Clinical Study Protocol

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

Product:	Epacadostat, Pembrolizumab, Azacitidine, INCB057643, and INCB059872
INDNumber:	132,309
EudraCT Number:	2016-004289-25
Phase of Study:	112
Sponsor:	Incyte Corporation 1801 Augustine Cut-Off Wilmington, DE 19803
Original Protocol (Version 0):	30 SEP 2016
Amendment (Version) 1:	04 NOV 2016
Amendment (Version) 2:	02 JUN 2017
Amendment (Version) 3:	20 OCT 2017
Amendment (Version) 4:	30 AUG 2018

This study will be perf01med in accordance with ethical principles that have their origin in the Declaration of Helsinki and conducted in adherence to the study Protocol, Good Clinical Practices as defmed in Title 21 of the US Code of Federal Regulations Parts 11, 50, 54, 56, and 312, as well as ICH GCP consolidated guidelines (E6) and applicable regulatory requirements.

INVESTIGATOR'S AGREEMENT

I have read the INCB 24360-206 Protocol Amendment 4 (Version 4 dated 30 AUG 2018) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all infmmation received or developed in connection with this Protocol.

(Plinted Name of Investigator)

(Signature of Investigator)

(Date)

SYNOPSIS

Name of Investigational Product: Epacadostat, Pembrolizumab, Azacitidine, INCB057643, and INCB059872

Title of Study: A Phase 112 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

Protocol Number: INCB 24360-206 **Study Phase:** 1/2

Indication: Advanced or metastatic solid ntmors and previously treated Stage IV or recunent non–small cell lung cancer (NSCLC) and Stage IV microsatellite stable (MSS) colorectal cancer (CRC)

Primary Objectives:

- Prut **1:** To evaluate the safety and tolerability and to detennine the maximum tolerated dose (MTD), maximum tested dose, or phannacologically active dose [PAD]) of the combinations in subjects with advanced or metastatic solid tumors.
- Prut 2: To evaluate the efficacy of the combinations in subjects with previously treated Stage IV or recunent NSCLC, Stage IV MSS CRC, and other select solid tumors by assessing objective response rate (ORR) per Response Evaluation Critelia in Solid Tumors (RECIST) v1.1 at the MTD, maximum tested dose, or PAD.

Secondary Objectives:

- Prut 1: To evaluate the efficacy ofthe combinations in subjects with advanced or metastatic solid tumors by assessing ORR per RECIST v1.1 at the MTD, maximum tested dose, or PAD.
- Prut 2: To evaluate the safety and tolerability of the combinations in subjects with previously treated Stage IV or recunent NSCLC, Stage IV MSS CRC, and select solid tumors at the MTD, maximum tested dose, or PAD.
- Pruts 1 and 2: To evaluate changes in T-cell infiltration in the ttlillor lnicroenvironment with the combinations in subjects with advanced or metastatic solid tumors, previously treated Stage IV or recunent NSCLC, and Stage IV MSS CRC.
- Pruts 1 and 2: To evaluate the efficacy of the combinations in subjects with advanced or metastatic solid ttlillors, previously treated Stage IV or recunent NSCLC, and Stage IV MSS CRC by assessing progression-free survival (PFS).
- Pruts 1 and 2: To evaluate the efficacy of the combinations in subjects with advanced or metastatic solid ttlillors, previously treated Stage IV or recunent NSCLC, and Stage IV MSS CRC by assessing duration of response (DOR).

[redacted]

[redacted]

Prima ry Endpoints:

- Patt 1: Safety and tolerability will be assessed by monitoring the frequency, duration, and severity of adverse events (AEs); through physical examinations; by evaluating changes in vital signs and electrocru·diograms (ECGs); and through clinicallaborat01y blood and mine sample evaluations.
- Patt 2: Objective response rate, defmed as the percentage of subjects having a complete response (CR) or pattial response (PR), will be detennined by investigator assessment of radiographic disease as per RECIST v1.1.

