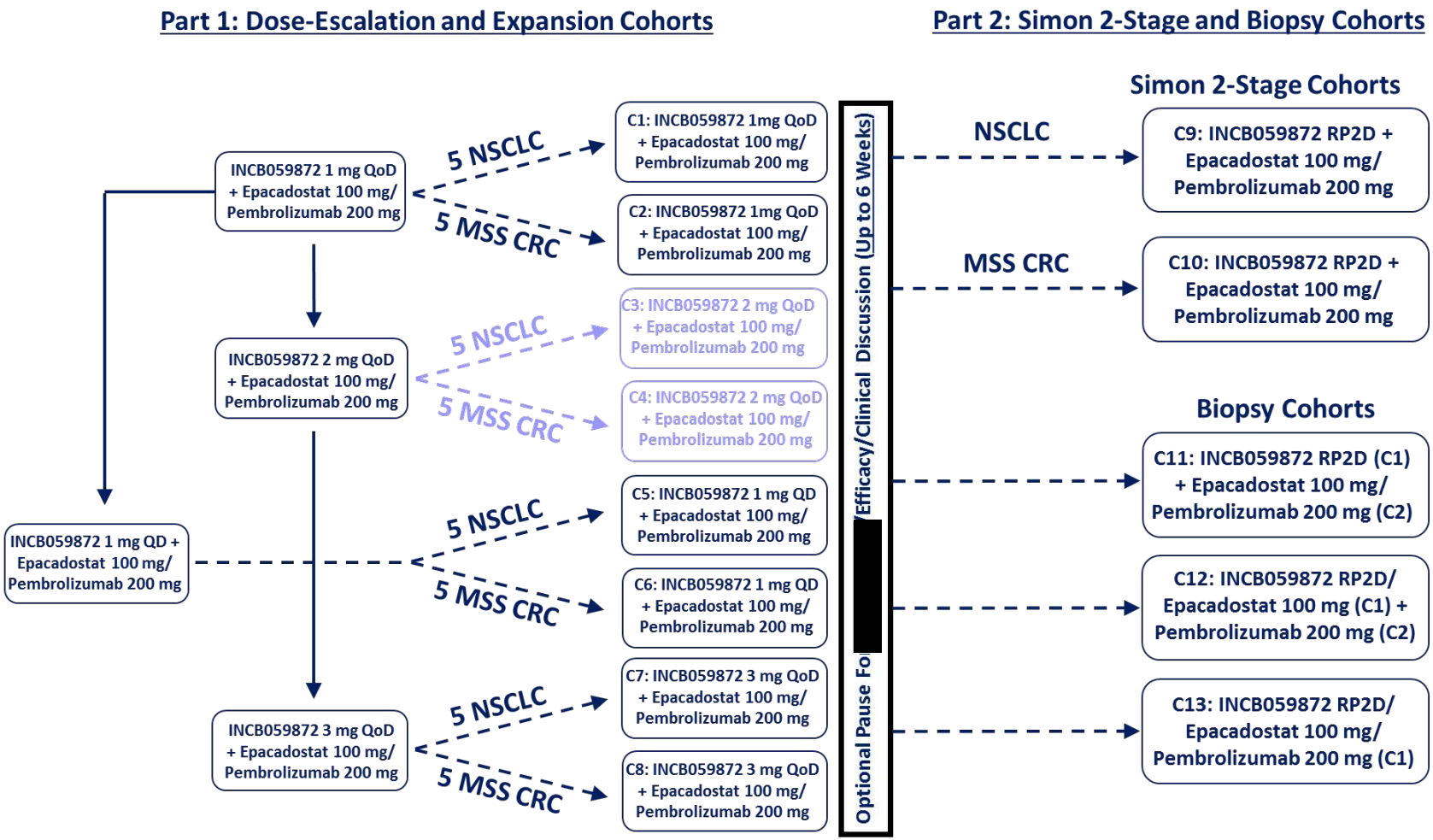


Figure 3: Study Design: Treatment Group C



3.1.2. Dose-Escalation Phase (All Treatment Groups)

A 3 + 3 + 3 design will be used to assess the MTD, maximum tested dose, or PAD of the triplet combination of azacitidine, INCB057643, or INCB059872 with pembrolizumab and epacadostat in 21-day treatment cycles. The MTD will be defined as the highest dose at which less than one-third of the subjects (with a minimum of 6 subjects) have a DLT. When the MTD, maximum tested dose, or PAD has been determined or reached, the dose will be recommended for Part 2. The Part 2 expansion will begin after the determination of the MTD, maximum tested dose, or PAD; however, enrollment priority will be given to the open Part 1 dose-escalation cohort.

A minimum of 3 subjects will initially be enrolled in Cohort 1, and each subject will be observed for 21 days from the start of triplet combination therapy before enrollment in the next cohort begins. The dose of azacitidine, INCB057643, or INCB059872 (or epacadostat) will be escalated if 0 of the first 3 evaluable subjects enrolled has a DLT. If 1 of 3 subjects in Cohort 1 has a DLT, the cohort will be expanded to 6 subjects. If 1 of 6 subjects in Cohort 1 has a DLT, a new cohort of 3 subjects will be treated at the next higher dose level (Cohort 2). If 2 of 6 subjects in Cohort 1 have a DLT, that cohort will be further expanded to a total of 9 subjects. If $\leq$ 2/9 subjects have a DLT, 3 subjects will be treated at the next higher dose level. If $\geq$ 2/3, 3/6, or 3/9 subjects have a DLT within a cohort, dose de-escalation will be required, and Cohorts -1 or -2 will be tested. The MTD is defined as the highest dose level at which $\leq$ 1/6 or $\leq$ 2/9 subjects experience a DLT.

Subjects must have received $\geq$ 75% of planned doses of study drug during the 21-day DLT (Treatment Group A) or 42-day DLT (Treatment Groups B and C) observation period or have had a DLT to be evaluable for dose tolerability (Treatment Group A: azacitidine [4 doses], epacadostat [32 doses], and pembrolizumab [1 dose]; Treatment Group B: INCB057643 [32 doses], epacadostat [32 doses], and pembrolizumab [1 dose]; Treatment Group C: INCB059872 [QD dosing, 32 doses; QoD dosing, 16 doses], epacadostat [32 doses], and pembrolizumab [1 dose]).

It is recognized that certain toxicities due to the combination agent (eg, including but not limited to gastrointestinal toxicity, including diarrhea; renal insufficiency; high-grade laboratory abnormalities; and 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 $\geq$ 75% of the prescribed dose during Cycle 1. In these cases, the principal investigators and medical monitor may assess subjects who receive dose intensities somewhat below 75% for the determination of DLTs, and consider in the adjudication process the specific toxicity encountered, the likely cause of the toxicity, and dose intensity and tolerability beyond Cycle 1. Additional subjects will be enrolled in a cohort to achieve the minimum of 3 evaluable subjects if dropouts or dose interruptions/reductions occur that result in a subject being nonevaluable for DLTs.

During the study, dose interruptions and/or dose modifications may be implemented based on toxicity as described in the Protocol, Section 5.4. However, dose modifications should not be made during the DLT observation period without discussion with the medical monitor. Intrasubject dose escalation is not permitted.

3.1.2.1. Treatment Group A: Azacitidine

Dose escalation will begin with starting doses of azacitidine 75 mg SC or IV for 5 days (5 doses may be administered over the Day 1-7 period) of the first 2 cycles, pembrolizumab 200 mg IV Q3W, and epacadostat 100 mg PO BID continuous dose administration. If the starting dose proves intolerable, then azacitidine 50 mg SC or IV for 5 days, pembrolizumab 200 mg IV Q3W, and epacadostat 100 mg PO BID will be evaluated. The cohorts and dose levels are shown in Table 1.

Table 1: Dose Levels: Treatment Group A

Cohort	Azacitidine	Pembrolizumab	Epacadostat
-2[a]	50 mg SC or IV for 5 days (5 doses over Day 1-7 period) in Cycle 1 & 2	200 mg IV Q3W	50 mg PO BID
-1[a]	50 mg SC or IV for 5 days (5 doses over Day 1-7 period) in Cycle 1 & 2	200 mg IV Q3W	100 mg PO BID
1	**75 mg SC or IV for 5 days (5 doses over Day 1-7 period) in Cycle 1 & 2**	**200 mg IV Q3W**	**100 mg PO BID**
2A[b]	75 mg SC or IV for 5 days (5 doses over Day 1-7 period) in Cycle 1 & 2	200 mg IV Q3W	300 mg PO BID
2B[b]	100 mg SC or IV for 5 days (5 doses over Day 1-7 period) in Cycle 1 & 2	200 mg IV Q3W	100 mg PO BID
3	100 mg SC or IV for 5 days (5 doses over Day 1-7 period) in Cycle 1 & 2	200 mg IV Q3W	300 mg PO BID

[a] If Cohort 1 proves intolerable, Cohort -1 may be evaluated. If Cohort -1 is not tolerable, Cohort -2 may be evaluated with epacadostat 50 mg PO BID. If a de-escalation cohort is determined to be safe and tolerable, the dose of azacitidine or epacadostat may be re-escalated in separate, additional cohorts based on the review of available safety data.

[b] For Cohort 2, escalation of azacitidine to 100 mg or epacadostat to 300 mg BID will be dependent on the observation of Grade 3 or greater immune-related or non–immune-related toxicities in Cohort 1 (toxicities that were not considered DLTs). If Grade 3 or greater immune-related toxicities are observed in Cohort 1, azacitidine will be escalated first (Cohort 2B). If nonimmune-related Grade 3 or greater toxicities are observed, epacadostat will be preferentially escalated (Cohort 2A). Dose-escalation Cohorts 2A and 2B may be opened in parallel if no Grade 3 AEs are observed in Cohort 1.

3.1.2.2. Treatment Group B: INCB057643

In Treatment Group B, dose escalation will begin with a starting dose of INCB057643 of 4 mg PO QD continuous dose administration beginning on Cycle 1 Day 1 for the first 21-day cycle. Beginning on Cycle 2 Day 1, pembrolizumab 200 mg IV Q3W and epacadostat 100 mg PO BID continuous dose administration will be added to INCB057643. If the starting dose level proves intolerable, INCB057643 4 mg PO QD in combination with pembrolizumab 200 mg IV Q3W and epacadostat 50 mg PO BID will be evaluated. The cohorts and dose levels are shown in Table 2.

Table 2: Dose Levels: Treatment Group B

Cohort	INCB057643	Pembrolizumab	Epacadostat
-1[a]	4 mg PO QD beginning C3D1	200 mg IV Q3W beginning C2D1	50 mg PO BID beginning C2D1
1	**4 mg PO QD beginning C1D1**	**200 mg IV Q3W beginning C2D1**	**100 mg PO BID beginning C2D1**
2	8 mg PO QD beginning C1D1	200 mg IV Q3W beginning C2D1	100 mg PO BID beginning C2D1
3	12 mg PO QD beginning C1D1	200 mg IV Q3W beginning C2D1	100 mg PO BID beginning C2D1

[a] If Cohort 1 proves intolerable, Cohort -1 may be evaluated. If Cohort -1 is not tolerable, lower doses or alternative dose schedules of INCB057643 may be tested; however, at this time, 4 mg tablets are the lowest dose formulation available. Any dose reduction in INCB057643 would be combined with pembrolizumab 200 mg IV Q3W and epacadostat 50 mg PO BID. If a de-escalation cohort is determined to be safe and tolerable, the dose of INCB057643 or epacadostat may be re-escalated in separate, additional cohorts based on the review of available safety data.

3.1.2.3. Treatment Group C: INCB059872

In Treatment Group C, dose escalation will begin with a starting dose of INCB059872 of 1 mg PO QoD continuous dose administration beginning on Cycle 1 Day 1 for the first 21-day cycle. Beginning on Cycle 2 Day 1, pembrolizumab 200 mg IV Q3W and epacadostat 100 mg PO BID continuous dose administration will be added to INCB059872. If the starting dose level proves intolerable, INCB059872 1 mg PO QoD in combination with pembrolizumab 200 mg IV Q3W and epacadostat 50 mg PO BID will be evaluated. The cohorts and dose levels are shown in Table 3.

Table 3: Dose Levels: Treatment Group C

Cohort	INCB059872	Pembrolizumab	Epacadostat
-1[a]	1 mg PO QoD beginning C1D1	200 mg IV Q3W beginning C2D1	50 mg PO BID beginning C2D1
1	**1 mg PO QoD beginning C1D1**	**200 mg IV Q3W beginning C2D1**	**100 mg PO BID beginning C2D1**
2A[b]	2 mg PO QoD beginning C1D1	200 mg IV Q3W beginning C2D1	100 mg PO BID beginning C2D1
2B[b]	1 mg PO QD beginning C1D1	200 mg IV Q3W beginning C2D1	100 mg PO BID beginning C2D1
3[c]	3 mg PO QoD beginning C1D1	200 mg IV Q3W beginning C2D1	100 mg PO BID beginning C2D1

[a] If Cohort 1 proves intolerable, Cohort -1 may be evaluated. If Cohort -1 is not tolerable, lower doses or alternative dose schedules of INCB059872 may be tested. Any dose reduction in INCB059872 would be combined with pembrolizumab 200 mg IV Q3W and epacadostat 50 mg PO BID. If a de-escalation cohort is determined to be safe and tolerable, the dose of INCB059872 or epacadostat may be re-escalated in separate, additional cohorts based on the review of available safety data.

[b] Dose-escalation Cohorts 2A and 2B may be opened in parallel if no Grade 3 AEs are observed in Cohort 1.

[c] Cohort 3 will be enrolled once Cohort 2A clears the DLT period. Enrollment into Cohort 3 is not dependent upon clearing the DLT period from Cohort 2B.

3.1.3. Dose-Expansion Phase

3.1.3.1. Treatment Group A

Once the safety profile of all doses tested has been characterized and the RP2D of the combination has been defined, the cohort expansion will be initiated at the RP2D. The doses selected for expansion will not exceed the MTD or maximum tested dose in Part 1.

The purpose of Phase 2 is to gather additional safety, tolerability [redacted] and preliminary efficacy information regarding the triplet combination in select tumor types where there is substantial room for improvement over mono- and doublet immunotherapies. The expansion will include:

1. Safety/efficacy cohorts in NSCLC (A-1) and MSS CRC (A-2) (2 tumor biopsies are required)
2. Treatment sequencing biopsy cohorts (3 tumor biopsies are required)
   a. A-3: azacitidine monotherapy followed by the pembrolizumab/epacadostat doublet
   b. A-4: pembrolizumab/epacadostat doublet followed by azacitidine
   c. A-5: pembrolizumab monotherapy followed by epacadostat and azacitidine

   Note: Only subjects with untreated (first-line) melanoma will be treated in the pembrolizumab monotherapy cohort (A-5).

3.1.3.1.1. Treatment Group A Safety/Efficacy Expansion Cohorts (Part 2)

Two cohorts will be evaluated as part of the safety/efficacy expansion. The eligible tumor types are NSCLC and MSS CRC. Subjects enrolled in the NSCLC tumor cohort must have had disease progression on a prior PD-1 pathway–targeted agent.

A Simon 2-stage design will be used with a stopping rule to allow for early termination of a particular cohort at the end of Stage 1 if there are insufficient responses observed. During Stage 1, 8 NSCLC subjects who progressed on a PD-1 pathway–targeted agent and 8 MSS CRC subjects will be enrolled. If no responses are observed in the NSCLC PD-1 failure and MSS CRC cohorts, the cohort(s) will be discontinued. If at least 1 response is observed in the NSCLC PD-1 failure or MSS CRC cohort, 19 additional NSCLC PD-1 failure or MSS CRC subjects will be enrolled (Stage 2), for a maximum of 27 subjects per cohort (see Table 4).