Secondary Endpoints:

- Patt 1: Objective response rate, defmed as the percentage of subjects having a CR or PR, will be detennined by investigator assessment of radiographic disease as per RECIST v1.1.
- Patt 2: Safety and tolerability will be assessed by monitoring the frequency, duration, and severity of AEs; through physical exaininations; by evaluating changes in vital signs and ECGs; and through clinicallaborat01y blood and mine sample evaluations.
- Patts 1 and 2: Percentage of responders, where a responder is defined as an increase in the nmnber of tmnor-infllltrating lymphocytes (TILs) or the ratio of CD8+ lymphocytes to T regulat01y cells (Tregs) infiltrating ntmor post-treatment versus pretreatment with pembrolizumab and epacadostat in combination with azacitidine, INCB057643, or INCB059872 (United States sites only) evaluated by immunohistochetnistiy, will be detemlined.
- Patts 1 and 2: Progression-free survival, defined as the time from date of first dose of study dmg until the eru·liest date of disease progression, will be detemlined by investigator assessment of objective radiographic disease assessments as per RECIST v1.1, or death due to any cause, if occuning sooner than progression.
- Pruts 1 and 2: Duration of response detennined by radiographic disease assessment, defined as the time from earliest date of disease response Imtil the eru·liest date of disease progression per RECIST v1.1, or death due to any cause, if occuning sooner than progression, will be detemlined.

[redacted]

Overall Study Design:

This is an open-label, multicenter, Phase 112 stttdy evaluating the addition of 3 different epigenetic priming regimens to an immunotherapy doublet in subjects with advanced or metastatic solid tt1mors.

Prut **1** of the study will be an open-label Phase **1** assessment to evaluate the safety and tolerability and to detemline the MTD, maximum tested dose, or PAD of the combinations in subjects with advanced or metastatic solid tt1mors.

Prut 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. Sepru·ate treatment sequencing tt1mor biopsy cohorts ru·e also included in Prut 2 to ftuther evaluate epigenetic changes and changes in the ttlmor nlicroenviromnent in subjects with select solid tt1mors.

Treatment Group A

In Treatment Group A, subjects will receive the DNA methyltransferase inhibitor azacitidine in combination with the progrrunmed death receptor-1 (PD-1) inhibitor pembrolizumab and the indoleanline 2,3-dioxygenase (IDO) 1 inhibitor epacadostat. Pa1t **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 Prut 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 Coh01ts A-4 and A-5, which will receive up to 5 cycles). In Pa1t 2 of Treatment Group A will consist of Simon 2-Stage coh01ts in previously treated NSCLC and MSS CRC. Sepru·ate treatment sequencing tumor biopsy coh01ts ru·e also included in Prut 2 to ftuther evaluate epigenetic changes and changes in the nunor nlicroenviromnent in subjects with select solid tt1mors. In Treatment Group A, subjects who have an initial response or stable disease (SD) for greater than 6 months but later relapse while receiving pembrolizumab and epacadostat will have the opp01tunity to repeat the azacitidine epigenetic pdnling regimen to which they were odginally assigned with medical molliter approval. Study treatment may continue as long as the subject is receiving benefit and has not met any cdteria for study withdrawal or until the subject has received 35 adnlimstrations ofpembrolizumab (approximately 2 years), whichever occurs first.

Treatment Groups B and C (Upon implementation of Amendment 4, these treatment groups are no longer applicable)

In Treatment Group B, subjects will receive the bromodomain and extra-tenninal (BET) inhibitor INCB057643 as a monotherapy printing regimen for 21 days in Cycle **1** and then initiate pembrolizumab and epacadostat on Cycle 2 Day 1. In Treatment Group C (Umted States sites only), subjects will receive the lysine-specific demethylase 1A (LSD1) inhibitor INCB059872 as a monotherapy priming regimen for 21 days in Cycle 1 and then initiate pembroliZlllffiab and epacadostat on Cycle 2 Day **1.** Pa1t **1** of Treatment Groups Band C will consist of a dose-escalation assessment of the safety and tolerability of the treatments in subjects with advanced or metastatic solid nunors. Prut **1** will also contain dose-expansion coh01ts in previously treated NSCLC and MSS CRC. Fo —— , there will be an optional stttdy hold for evaluation of safety, efficacy, and to facilitate a go/no-go decision regru·ding emolhnent of Prut 2. Pa1t 2 of Treatment Groups Band C will consist of Simon 2-Stage coh01ts in previously treated NSCLC and MSS CRC. Sepru-ate treatment sequencing tt1mor biopsy cohorts rue also included in Prut 2 to ftuther evaluate epigenetic changes and changes in the tt1mor Inicroenvironment in subjects with select solid ttlmors. Emolhnent of the treatment sequencing tt1mor biopsy cohorts is contingent upon passing Stage **1 in 1** of the 2 coh01ts, for each respective treatment group. Stttdy treatment may continue as long as the subject is receiving benefit and has not met any criteda for stttdy withdrawal or lmtil the subject has received 35 adnlimstrations of pembrolizumab (approximately 2 yerus), whichever occurs first.

Tumor biopsy samples are required at baseline and on study for subject patticipation in all dose-escalation coh01ts and Stage **1** of the Simon 2-stage coh01ts. Mandat01y tumor biopsies will be collected at baseline (before Day **1** administration) and while the subject is receiving study treatment as specified below:

- An additional on-treatment biopsy will be required to be collected during Week 5 or Week 6 (Treatment Group A) or Week 8 or Week 9 (Treatment Groups Band C); the on-treatment biopsy is optional for Stage 2 coh01ts in Pmt 2.
- Coh01ts A-3, A-4, A-5, B-9, B-10, C-11, and C-12: A baseline biopsy and 2 on-treatment biopsies m·e required for subjects emolled in the treatment sequencing biopsy coh01ts.
- An additional optional biopsy may be collected once the subject meets the requirements for SD, response, or progression by radiographic disease assessment.

Note: On-treatment biopsies should be collected from the same tumor lesion that was biopsied at baseline.

Note: If a subject is scheduled to have a tumor biopsy for the purposes of this study, and it is subsequently detennined that ntmor tissue cannot safely be obtained, then the subject may still emoll in the study, and an m·chived tumor specimen, if available, can be subinitted. Such subjects may be replaced.

Note: As a quality control step, prior to subtnitting the ntmor tissue to the centra**ll**aboratOiy vendor, all tumor tissue will be fonnalin-fixed and pm·affin-embedded locally. A hematoxylin and eosin stain will be perfonned and reviewed by a local pathologist to verify the adequacy of the tumor biopsy. Additionally, a quality control f01m will be signed and dated by the reviewing pathologist. For the screening biopsy, this fonn will ideally be subtnitted to the sponsor at the same time the registration fonn is subinitted for emollment.

3 criteria.

Dose-Escalation Phase CAll 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 defmed as the highest dose at which less than one-third of the subjects (with a tninimum of 6 subjects) have a dose-liiniting toxicity (DLT). When the MTD, maximum tested dose, or PAD has been detetmined or reached, the dose will be recommended for Pmt 2. The Pmt 2 expansion will begin after the detetmination of the MTD, maximum tested dose, or PAD; however, emolhnent priodty will be given to the open Pmt 1 dose-escalation coh01t.

A minimum of 3 subjects will initially be emolled in Coh01t 1, and each subject will be observed for 21 days from the strut oftdplet combination therapy before emollment in the next coh01t begins. The dose of azacitidine, INCB057643, or INCB059872 (or epacadostat) will be escalated if 0 of the first 3 evaluable subjects emolled has a DLT. If **1** of 3 subjects in Coh01t **1** has a DLT, the coh01t will be expanded to 6 subjects. If **1** of 6 subjects in Coh01t **1** has a DLT, a new coh01t of 3 subjects will be treated at the next higher dose level (Coh01t 2). If2 of 6 subjects in Coh01t **1** have a DLT, that coh01t will be fmther expanded to a total of9 subjects. If2/9 subjects has a DLT, 3 subjects will be treated at the next higher dose level. If2/3, 3/6, or 3/9 subjects have DLTs within a coh01t, dose de-escalation will be required, and Coh01t **-1** or -2 will be tested. The MTD is defined as the highest dose level at which1/6 or2/9 subjects expedence a DLT.

Subjects must have received75% of planned doses of study dmg during the 21-day DLT (Treatment Group A) or 42-day DLT (Treatment Groups Band C) observation pedod or have had a DLT to be evaluable for dose tolerability (Treatment Group A: azacitidine [4 doses], epacadostat [32 doses], and embrolizurnab 1 dose ; Treatment Grou B: INCB057643 32 doses , e acadostat 32 doses , and

pembrolizumab [1 dose]; Treatment Group C: INCB059872 [once daily (QD) dosing, 32 doses; eve1y other day (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 dianhea; renal insufficiency; high-grade laborat01y abn01malities; 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 receive75% of the presciibed 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 detennination ofDLTs, 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 emolled in a coh01t to achieve the minimum of 3 evaluable subjects if dropouts or dose intenuptions/reductions occur that result in a subject being nonevaluable for DLTs.

Dming the study, dose intenuptions and/or dose modifications may be implemented based on toxicity as described in the Protocol. However, dose modifications should not be made dming the DLT observation period without discussion with the medical monitor. Intrasubject dose escalation is not pe1mitted.