Table 4: Treatment Group A Safety/Efficacy Expansion Cohorts (Part 2)

Cohort	Treatment	Tumor Type (n)
Expansion Cohort A-1	MTD or maximum tested dose for the azacitidine + pembrolizumab + epacadostat combination.	A maximum of 27 subjects with previously treated Stage IV or recurrent NSCLC with progression on a prior PD-1 pathway–targeted agent.
Expansion Cohort A-2	MTD or maximum tested dose for the azacitidine + pembrolizumab + epacadostat combination.	A maximum of 27 subjects with previously treated Stage IV MSS CRC.

Continuous evaluation of toxicity events will be performed throughout the expansion. In the expansion, after the sixth subject in Stage 1 has been enrolled, if > 40% of subjects have an AE ≥ Grade 3 that is attributable to the investigational agents, further enrollment of subjects will be suspended until the sponsor, investigators, and regulatory authorities (if applicable) have determined the appropriate course of action. If an expansion cohort is discontinued because of toxicity, a new cohort may be initiated at a previously tested lower dose level.

3.1.3.1.2. Treatment Group A Treatment Sequencing Tumor Biopsy Cohorts (Part 2)

The sequencing biopsy cohorts require 3 tumor biopsies to identify epigenetic changes and changes in the tumor microenvironment induced by each of the components of the regimen. All subjects will have tumor biopsies at baseline and 2 additional biopsies while on study treatment.

Approximately 25 subjects will be enrolled in Expansion Cohorts A-3 and A-4, and approximately 10 subjects will be enrolled in Expansion Cohort A-5. The eligible tumor types for Expansion Cohorts A-3, A-4, and A-5 are HNSCC, melanoma, UC, and MSS CRC. In Expansion Cohorts A-3 and A-4, subjects with tumor types other than MSS CRC must have had disease progression on a prior PD-1 pathway–targeted agent.

Five to 8 evaluable subjects per tumor type in Expansion Cohorts A-3 and A-4, and 10 subjects in Expansion Cohort A-5 will initiate treatment and have tumor biopsies performed as indicated in Table 5.

Table 5: Treatment Group A Treatment Sequencing Tumor Biopsy Cohorts (Part 2)

Cohort	Treatment Sequence	Biopsy Sequence	Tumor Type (n)
Expansion Group A-3	Azacitidine monotherapy during Week -1 (5 doses), initiate pembrolizumab and epacadostat on C1D1 (after biopsy #2), 5 doses of azacitidine will be administered in Cycles 2 and 3.	Biopsy #1 at baseline. Biopsy #2 on C1D1 (window Day -5 to C1D1, biopsy before pembrolizumab/epacadostat administration). Biopsy #3 during Week 5 or 6.	HNSCC (5-8) Melanoma (5-8) UC (5-8) MSS CRC (5-8)
Expansion Group A-4	Pembrolizumab and epacadostat for 1 cycle, initiate azacitidine after biopsy #2, 5 doses of azacitidine will be administered in Cycles 2 and 3.	Biopsy #1 at baseline. Biopsy #2 on C2D1 (window C1D20 to C2D1, biopsy before azacitidine administration). Biopsy #3 during Week 8 or 9.	HNSCC (5-8) Melanoma (5-8) UC (5-8) MSS CRC (5-8)
Expansion Group A-5	Pembrolizumab monotherapy for 1 cycle, initiate epacadostat and azacitidine after biopsy #2, 5 doses of azacitidine will be administered in Cycles 2 and 3.	Biopsy #1 at baseline. Biopsy #2 on C2D1 (window C1D20 to C2D1, biopsy before epacadostat/azacitidine administration). Biopsy #3 during Week 8 or 9.	First-line melanoma (10)

Subjects in Expansion Cohort A-3 will receive up to 6 cycles of azacitidine. Subjects in Expansion Cohorts A-4 and A-5 will receive up to 5 cycles of azacitidine. The sponsor will manage enrollment so that there are approximately 5 to 8 evaluable subjects for a given tumor type. Subjects may be replaced if they have not completed all of the biopsy requirements.

3.1.3.2. Treatment Group B

3.1.3.2.1. Treatment Group B Dose Expansion Cohorts (Part 1)

Because higher doses of epigenetic priming regimens may be deleterious to immune function, expansion cohorts at each dose level tested that cleared the DLT window will be opened for signal detection [redacted] analysis to guide an RP2D. Once an RP2D is determined, this dose will be used in Part 2 in the Simon 2-stage and treatment sequencing tumor biopsy cohorts. During dose expansion, 5 NSCLC subjects who progressed on a PD-1 pathway–targeted agent and 5 MSS CRC subjects will be enrolled at each dose level with DLT clearance as detailed below.

The expansion will include:

1. Safety/efficacy cohorts in NSCLC (2 tumor biopsies are required)
    a. B-1: INCB057643 4 mg QD followed by the pembrolizumab/epacadostat doublet
    b. B-3: INCB057643 8 mg QD followed by the pembrolizumab/epacadostat doublet
    c. B-5: INCB057643 12 mg QD followed by the pembrolizumab/epacadostat doublet
2. Safety/efficacy cohorts in MSS CRC (2 tumor biopsies are required)
    a. B-2: INCB057643 4 mg QD followed by the pembrolizumab/epacadostat doublet
    b. B-4: INCB057643 8 mg QD followed by the pembrolizumab/epacadostat doublet
    c. B-6: INCB057643 12 mg QD followed by the pembrolizumab/epacadostat doublet

The following cohorts will be expanded only under certain circumstances, as listed below:

1. Cohorts B-1 and B-2: Objective responses have been seen in subjects dosed with INCB057643 at 8 and 12 mg QD and, as such, are known PADs. However, 4 mg QD dosing has not been evaluated in humans. To ensure 4 mg QD is a PAD, Cohorts B-1 and B-2 will only be enrolled if $\geq$ 1/3 of the subjects in the dose-escalation cohort have a 25% drop in platelet count from Cycle 1 Day 1 to Cycle 2 Day 1.

Continuous evaluation of toxicity events will be performed throughout the expansion cohorts. After the dose-expansion cohorts have been enrolled, beginning with the sixth patient for a specific regimen, if > 40% of subjects have an AE $\geq$ Grade 3 that is attributable to the investigational agents, further enrollment of subjects will be suspended until the sponsor, investigators, and regulatory authorities (if applicable) have determined the appropriate course of action. If an expansion cohort is discontinued because of toxicity, a new cohort may be initiated at a previously tested lower dose level.

Following completed enrollment of the safety/efficacy expansion cohorts, there will be an optional 8-week pause to utilize [redacted] data for RP2D determination. During this time period, no subject enrollment may be allowed. If there is no evidence of clinical efficacy [redacted] in the dose-expansion cohorts, enrollment in the respective treatment group will be stopped prior to Part 2.

3.1.3.2.2. Treatment Group B Simon 2-Stage Cohorts (Part 2)

Following safety, efficacy, [redacted] data evaluation, an RP2D will be determined. A Simon 2-stage design will be used with a stopping rule to allow for early termination of a particular cohort at the end of Stage 1 if there are insufficient responses observed. During Stage 1, 8 NSCLC subjects who progressed on a PD-1 pathway–targeted agent and 8 MSS CRC subjects will be enrolled. If no responses are observed in the NSCLC PD-1 failure and MSS CRC cohorts, the cohort(s) will be discontinued. If at least 1 response is observed in the NSCLC PD-1 failure or MSS CRC cohort, 19 additional NSCLC PD-1 failure or MSS CRC subjects will be enrolled (Stage 2), for a maximum of 27 subjects per cohort (see Table 6).

Table 6: Treatment Group B Safety/Efficacy Expansion Cohorts (Part 2)

Cohort	Treatment	Tumor Type (n)
Expansion Cohort B-7	MTD, maximum tested dose, or PAD for the INCB057643 + pembrolizumab + epacadostat combination.	A maximum of 27 subjects with previously treated Stage IV or recurrent NSCLC with progression on a prior PD-1 pathway-targeted agent.
Expansion Cohort B-8	MTD, maximum tested dose, or PAD for the INCB057643 + pembrolizumab + epacadostat combination.	A maximum of 27 subjects with previously treated Stage IV MSS CRC.

3.1.3.2.3. Treatment Group B Treatment Sequencing Tumor Biopsy Cohorts (Part 2)

The sequencing biopsy cohorts require 3 tumor biopsies (except for Cohort B-11, which requires 2 tumor biopsies) to identify epigenetic changes and changes in the tumor microenvironment induced by each of the components of the regimen. All subjects will have tumor biopsies at baseline and 2 additional biopsies while on study treatment.

If Stage 1 is passed in Cohort B-7 or B-8, approximately 25 subjects will be enrolled in Expansion Cohorts B-9, B-10, and B-11. The eligible tumor types for Expansion Cohorts B-9, B-10, and B-11 are HNSCC, melanoma, UC, and MSS CRC. In Expansion Cohorts B-9, B-10, and B-11, subjects with tumor types other than MSS CRC must have had disease progression on a prior PD-1 pathway–targeted agent.

Five to 8 evaluable subjects per tumor type in Expansion Cohorts B-9, B-10, and B-11 will initiate treatment and have tumor biopsies performed as indicated in Table 7.

Table 7: Treatment Group B Treatment Sequencing Tumor Biopsy Cohorts (Part 2)

Cohort	Treatment Sequence	Biopsy Sequence	Tumor Type (n)
Expansion Cohort B-9	INCB057643 continuous monotherapy during C1, initiate pembrolizumab and epacadostat on C2D1 after biopsy #2.	Biopsy #1 at baseline. Biopsy #2 on C2D1 (window C1D15 to C2D1, biopsy before pembrolizumab/ epacadostat administration). Biopsy #3 during Week 8 or 9.	HNSCC (5-8) Melanoma (5-8) UC (5-8) MSS CRC (5-8)
Expansion Cohort B-10	INCB057643 and epacadostat for 1 cycle, initiate pembrolizumab after biopsy #2.	Biopsy #1 at baseline. Biopsy #2 on C2D1 (window C1D15 to C2D1, biopsy before pembrolizumab administration). Biopsy #3 during Week 8 or 9.	HNSCC (5-8) Melanoma (5-8) UC (5-8) MSS CRC (5-8)
Expansion Cohort B-11	INCB057643, epacadostat, and pembrolizumab beginning C1.	Biopsy #1 at baseline. Biopsy #2 during Week 5 or 6.	HNSCC (5-8) Melanoma (5-8) UC (5-8) MSS CRC (5-8)

The sponsor will manage enrollment so that there are 5 to 8 evaluable subjects for a given tumor type. Subjects may be replaced if they have not completed all of the biopsy requirements.

3.1.3.3. Treatment Group C

3.1.3.3.1. Treatment Group C Dose Expansion Cohorts (Part 1)

Because higher doses of epigenetic priming regimens may be deleterious to immune function, expansion cohorts at each dose level tested that clear the DLT window will be opened for signal detection [redacted] analysis to guide an RP2D. Once an RP2D is determined, this dose will be used in Part 2 in the Simon 2-stage and treatment sequencing tumor biopsy cohorts. During dose expansion, 5 NSCLC subjects who progressed on a PD-1 pathway–targeted agent and 5 MSS CRC subjects will be enrolled at each dose level with DLT clearance as detailed below.

The expansion will include:

1. Safety/efficacy cohorts in NSCLC (2 tumor biopsies are required)
    a. C-1: INCB059872 1 mg QoD followed by the pembrolizumab/epacadostat doublet
    b. C-3: INCB059872 2 mg QoD followed by the pembrolizumab/epacadostat doublet
    c. C-5: INCB059872 1 mg QD followed by the pembrolizumab/epacadostat doublet
    d. C-7: INCB059872 3 mg QoD followed by the pembrolizumab/epacadostat doublet
2. Safety/efficacy cohorts in MSS CRC (2 tumor biopsies are required)
    a. C-2: INCB059872 1 mg QoD followed by the pembrolizumab/epacadostat doublet
    b. C-4: INCB059872 2 mg QoD followed by the pembrolizumab/epacadostat doublet
    c. C-6: INCB059872 1 mg QD followed by the pembrolizumab/epacadostat doublet
    d. C-8: INCB059872 3 mg QoD followed by the pembrolizumab/epacadostat doublet

The following cohorts will be expanded only under certain circumstances, as listed below:

1. Cohorts C-1, C-2, C-5, and C-6: Objective responses have been seen in subjects dosed with INCB059872 2 and 3 mg QoD and above and, as such, are PADs. However, 1 mg QoD has not been evaluated in humans, and there is no objective data to show that 1 mg QD is a PAD. To ensure that 1 mg QD and 1 mg QoD are PADs, Cohorts C-1, C-2, C-5, and C-6 will only be enrolled if ≥ 1/3 of the subjects in the dose-escalation cohorts have a 25% drop in platelet count from Cycle 1 Day 1 to Cycle 2 Day 1.
2. Cohorts C-3 and C-4 will only be expanded if both of the following occur:
    a. The INCB059872 1 mg QD cohort does not clear its DLT window or is deemed not tolerated for reasons outside of strict DLT criteria.
    b. The INCB059872 2 mg QoD cohort clears its DLT window and is deemed to have acceptable tolerability.

Continuous evaluation of toxicity events will be performed throughout the expansion cohorts. After the dose-expansion cohorts have been enrolled, beginning with the sixth patient for a specific regimen, if > 40% of subjects have an AE ≥ Grade 3 that is attributable to the investigational agents, further enrollment of subjects will be suspended until the sponsor, investigators, and regulatory authorities (if applicable) have determined the appropriate course of action. If an expansion cohort is discontinued because of toxicity, a new cohort may be initiated at a previously tested lower dose level.

Following completed enrollment of the safety/efficacy expansion cohorts, there will be an optional 8-week pause to utilize [redacted] data for RP2D determination. During this time period, no subject enrollment may be allowed. If there is no evidence of clinical efficacy [redacted] in the dose-expansion cohorts, enrollment in the respective treatment group will be stopped prior to Part 2.

3.1.3.3.2. Treatment Group C Simon 2-Stage Cohorts (Part 2)

Following safety, efficacy, [redacted] data evaluation, an RP2D will be determined. A Simon 2-stage design will be used with a stopping rule to allow for early termination of a particular cohort at the end of Stage 1 if there are insufficient responses observed. During Stage 1, 8 NSCLC subjects who progressed on a PD-1 pathway–targeted agent and 8 MSS CRC subjects will be enrolled. If no responses are observed in the NSCLC PD-1 failure and MSS CRC cohorts, the cohort(s) will be discontinued. If at least 1 response is observed in the NSCLC PD-1 failure or MSS CRC cohort, 19 additional NSCLC PD-1 failure or MSS CRC subjects will be enrolled (Stage 2), for a maximum of 27 subjects per cohort (see Table 8).

Table 8: Treatment Group C Safety/Efficacy Expansion Cohorts (Part 2)

Cohort	Treatment	Tumor Type (n)
Expansion Cohort C-9	MTD, maximum tested dose, or PAD for the INCB059872 + pembrolizumab + epacadostat combination.	A maximum of 27 subjects with previously treated Stage IV or recurrent NSCLC with progression on a prior PD-1 pathway–targeted agent.
Expansion Cohort C-10	MTD, maximum tested dose, or PAD for the INCB059872 + pembrolizumab + epacadostat combination.	A maximum of 27 subjects with previously treated Stage IV MSS CRC.