Treatment Group A: Azacitidine

In Treatment Group A, dose escalation will begin with sta1ting doses of azacitidine 75 mg subcutaneous (SC) or intravenous (IV) injection for 5 days (5 doses may be administered over the Day 1-7 period) of the first 2 cycles, pembrolizumab 200 mg IV eve1y 3 weeks (Q3W), and epacadostat 100 mg orally (PO) twice daily (BID) continuous dose administration. If the sta1ting dose proves intolerable, azacitidine 50 mg SC or IV for 5 days, pembrolizumab 200 mg IV Q3W, and epacadostat 100 mg PO BID will be evaluated. The coh01ts and dose levels are shown in the following table.

Treatment Group A: Azacitidine

Cohort	Azacitidine	Pembrolizumab	Epacadostat
-2·	50 mg SC or IV for 5 days (5 doses over Day 1-7 period) in Cycle 1 & 2	200mgiVQ3W	50mgPOBID
-1"	50 mg SC or IV for 5 days (5 doses over Day 1-7 period) in Cycle 1 & 2	200mgiVQ3W	100 mg PO BID
1	75 mg SC or IV for 5 days (5 dost>s over Day 1-7 period) in Cycle 12	200 mg iV Q3W	100 mg PO BID
	75 mg SC or IV for 5 days (5 doses over Day 1-7 period) in Cycle 1 & 2	200mgiVQ3W	300mgPOBID
	100 mg SC or IV for 5 days (5 doses over Day 1-7 period) in Cycle 1 & 2	200mgiVQ3W	100 mg PO BID
3	100 mg SC or IV for 5 days (5 doses over Day 1-7 period) Days 1-5 in Cycle 1 & 2	200mgiVQ3W	300mgPOBID

• If Cohort I proves intolerable, Coh01t -1 may be evaluated. If Coh01t -I is not tolerable, Coh01t -2 may be evaluated with epacadostat 50 mg PO BID. If a de-escalation cohort is detennined to be safe and tolerable, the dose ofazacitidine or epacadostat may be re-escalated in separate, additional coh01ts based on the review of available safety data.

b For Coh01t 2, escalation of azacitidine to 100 mg or epacadostat to 300 mg BID will be dependent on the obse1vation of Grade 3 or greater immtme-related or non–imnume-related toxicities in Cohort I (toxicities that were not considered DLTs). If Grade 3 or greater immtme-related toxicities are obse ved in Coh01t 1, azacitidine will be escalated first (Cohort 2B). If non–immune-related Grade 3 or greater toxicities are observed, epacadostat will be preferentially escalated (Coh01t 2A). Dose-escalation coh01ts 2A and 2B may be opened in parallel if no Grade 3 AEs are observed in Cohort I.

Treatment Group B: INCB057643

In Treatment Group B, dose escalation will begin with a sta1ting dose ofiNCB057643 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 adlninistration will be added to INCB057643. If the struting 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 coho1ts and dose levels are shown in the table below.

Treatment Group B: INCB057643

Cohort	INCB057643	Pembrolizumab	Epacadostat
-1"	4mgPOQD beginning C3D1	200mgiVQ3W beginning C2Dl	50mgPOBID beginning C2D1
1	4 mg PO QD beginning C1D1	200mg iVQ3W beginning C2D1	100 mg POBID beginning C2D1
2	8mgPOQD beginning C1D1	200mgiVQ3W beginning C2Dl	100 mgPOBID beginning C2D1
3	12mgPOQD beginning C1D1	200mgiVQ3W beginning C2Dl	100 mgPOBID beginning C2D1

a If Cohort I proves intolerable, Coh01t -I may be evaluated. If Coh01t -I is not tolerable, lower doses or alternative dose schedules ofiNCB057643 may be tested, however at this time 4mg tablets are the lowest dose fonnulation 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 coh0lt is detemrined 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.

Treatment Group C: INCB059872

In Treatment Group C (United States sites only), 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 sta1ting 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 coho1ts and dose levels rue shown in the table below.

Treatment Group C: INCB059872

Cohort	INCB059872	Pembrolizumab	Epacadostat
-1"	1 mgPO QoD beginning C1D1	200mgiVQ3W beginning C2Dl	50mgPO BID beginning C2D1
1	1 mgPOQoD beginning C1D1	200mg iVQ3W beginning C2D1	100 mg POBID beginning C2D1
2Ah	2 mgPO QoD beginning C1D1	200mgiVQ3W beginning C2Dl	100 mgPO BID beginning C2D1
2Bb	1 mgPOQD beginning C1D1	200mgiVQ3W beginning C2Dl	100 mgPO BID beginning C2D1
3C	3 mgPO QoD beginning C1D1	200mgiVQ3W beginning C2Dl	100 mgPO BID beginning C2D1

a If Coh01t I proves intolerable, Coh01t -I may be evaluated. If Cohort -I is not tolerable, lower doses or altemative dose schedules ofiNCB059872 may be tested. Any dose reduction in INCB059872 would be combined with pembroliztunab 200 mg IV Q3W and epacadostat 50mg PO BID. If a de-escalation coh01t is detennined to be safe and tolerable, the dose of INCB059872 or epacadostat may be re-escalated in separate, additional coh01ts 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 I.