3.1.3.3.3. Treatment Group C Treatment Sequencing Tumor Biopsy Cohorts (Part 2)

The sequencing biopsy cohorts require 3 tumor biopsies (except for Cohort C-13, which requires 2 tumor biopsies) to identify epigenetic changes and changes in the tumor microenvironment induced by each of the components of the regimen.

If Stage 1 is passed in Cohort C-9 or C-10, approximately 25 subjects will be enrolled in Expansion Cohorts C-11, C-12, and C-13. The eligible tumor types for Expansion Cohorts C-11, C-12, and C-13 are HNSCC, melanoma, UC, and MSS CRC. In Expansion Cohorts C-11, C-12, and C-13, subjects with tumor types other than MSS CRC must have had disease progression on a prior PD-1 pathway–targeted agent.

Five to 8 evaluable subjects per tumor type in Expansion Cohorts C-11, C-12, and C-13 will initiate treatment and have tumor biopsies performed as indicated in Table 9.

Table 9: Treatment Group C Treatment Sequencing Tumor Biopsy Cohorts (Part 2)

Cohort	Treatment Sequence	Biopsy Sequence	Tumor Type (n)
Expansion Cohort C-11	INCB059872 continuous monotherapy during C1, initiate pembrolizumab and epacadostat on C2D1 (after biopsy #2).	Biopsy #1 at baseline. Biopsy #2 on C2D1 (window C1D15 to C2D1, biopsy before pembrolizumab/epacadostat administration). Biopsy #3 during Week 8 or 9.	HNSCC (5-8) Melanoma (5-8) UC (5-8) MSS CRC (5-8)
Expansion Cohort C-12	INCB059872 and epacadostat for 1 cycle, initiate pembrolizumab after biopsy #2.	Biopsy #1 at baseline. Biopsy #2 on C2D1 (window C1D15 to C2D1, biopsy before pembrolizumab administration). Biopsy #3 during Week 8 or 9.	HNSCC (5-8) Melanoma (5-8) UC (5-8) MSS CRC (5-8)
Expansion Cohort C-13	INCB059872, epacadostat and pembrolizumab beginning C1.	Biopsy #1 at baseline. Biopsy #2 during Week 5 or 6	HNSCC (5-8) Melanoma (5-8) UC (5-8) MSS CRC (5-8)

The sponsor will manage enrollment so that there are 5 to 8 evaluable subjects for a given tumor type. Subjects may be replaced if they have not completed all of the biopsy requirements.

3.1.4. Re-Treatment

3.1.4.1. Re-Treatment With Pembrolizumab or the Combination

Subjects who stop pembrolizumab or the combination with SD, PR, or CR may be eligible for up to an additional 17 cycles (approximately 1 year) of additional combination therapy or pembrolizumab if they experience disease progression after stopping the combination treatment or pembrolizumab. Re-treatment with pembrolizumab or the combination must be discussed and approved by the medical monitor. [redacted]

3.1.4.2. Re-Treatment With Azacitidine, INCB057643, or INCB059872

Re-treatment with azacitidine, INCB057643, or INCB059872 (based on original treatment assignment) along with pembrolizumab and epacadostat may be administered for subjects who had a CR, PR, or SD (for > 6 months) and later had evidence of PD while receiving pembrolizumab and epacadostat. Three additional cycles of azacitidine are permitted (for subjects originally enrolled in Treatment Group A). Cycle 1 Day 1 (or Day 1 of Week -1 for Expansion Cohort A-3) must be no more than 28 days after the subject has signed the ICF.

3.2. Randomization

Not applicable.

3.3. Control of Type I Error

For the primary efficacy endpoint in the Part 2 Simon 2-stage cohorts, the 1-sided Type I error will be controlled at 0.05 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.

3.4. Sample Size Considerations

3.4.1. Sample Size in Part 1

3.4.1.1. Part 1 Dose Escalation

In Part 1, a 3 + 3 + 3 design will be used to assess the primary objective of determining the MTD, maximum tested dose, or PAD of the triplet combination of azacitidine, INCB057643, or INCB059872 with pembrolizumab and epacadostat in 21-day treatment cycles. Based on the 3 + 3 + 3 design algorithm, a minimum of 3 subjects and up to 9 subjects will be enrolled at each dose level. The total number of subjects will depend on the frequency of DLTs and number of dose levels tested before the MTD, maximum tested dose, or PAD is established.

3.4.1.2. Part 1 Dose Expansion

In addition to the dose-escalation cohorts, dose-expansion cohorts for Treatment Groups B and C in 5 NSCLC subjects who progressed on a PD-1 pathway–targeted agent and 5 MSS CRC subjects will be opened at each dose level tested that clears the DLT window for signal detection [redacted] analysis to guide an RP2D. See Sections 3.1.3.2.1 and 3.1.3.3.1 for Treatment Group B and C dose-expansion cohorts, respectively.

3.4.2. Sample Size in Part 2 Safety/Efficacy Expansion Cohorts

3.4.2.1. Part 2 Simon 2-Stage Cohorts

The safety/efficacy expansion in Part 2 will include 2 cohorts per treatment group, subjects with NSCLC who have had disease progression on a prior PD-1 pathway–targeted agent and subjects with MSS CRC. A Simon 2-stage design will be used for each of the cohorts (Simon 1989). 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 10. The calculation is based on a 1-sided Type I error of 0.05 and power of 80%.

Table 10: Simon 2-Stage Design

Cohort	Tumor Type	p_0	p_1	n_1	n_2	n	r_1	r
Expansion Cohort A-1	NSCLC subjects who have had disease progression on a prior PD-1 pathway-targeted agent	3%	20%	8	19	27	0	2
Expansion Cohort A-2	MSS CRC	3%	20%	8	19	27	0	2
Expansion Cohort B-7	NSCLC subjects who have had disease progression on a prior PD-1 pathway–targeted agent	3%	20%	8	19	27	0	2
Expansion Cohort B-8	MSS CRC	3%	20%	8	19	27	0	2
Expansion Cohort C-9	NSCLC subjects who have had disease progression on a prior PD-1 pathway–targeted agent	3%	20%	8	19	27	0	2
Expansion Cohort C-10	MSS CRC	3%	20%	8	19	27	0	2

3.4.2.2. Part 2 Treatment Sequencing Tumor Biopsy Cohorts

Three treatment sequencing tumor biopsy cohorts per treatment group will be enrolled to evaluate epigenetic and tumor microenvironment changes. Five to 8 evaluable subjects per each tumor type will be enrolled in Expansion Cohorts A-3, A-4, B-9 through B-11, and C-11 through C-13. The eligible tumor types are HNSCC, melanoma, UC, and MSS CRC. Subjects with tumor types other than MSS CRC must have had disease progression on a prior PD-1 pathway–targeted agent. Ten subjects with first-line melanoma will be enrolled in Expansion Cohort A-5. See Table 5, Table 7, and Table 9 for more details regarding treatment sequences and biopsy sequences for Treatment Groups A, B, and C, respectively.

Assuming the true rate of subjects positive for the biomarker is 70%, the probability of observing 16 or more subjects out of 25 subjects with the biomarker is 81% for Expansion Cohorts A-3, A-4, B-9 through B-11, and C-11 through C-13, and the probability of observing 6 or more subjects out of 10 subjects with the biomarker is 85% for Expansion Cohort A-5.

3.5. Schedule of Assessments

See Protocol Amendment 3 dated 20 OCT 2017 for a full description of all study procedures and assessment schedules for this study.

4. DATA HANDLING DEFINITIONS AND CONVENTIONS

4.1. General Considerations

Due to the early termination of the study, only subjects in Treatment Group A have been enrolled. No analyses on Treatment Groups B and C will be conducted.

4.2. Scheduled Study Evaluations and Study Periods

4.2.1. Day 1

For Expansion Group A-3, Day 1 is the date that the first dose of epacadostat or pembrolizumab is administered to subjects.

For all other treatment groups, Day 1 is the date that the first dose of any study drug (epacadostat, pembrolizumab, or azacitidine) is administered to subjects.

4.2.2. 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.

4.2.3. Baseline Value

Baseline is the last nonmissing measurement obtained before the first administration of any study drug (epacadostat, pembrolizumab, or azacitidine) is administered to subjects.

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.

4.2.4. 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.

4.2.5. Cycle Length and Duration

For Treatment Group A, Cycle 1 Day 1 is the day that the first dose of pembrolizumab is administered. Scheduled cycle length is 21 days. Actual Day 1 of subsequent cycles will correspond with the first day of administration of pembrolizumab for Treatment Group A in that cycle; thus, treatment cycles may become out of sync with the originally planned schedule, and cycle length may be different from 21 days (± 3-day window for subsequent cycles). The date of Day 1 of subsequent cycles recorded on the eCRF will be used as Day 1 of the subsequent cycles.

4.3. Variable Definitions

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

4.3.1. 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 informed consent form, 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 in the eCRF, the reported age will substitute for the calculated age.

4.3.2. Body Mass Index

Body mass index will be calculated as follows:

BMI (kg/m^2) = [weight (kg)] / [height (m)]^2.

4.3.3. Prior and Concomitant Medication

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

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

- Before the date of first administration of epacadostat, pembrolizumab, or azacitidine, 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 azacitidine 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 azacitidine. 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, figures, 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. Summary tables and figures will be provided only for initial treatment phase. Only listings will be provided for re-treatment phase, if applicable.

5.2. Treatment Groups

This is an open-label, multicenter, Phase 1/2 study evaluating the addition of an epigenetic priming regimen to an immunotherapy doublet in subjects with advanced or metastatic solid tumors. The study will be conducted in 2 parts.

Due to the stop of study enrollment, only subjects in Treatment Group A have been enrolled into Parts 1 and 2. Data from Parts 1 and 2 for Treatment Group A will be summarized together by dose level. The dose levels for Treatment Group A are shown in Table 1.

5.3. Analysis Populations

5.3.1. Response Evaluable Population

The response evaluable population includes all subjects enrolled in the study who received at least 1 dose of study drug (epacadostat, pembrolizumab, or azacitidine), completed a baseline scan, and met at least 1 of the following criteria:

- The subject has ≥ 1 postbaseline scan.
- The subject has been on study for a minimum of 70 days of follow-up.
- The subject has discontinued from treatment.

All RECIST-based response analyses will be conducted using the response evaluable population.

5.3.2. Safety Population

The safety population includes all subjects enrolled in the study who received at least 1 dose of study drug (epacadostat, pembrolizumab, or azacitidine). All safety analyses will be conducted using the safety population.

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

- Epacadostat safety population
- Pembrolizumab safety population
- Azacitidine safety population

6. BASELINE, EXPOSURE, AND DISPOSITION VARIABLES AND ANALYSES

Appendix A provides a list of planned tables and listings.

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

6.1.1. Demographics

The following demographics will be summarized for the safety population by dose level for Treatment Group A in Parts 1 and 2 combined: age, sex, race, and ethnicity.

6.1.2. Baseline Disease Characteristics and Disease History

Primary diagnosis, TNM staging, stage at diagnosis, current stage, disease histology, and primary site of disease will be summarized for all subjects in the safety population by dose level for Treatment Group A in Parts 1 and 2 combined.

ECOG performance status will be summarized for all subjects in the safety population by dose level for Treatment Group A in Parts 1 and 2 combined.

6.1.3. Prior Therapy

Number of prior systemic cancer therapy regimens will be summarized for all subjects in the safety population by dose level for Treatment Group A in Parts 1 and 2 combined. 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 dose level for Treatment Group A in Parts 1 and 2 combined. 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 dose level for Treatment Group A in Parts 1 and 2 combined. Date and description of the surgery/procedure will be listed.

6.1.4. Medical History

Medical history will be summarized for all subjects in the safety population by dose level for Treatment Group A in Parts 1 and 2 combined. This summation will include the number and percentage of subjects with significant medical history for each body SOC as documented on the eCRF.

6.2. Disposition of Subjects

The number and percentage of subjects who entered the initial treatment phase, the initial follow-up phase, the re-treatment phase, and the re-treatment follow-up phase will be summarized. Under each phase (initial treatment phase and re-treatment phase), the number and percentage of subjects who discontinued study treatment with primary reason for discontinuation and withdrew from the study with a primary reason for study withdrawal will be summarized for all subjects in the safety population by dose level for Treatment Group A in Parts 1 and 2 combined. The number of subjects enrolled by site will also be provided for the safety population by dose level for Treatment Group A in Parts 1 and 2 combined.

6.3. Protocol Deviations and Violations

Protocol deviations and violations recorded on the eCRF will be presented in the subject data listings. If data warrant, protocol deviations and violations will be summarized descriptively.

6.4. Exposure

For subjects in the safety population, exposure to epacadostat, pembrolizumab, and azacitidine will be summarized descriptively.

6.4.1. Exposure for Epacadostat

Exposure for epacadostat will be summarized as follows:

- **Duration of treatment (days):** Date of last dose of epacadostat – date of first dose of epacadostat + 1.
- **Average daily dose (mg/day):** Total dose administered (mg) / duration of treatment (days).
- Number and percentage of subjects with 0 to 3, > 3, > 6, and > 9 months duration of exposure.

6.4.2. Exposure for Pembrolizumab

Exposure for pembrolizumab will be summarized as follows:

- **Total number of infusions:** Total number of infusions per subject with a nonzero dose of pembrolizumab.
- **Total dose administered (mg):** Sum of the cumulative dose of pembrolizumab that has been administered.

  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

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

- **Duration of treatment (days):** Date of last dose of pembrolizumab – date of first dose of pembrolizumab + 1.

6.4.3. Exposure for Azacitidine

Exposure for azacitidine will be summarized as follows:

- **Total number of administrations:** Total number of infusions and injections per subject with a nonzero dose of azacitidine.
- **Total dose administered (mg):** Sum of the cumulative dose of azacitidine that has been administered.

  For an infusion/injection i, let C_i be the concentration (mg/mL) of azacitidine and V_i be the total volume administered (mL) reported on the azacitidine dosing eCRF if the ith administration is through IV; let M_i be the actual dose administered (mg) if the ith administration is through SC. Let

$$I_{IV,i} = \begin{cases} 1, & \text{administered through IV} \\ 0, & \text{administered through SC} \end{cases},$$

$$I_{SC,i} = \begin{cases} 1, & \text{administered through SC} \\ 0, & \text{administered through IV} \end{cases},$$

  Suppose N is the total number of infusions and injections,

$$\text{Total dose administered (mg)} = \sum_{i=1}^{N}(C_i \times V_i \times I_{IV,i} + M_i \times I_{SC,i})$$

- **Average dose (mg):** Total dose administered (mg) / total number of injections and infusions.
- **Duration of treatment (days):** Date of last dose of azacitidine – date of first dose of azacitidine + 1.

6.5. Study Drug Compliance

For subjects in the safety population, overall compliance (%) for epacadostat will be calculated for all subjects as

Compliance (%) = 100 × [total dose actually taken] / [total prescribed dose].

The total prescribed dose is defined as the sum of the doses prescribed by the investigator accounting for dose modifications.

The total actual dose taken will be calculated based on information entered on the drug accountability eCRF. If there is dispensed drug that has not been returned yet, this dispensed drug kit will not be considered.

Compliance calculations are not necessary for IV or SC administered agents (eg, pembrolizumab and azacitidine).