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

Dose-Expansion Phase

Treatment Group A

Once the safety profile of all doses tested has been charactelized and the recommended Phase 2 dose (RP2D) of the azacitidine combination has been defmed, the cohort expansion will be initiated at the RP2D. The doses selected for expansion will not exceed the MTD or maximum tested dose in Prut 1.

The purpose of Phase 2 is to gather additional safety, and preliminruy efficacy infmmation regru·ding the t1iplet combination in select tumor types where there is substantial room for improvement over mono- and doublet inummotherapies. The expansion will include:

1. Safety/efficacy cohmts in NSCLC (A-1) and MSS CRC (A-2) (2 tumor biopsies are required)
2. Treatment sequencing biopsy cohmts that will initiate treatment (3 tumor biopsies ru·e 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 (flrst-line) melanoma will be treated in the pembrolizumab monotherapy cohmt (A-5).

Treatment Group A Safety/Efficacy Expansion Cohorts

Two cohmts will be evaluated as prut of the safety/efficacy expansion. The eligible tumor types ru·e NSCLC and MSS CRC. Subjects emolled in the NSCLC tumor cohmt must have had disease progression on a prior PD-1 pathway–tru·geted agent.

A Simon 2-stage design will be used with a stopping mle to allow for early tetmination of a pruticular cohmt at the end of Stage 1 if there ru·e 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 ru·e observed in the NSCLC PD-1 failure and MSS CRC cohmts, the cohmt(s) will be discontinued. If at least 1 response is observed in the NSCLC PD-1 failure or MSS CRC cohmt, 19 additional NSCLC PD-1 failure or MSS CRC subjects will be emolled (Stage 2), for a maximum of 27 subjects per cohmt (see the table below).

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 +pembrolizmnab + epacadostat combination.	A maximum of27 subjects with previously treated Stage IV or recunent NSCLC with progression on a prior PD-1 pathway–targeted agent.
Expansion Cohmt A-2	MTD or maximum tested dose for the azacitidine +pembrolizmnab + epacadostat combination.	A maximum of27 subjects with previously treated Stage IV MSS CRC.

Continuous evaluation of toxicity events will be petfmmed throughout the expansion. In the expansion, after the sixth patient in Stage 1 has been emolled, if > 40% of subjects have an AE Grade 3 that is attlibutable to the investigational agents, ftuther enrollment of subjects will be suspended lmtil the sponsor, investigators, and regulatmy authmities (if applicable) have detennined the appropliate course of action. If an expansion cohort is discontinued because of toxicity, a new cohmt may be initiated at a previously tested lower dose level.

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

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

Approximately 25 subjects will be emolled in Expansion Cohmts A-3 and A-4 and 10 subjects in Ex ansion Cohmt A-5. The eli ·ble nunor es for Ex ansion Cohmts A-3, A-4, and A-5 ru·e head and

neck squamous cell carcinoma (HNSCC), melanoma, urothelial carcinoma, and MSS CRC. In Expansion Coho1ts A-3 and A-4, subjects with tumor types other than MSS CRC must have had disease progression on a p1ior PD-1 pathway–targeted agent.

Five to 8 evaluable subjects per nlmor type in Expansion Coho1ts A-3 and A-4, and 10 subjects in Expansion Cohmt A-5 will initiate treatment and have tumor biopsies pe1foimed as indicated in the table below.

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

Cohort	Treatment Sequence	Biopsy Sequence	Tumor Type (n)
Expansion Cohort A-3	Azacitidine monotherapy during Week -1 (5 doses), initiate pembrolizumab and epacadostat on C1D1 (window + 5 days fi:om the date of the fifth azacitidine dose; should begin after biopsy #2), 5 doses of azacitidine will be administered in Cycles 2 and 3.	Biopsy #1 at baseline. Biopsy #2 on ClD1 (window Day -5 to C1D1, biopsy before pembrolizumab/epacadostat administration). Biopsy #3 during Week 5 or 6.	HNSCC (5-8) Melanoma (5-8) Urothelial carcinoma (5-8) MSS CRC (5-8)
Expansion Coh01t 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 C2Dl (window C1Dl5 to C2D1, biopsy before azacitidine administration). Biopsy #3 during Week 8 or 9.	HNSCC (5-8) Melanoma (5-8) Urothelial carcinoma (5-8) MSS CRC (5-8)
Expansion Coh01t 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 C2Dl (window C1Dl5 to C2D1, biopsy before epacadostat/azacitidine administration). Biopsy #3 during Week 8 or 9.	First-line melanoma (10)

Subjects in Expansion Coho1t A-3 will receive up to 6 cycles of azacitidine. Subjects in Expansion Coho1ts A-4 and A-5 will receive up to 5 cycles of azacitidine. The sponsor will manage emolhnent 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.

Treatment Group B

Treatment Group B Part 1 Dose-Expansion Cohorts (Part 1)

Because higher doses of epigenetic priming regimens may be deleterious to immune function, expansion coho1ts at each dose level tested that cleared the DLT window will be opened for signal detection – —— analysis to guide an RP2D. Once an RP2D is dete1mined, this dose will be usecr:-Part stage and treatment sequencing ttllllor biopsy cohorts. Dming dose expansion, 5 NSCLC subjects who progressed on a PD-1 pathway–targeted agent and 5 MSS CRC subjects will be emolled at each dose level with DLT clearance as detailed below.

The expansion will include:

1. Safety/efficacy coho1ts 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 12mg QD followed by the pembrolizumab/epacadostat doublet
2. Safety/efficacy coho1ts 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 12mg QD followed by the pembrolizumab/epacadostat doublet

The following coh01ts will be expanded only lllder ce1tain circumstances as listed below:

1. Coh01ts B-1 and B-2: Objective responses 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, Coh01ts B-1 and B-2 will only be enrolled if 1/3 of the subjects in the dose-escalation coh01t have a 25% drop in platelet cmmt from Cycle 1 Day 1 to Cycle 2 Day 1.

Continuous evaluation of toxicity events will be pe1f01med throughout the expansion coh01ts. After the dose-expansion coh01ts been emolled, beginning with the sixth patient for a specific regimen, if > 40% of subjects have an AEGrade 3 that is attributable to the investigational agents, fmther enrollment of subjects will be suspended until the sponsor, investigators, and regulat01y authodties (if applicable) have dete1mined the appropriate course of action. If an expansion coh01t 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 coh01ts, there will be an optional 8-week pause to utilize data for RP2D dete1mination. this time no subject emollment may be allo is no evidence of clinical --- efficacy [redacted] in the dose-expansion coh01ts, emollment in the respective treatment group will be stopped prior to Part 2.

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

Following safety, efficacy, data evaluation, an RP2D will be detennined. A Simon 2-stage design will be mle to allow for early te1mination of a pmticular coh01t 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–tm·geted agent and 8 MSS CRC subjects will be enrolled. If no responses are observed in the NSCLC PD-1 failure and MSS CRC coh01ts, the coh01t(s) will be discontinued. If at least 1 response is observed in the NSCLC PD-1 failure or MSS CRC coh01t, 19 additional NSCLC PD-1 failure or MSS CRC subjects will be enrolled (Stage 2), for a maximum of27 subjects per coh01t (see the table below).

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 maximmn of27 subjects with previously treated Stage IV or recmrent 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 maximmn of27 subjects with previously treated Stage IV MSS CRC.

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

The sequencing biopsy coh01ts require 3 ntmor biopsies (except for Coh01t B-11 which requires 2 rumor biopsies) to identify epigenetic changes and changes in the ntmor lnicroenviromnent induced by each of the components of the regimen. All subjects will have ttlillor biopsies at baseline and 2 additional biopsies while on sntdy treatment.

Approximately 25 subjects will be enrolled in Expansion Coh01ts B-9, B-10, and B-11. The eligible tumor types for Expansion Coh01ts B-9, B-10, and B-11 are HNSCC, melanoma, urothelial carcinoma, and MSS CRC. In Expansion Coh01ts 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-tm·geted agent.

Five to 8 evaluable subjects per ntmor type in Expansion Coh01ts B-9, B-10, and B-11 will initiate treatment and have ntmor biopsies pe1fonned as indicated in the table below.