6.6. 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 PT and WHO drug class.

7. EFFICACY

A list of planned tables and listings is provided in Appendix A.

7.1. General Considerations

Efficacy endpoints of this study include ORR, DOR, PFS and OS by investigator assessment based on RECIST v1.1. Listings of response assessment at each visit will be provided.

7.2. Analysis of the Efficacy Parameters

7.2.1. 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.

7.2.2. 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. CIs 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 data to ascertain response will be included in the denominators in the calculation of ORR.

In general, the best response is determined on subject level 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 days (9 weeks – 7-day window). 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.

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 of study drug at a minimum of 56 days (9 weeks – 7-day window). 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 11 can be used to determine the overall disease status at a given time point based on the target lesion, nontarget lesion, and new lesion assessment.

Table 11: 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

7.2.3. Duration of Response

Duration of response will be assessed by RECIST v1.1.

Censoring of DOR will follow the same algorithm as the censoring of PFS. The KM estimate of median DOR will be presented with its 95% CI. The 95% CI will be calculated using Brookmeyer and Crowley's method (1982).

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

For each subject in the response evaluable 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.

Per RECIST v1.1, 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.

7.2.5. Progression-Free Survival

Progression-free survival will be assessed by RECIST v1.1.

Censoring for PFS will follow the algorithm outlined in Table 12, which is based on the FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA 2007).

The KM estimate of median PFS will be presented with its 95% CI. The 95% CI will be calculated using Brookmeyer and Crowley's method (1982).

Table 12: Evaluation and Censoring of Progression-Free Survival

Situation	Outcome	Date of Progression or Censoring
No baseline tumor assessments	Censored	Date of Day 1
No valid postbaseline response assessments	Censored	Date of Day 1
Progression documented between scheduled response assessments	Progressed	Date of first overall response of PD
No progression	Censored	Date of last valid radiologic assessment (not NE and not missing)
Study discontinuation for undocumented progression	Censored	Date of last valid radiologic assessment (not NE and not missing)
Study discontinuation for toxicity or other reason	Censored	Date of last valid radiologic assessment (not NE and not missing)
New anticancer treatment started	Censored	Date of last valid radiologic assessment (not NE and not missing) on/before starting a new anticancer treatment.
Death before first progressive response assessment	Progressed	Date of death
Death between adequate response assessments	Progressed	Date of death
Death or progression after more than 1 missed assessment	Censored	Date of last valid radiologic assessment (not NE and not missing) prior to death

Under RECIST v1.1, PFS is defined as the length of time between the baseline visit (Day 1) and the earlier of death or first assessment of PD. Date of death will be determined using the Death Report, Survival Follow-Up, and Subject Status eCRFs.

8. SAFETY AND TOLERABILITY

A list of planned tables and listings is provided in Appendix A.

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 the first dose of study drug (epacadostat, pembrolizumab, and azacitidine). 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 drug will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study drug, the AE will be considered to be treatment-related. The incidence of AEs and treatment-related AEs will be tabulated. In addition, SAEs 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 Part 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. Adverse Events of Special Interest

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

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

8.2.5. Adverse Event Summaries

An overall summary of AEs by dose level in Treatment Group A will include:

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

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 TEAEs by SOC, PT, and maximum severity
- Summary of Grade 3 or 4 TEAEs by SOC and PT
- Summary of epacadostat treatment-related AEs by SOC and PT
- Summary of pembrolizumab treatment-related AEs by SOC and PT
- Summary of azacitidine treatment-related AEs by SOC and PT
- 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 descending order of frequency
- Summary of nonserious TEAEs by SOC and PT
- Summary of TEAEs leading to epacadostat dose reduction by SOC and PT
- Summary of TEAEs leading to azacitidine dose reduction by SOC and PT
- Summary of TEAEs leading to epacadostat dose interruption by SOC and PT
- Summary of TEAEs leading to pembrolizumab dose interruption by SOC and PT
- Summary of TEAEs leading to azacitidine dose interruption by SOC and PT
- Summary of TEAEs leading to discontinuation of epacadostat by SOC and PT
- Summary of TEAEs leading to discontinuation of pembrolizumab by SOC and PT
- Summary of TEAEs leading to discontinuation of azacitidine by SOC and PT
- An overall summary of treatment-emergent irAEs

8.3. Clinical Laboratory Tests

8.3.1. Laboratory Value Definitions

Laboratory values and change from baseline values will be summarized descriptively by visit. Baseline will be determined according to Section 4.2.3. If there are multiple values that meet the criteria for baseline, 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, central laboratory values have higher priority over local laboratory values. If a tie still exists, 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, 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 pulse, systolic blood pressure, diastolic blood pressure, respiration rate, body temperature, and weight will be summarized descriptively.

Criteria for clinically notable vital sign abnormalities are defined in Table 13. 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 from baseline greater than 25%. The abnormal values for subjects exhibiting alert vital sign abnormalities will be listed.

Table 13: Criteria for Clinically Notable Vital Sign Abnormalities

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

8.5. Electrocardiograms

Twelve-lead ECGs including RR, QRS, QT, QTcF, QTcB, and JTc intervals will be obtained for each subject during the study. Values at each scheduled visit, change, and percent change from baseline will be summarized for each ECG parameter. Baseline will be determined as the average of all nonmissing values before the first administration of epacadostat, pembrolizumab, or azacitidine.

Criteria for clinically notable ECG abnormalities are defined in Table 14. Subjects exhibiting clinically notable ECG abnormalities will 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 14: Criteria for Clinically Notable Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold
QTcF	> 460 ms	< 295 ms
PR	> 220 ms	< 75 ms
QRS	> 120 ms	< 50 ms
QT	> 500 ms	< 300 ms
RR	> 1330 ms	< 600 ms

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 dose level for Treatment Group A in Parts 1 and 2 combined. Incidences of abnormalities will be listed with study visit, assigned treatment group, and a description of the abnormality.

9. INTERIM ANALYSES

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

Since the study was terminated prior to the interim analyses, no interim analyses will be conducted for Part 2.

10. CHANGES AND MODIFICATIONS TO THE ANALYSIS PLAN

All versions of the SAP are listed in Table 15.

Table 15: Statistical Analysis Plan Versions

SAP Version	Date
Original	12 JAN 2018
Amendment 1	18 JUL 2018

10.1. Changes to Protocol-Defined Analyses

10.1.1. Efficacy Analyses

- The efficacy endpoints will only be summarized per RECIST v1.1. [redacted]
- The confirmation of responses will not be included.

[redacted]

10.1.3. Interim Analyses

- Simon 2-stage design will not be performed due to the early termination of the study. No interim analyses will be conducted for Part 2.

10.2. Changes to the Statistical Analysis Plan

- All planned figures will be eliminated.
- The analyses of Treatment Groups B and C will be eliminated due to the early termination of the study.
- Please see Section 10.1 for other changes from the original SAP.

11. REFERENCES

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics 1982;38:29-41.

Food and Drug Administration (FDA). Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. 2007. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071590.pdf. Accessed January 4, 2016.

Koyama T, Chen H. Proper inference from Simon's two-stage designs. Stat Med 2008;27:3145-3154.