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 dming C1, initiate pembrolizmnab and epacadostat on C2D1 after biopsy#2.	Biopsy #1 at baseline. Biopsy #2 on C2D1 (window C1D15 to C2D1, biopsy before pembroliztunab/ epacadostat administration). Biopsy #3 dming Week 8 or 9.	HNSCC (5-8) Melanoma (5-8) Urothelial carcinoma (5-8) MSS CRC (5-8)
Expansion Cohort B-10	INCB057643 and epacadostat for 1 cycle, initiate pembrolizmnab after biopsy#2.	Biopsy #1 at baseline. Biopsy #2 on C2D1 (window C1D15 to C2D1, biopsy before pembroliztunab administration). Biopsy #3 dming Week 8 or 9.	HNSCC (5-8) Melanoma (5-8) Urothelial carcinoma (5-8) MSS CRC (5-8)
Expansion Cohort B-11	INCB057643, epacadostat, and pembrolizmnab beginning C1.	Biopsy #1 at baseline. Biopsy #2 dming Week 5 or 6.	HNSCC (5-8) Melanoma (5-8) Urothelial carcinoma (5-8) MSS CRC (5-8)

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

Treatment Group C

Treatment Group C Dose-Expansion Cohorts (Part 1; United States Sites Only)

Because higher doses of epigenetic pdming regimens may be deleterious to immune function, expansion coh01ts at each dose level tested which clear the DLT window will be opened for signal detection – analysis to guide an RP2D. Once an RP2D is detennined, this dose will be used in Prut stage and treatment sequencing ttlillor biopsy cohorts. Dming dose expansion, 5 NSCLC subjects who progressed on a PD-1 pathway–tru·geted agent and 5 MSS CRC subjects will be emolled at each dose level with DLT cleru·ance as detailed below.

The expansion will include:

1. Safety/efficacy coh01ts in NSCLC (2 tumor biopsies rure 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 coh01ts in MSS CRC (2 tumor biopsies rure 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 coh01ts will be expanded only under cettain circumstances as listed below:

1. Coh01ts C-1, C-2, C-5, and C-6 (United States sites only): Objective responses have been seen in subjects dosed with INCB059872 2 and 3mg QoD and, as such, rure PADs. However, 1 mg QoD has not been evaluated in hmnans, and there is no objective data to show that 1mg QD is a PAD. To ensme that 1 mg QD and 1 mg QoD are PADs, Cohorts C-1, C-2, C-5, and C-6 will only be emolled if ≥ 1/3 of the subjects in the dose expansion coh01t have a 25% drop in platelet count from Cycle 1 Day 1 to Cycle 2 Day 1.

2. Coh011s C-3 and C-4 will only be expanded if both of the following occm:
   a. The INCB059872 1 mg QD coho1t does not clear its DLT window or is deemed not tolerated for reasons outside ofDLT criteria.
   b. The INCB059872 2 mg QoD coho1t clears its DLT window and is deemed to have acceptable tolerability.

Continuous evaluation of toxicity events will be pe1fo1med throughout the expansion cohorts. After the dose-expansion coho1ts have been emolled, beginning with the sixth subject for a specific regimen, if > 40% of subjects have an AE Grade 3 that is attlibutable to the investigational agents, ftuther enrollment of subjects will be suspended lmtil the sponsor, investigators, and regulato1y authorities (if applicable) have detennined the appropriate course of action. If an expansion coho1t is discontinued because of toxicity, a new coho1t may be initiated at a previously tested lower dose level.

Following comment of the safety/efficacy expansion coho1ts there will be an optional8-week pause to utilize data for RP2D detennination. this time no subject emollment may be allowed. If there is no evidence of clinical in the dose-expansion coho1ts, emollment in the respective treatment group 2.

Treatment Group C Simon 2-Stage Cohorts (Part 2; United States Sites Only)

Following safety, efficacy, data evaluation, an RP2D will be detennined. A Simon 2-stage design will be mle to allow for early te1mination of a particular coho1t at the end of Stage 1 if there are insufficient responses observed. Dming Stage 1, 8 NSCLC subjects who progressed on a PD-1 pathway–tm·geted agent and 8 MSS CRC subjects will be emolled. If no responses are observed in the NSCLC PD-1 failme and MSS CRC coho1ts, the coho1t(s) will be discontinued. If at least 1 response is observed in the NSCLC PD-1 failme or MSS CRC coho1t, 19 additional NSCLC PD-1 failme or MSS CRC subjects will be enrolled (Stage 2), for a maximum of 27 subjects per coho1t (see table below). Treatment Group C with INCB059872 is only for use in the United States sites.