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

APPENDIX A. PLANNED TABLES AND LISTINGS

Tables

Table No.	Title	Population	Standard	In-Text
Baseline and Demographic Characteristics				
1.1 Disposition				
1.1.1	Analysis Populations	Safety	X	X
1.1.2	Summary of Subject Disposition	Safety	X	X
1.1.3	Summary of Number of Subjects Enrolled by Site	Safety	X	
1.2 Demography				
1.2.1	Summary of Demographics	Safety	X	X
1.3 Baseline Characteristics				
1.3.1	Summary of Cancer History and Baseline Disease Characteristics	Safety		X
1.4 Prior Medication and Concomitant Medication				
1.4.1	Summary of Prior Cancer Therapy	Safety		X
1.4.2	Summary of Prior Medications	Safety	X	
1.4.3	Summary of Concomitant Medications	Safety	X	
1.5 Others				
1.5.1	Summary of General Medical History	Safety	X	
2 Efficacy				
2.1.1	Summary of Best Response, Duration of Response Under RECIST v1.1 for Subjects in the Initial Treatment Phase	Response Evaluable		X
2.2.1	Summary of Progression-Free Survival Under RECIST v1.1 for Subjects in the Initial Treatment Phase	Response Evaluable		X
[redacted]	[redacted]	[redacted]		[redacted]
2.3.2	Summary of Largest Percentage Reduction in Sum of Diameters of Target Lesions	Response Evaluable		
Safety				
3.1 Dose Exposure				
3.1.1.1	Summary of Exposure to Epacadostat for Subjects in the Initial Treatment Phase	Epacadostat Safety		X
3.1.1.2	Summary of Exposure to Pembrolizumab for Subjects in the Initial Treatment Phase	Pembrolizumab Safety		X
3.1.1.3	Summary of Exposure to Azacitidine for Subjects in the Initial Treatment Phase	Azacitidine Safety		X
3.1.2.1	Summary of Epacadostat Compliance	Epacadostat Safety		X
3.2 Adverse Events				
3.2.1	Overall Summary of Treatment-Emergent Adverse Events	Safety	X	X
3.2.2	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X	X
3.2.3	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety	X	X
3.2.4	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity	Safety	X	

Table No.	Title	Population	Standard	In-Text
3.2.5	Summary of Grade 3 or 4 Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X	X
3.2.6.1	Summary of Epacadostat Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term	Epacadostat Safety	X	
3.2.6.2	Summary of Pembrolizumab Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term	Pembrolizumab Safety	X	
3.2.6.3	Summary of Azacitidine Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term	Azacitidine Safety	X	
3.2.7	Summary of Treatment-Emergent Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term	Safety	X	X
3.2.8	Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X	
3.2.9	Summary of Serious Treatment-Emergent Adverse Events by Preferred Term in Decreasing Order of Frequency	Safety	X	X
3.2.10	Summary of Nonserious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X	
3.2.11.1	Summary of Treatment-Emergent Adverse Events Leading to Epacadostat Dose Reduction by MedDRA System Organ Class and Preferred Term	Epacadostat Safety	X	
3.2.11.2	Summary of Treatment-Emergent Adverse Events Leading to Azacitidine Dose Reduction by MedDRA System Organ Class and Preferred Term	Azacitidine Safety	X	
3.2.12.1	Summary of Treatment-Emergent Adverse Events Leading to Epacadostat Dose Interruption by MedDRA System Organ Class and Preferred Term	Epacadostat Safety	X	
3.2.12.2	Summary of Treatment-Emergent Adverse Events Leading to Pembrolizumab Dose Interruption by MedDRA System Organ Class and Preferred Term	Pembrolizumab Safety	X	
3.2.12.3	Summary of Treatment-Emergent Adverse Events Leading to Azacitidine Dose Interruption by MedDRA System Organ Class and Preferred Term	Azacitidine Safety	X	
3.2.13.1	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Epacadostat by MedDRA System Organ Class and Preferred Term	Epacadostat Safety	X	X
3.2.13.2	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Pembrolizumab by MedDRA System Organ Class and Preferred Term	Pembrolizumab Safety	X	
3.2.13.3	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Azacitidine by MedDRA System Organ Class and Preferred Term	Azacitidine Safety	X	
3.2.14	An Overall Summary of Treatment-Emergent Immune-Related Adverse Events	Safety	X	

Table No.	Title	Population	Standard	In-Text
3.3 Laboratory				
3.3.1	Summary of Laboratory Values - Hematology	Safety	X	
3.3.2	Shift Summary of Hematology Laboratory Values in CTC Grade - to the Worst Abnormal Value	Safety	X	X
3.3.3	Summary of Laboratory Values - Chemistry	Safety	X	
3.3.4	Shift Summary of Chemistry Laboratory Values in CTC Grade - to the Worst Abnormal Value	Safety	X	X
3.3.5	Summary of Laboratory Values - Coagulation	Safety	X	
3.3.6	Shift Summary of Coagulation Values - to the Worst Abnormal Value	Safety	X	
3.3.7	Summary of Laboratory Values - Endocrine	Safety	X	
3.3.8	Shift Summary of Endocrine Values - to the Worst Abnormal Value	Safety	X	
3.4 Vital Signs				
3.4.1	Summary of Systolic Blood Pressure	Safety	X	
3.4.2	Summary of Diastolic Blood Pressure	Safety	X	
3.4.3	Summary of Pulse	Safety	X	
3.4.4	Summary of Respiration Rate	Safety	X	
3.4.5	Summary of Body Temperature	Safety	X	
3.4.6	Summary of Weight	Safety	X	
3.5 ECGs				
3.5.1	Summary of PR Interval (ms) From 12-Lead ECG	Safety	X	
3.5.2	Summary of QRS Interval (ms) From 12-Lead ECG	Safety	X	
3.5.3	Summary of QT Interval (ms) From 12-Lead ECG	Safety	X	
3.5.4	Summary of QTcB Interval (ms) From 12-Lead ECG	Safety	X	
3.5.5	Summary of QTcF Interval (ms) From 12-Lead ECG	Safety	X	
3.5.6	Summary of JTc Interval (ms) From 12-Lead ECG	Safety	X	
3.5.7	Summary of Heart Rate From 12-Lead ECG	Safety	X	
3.5.8	Summary of Outliers of QT, QTcB, and QTcF Interval Values From 12-Lead ECG	Safety	X	X

Listings

Listing No.	Title
2.1 Discontinued Subjects (Subject Disposition)	
2.1.1	Subject Enrollment and Disposition Status
2.1.2	Subject Inclusion and Exclusion Criteria Violations
2.2 Protocol Deviations	
2.2	Protocol Deviations
2.3 Data Excluded From [redacted] Efficacy, and/or Safety Analyses	
2.3	Analysis Populations
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 Medications
2.5 Drug Compliance	
2.5	Study Drug Compliance

Listing No.	Title
2.6 Efficacy	
2.6.1	Deaths
2.6.2	Best Overall Response, Duration of Response, and Progression-Free Survival
2.6.3	Overall Response Assessment by Visit
2.6.4	Response Assessment: Target Lesions
2.6.5	Response Assessment: Non-Target Lesions
2.6.6	Response Assessment: New Lesions
2.6.7	Largest Percentage Reduction in Sum of Diameters of Target Lesions
2.6.8	ECOG Status
2.7 Adverse Events (and Exposure)	
2.7.1	Study Drug Administration
2.7.2	Adverse Events
2.7.3	Dose-Limiting Toxicities
2.7.4	Serious Adverse Events
2.7.5	Fatal Adverse Events
2.7.6	Adverse Events Leading to Discontinuation of Epacadostat, Pembrolizumab, or Azacitidine
2.8 Laboratory Data	
2.8.1	Clinical Laboratory Values – Hematology
2.8.2	Clinical Laboratory Values – Chemistry
2.8.3	Clinical Laboratory Values – Urinalysis
2.8.4	Clinical Laboratory Values – Coagulation
2.8.5	Clinical Laboratory Values – Endocrine
2.8.6	Clinical Laboratory Values – Serology
2.8.7	Abnormal Clinical Laboratory Values
2.9 Vital Signs	
2.9.1	Vital Signs
2.9.2	Abnormal Vital Sign Values
2.9.3	Alert Vital Sign Values
2.10 Electrocardiograms	
2.10.1	12-Lead ECG Values
2.10.2	Abnormal 12-Lead ECG Values
2.10.3	Alert 12-Lead ECG Values
2.11 Physical Examinations	
2.11.1	Physical Examinations
2.11.2	Body Weight

Signature Manifest

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