Treatment Group C Safety/Efficacy Expa nsion Cohorts (Pa rt 2)

Cohort	Treatment	Tumor Type (n)
Expansion Cohort C-9	MTD, maximum tested dose, or PAD for the INCB059872 + pembrolizmnab + epa.cadostat combination.	A maximum of27 subjects with previously treated Stage IV or rectuTent NSCLC with progression on a prior PD-1 pathway–targeted agent.
Expansion Cohort C-10	MTD, maximum tested dose, or PAD for the INCB059872 + pembrolizmnab + epa.cadostat combination.	A maximum of27 subjects with previously treated Stage IV MSS CRC.

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

The sequencing biopsy coho1ts require 3 nlmor biopsies (except for Coho1t C-13, which requires 2 nlmor biopsies) to identify epigenetic changes and changes in the nlmor Inicroenvironment induced by each of the components of the regimen.

Approximately 25 subjects will be emolled in Expansion Coho1ts C-11, C-12, and C-13. The eligible tumor types for Expansion Coho11s C-11, C-12, and C-13 are HNSCC, melanoma, mothelial cm·cinoma, and MSS CRC. In Expansion Coho1ts C-11, C-12, and C-13, subjects with nlmor types other than MSS CRC must have had disease progression on a prior PD-1 pathway–tm·geted agent.

Five to 8 evaluable subjects per nlmor type in Expansion Coho1ts C-11, C-12, and C-13 will initiate treatment and have nlmor biopsies pe1fo1med as indicated in the table below.

Treatment Group C Treatment Sequencing Tumor Biopsy Cohorts

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

The sponsor will manage emolhnent 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.

Study Population:

Prut 1 – Dose Escalation: Subjects with advanced or metastatic solid ntmors who have failed previous approved available therapy (or refused therapy) will be emolled.

Prut 2 – Safety/Efficacy Expansion Cohorts: Subjects with Stage IV or recunent NSCLC and Stage IV MSS CRC who have failed previous approved available therapy (or refused therapy) will be emolled.

Prut 2 – Treatment Sequencing Tumor Biopsy Cohmts: Subjects with advanced or metastatic HNSCC, melanoma, and urothelial carcinoma that have had disease progression on a PD-1 pathway-targeted agent and subjects with Stage IV MSS CRC that have failed previous approved available therapy (or refused therapy) will be emolled. Only subjects with untreated (first-line) melanoma will be emolled in Cohmt A-5.

Key Inclusion Criteria:

Both Prut 1 and Patt 2

- Male or female subjects, age 18 yeru·s or older on day of signing consent.
- Willingness to provide written infmmed consent for the study.
- Willingness to lmdergo a pretreatment and on-treatment ntmor biopsy to obtain tumor tissue. On-treatment biopsy is optional in Stage 2 of Prut 2. Two on-treatment biopsies ru·e mandatmy in the Prut 2 Treatment Sequencing Biopsy Expansion Cohmts (except for Cohmts B-11 and C-13, which require 1 on-treatment biopsy).

  Note: If a subject is scheduled to have a tumor biopsy for the purposes of this sntdy, and it is subsequently detennined that ntmor tissue cannot be then the ect still emoll in the study. [redacted]

  Note: Care should be taken to biopsy the same lesion for the baseline and on-treatment samples. If a subject has a solitary target lesion, this should not be biopsied. [redacted]

- ECOG perfo1mance status of 0 to 1.
- Presence of measureable disease per RECIST v.1.1 as dete1mined by the site study team. Tumor lesions sinlated in a previously inadiated area are considered measureable if progression has been demonstrated in such lesions. The lesion selected for pre- and/or post-treatment biopsy cannot be the only measurable lesion.

Prut 1 Only

- Subjects with histologically or cytologically confi1med advanced or metastatic solid ttllllors that have failed prior standru·d therapy (disease progression; subject refusal or intolerance is also allowable).

Note: There is no limit to the number of prior treatment regimens.

Prut2 Only

Note: Subjects must have failed available therapies that ru·e known to confer clinical benefit as indicated below, unless they ru·e ineligible, intolerant, or refused standard treatment.

Subjects with histologically or cytologically confi1med NSCLC:

- Metastatic (Stage IV) or recunent NSCLC (according to American Joint Committee on Cancer 7th edition guidelines) who have had disease progression after available therapies for advanced or metastatic disease that are known to confer clinical benefit, been intolerant to treatment, or refused standard treatment.
- Prior systemic regimens must include previously approved therapies, including a platinllllll-containing chemotherapy regimen; a tyrosine kinase inhibitor for tumors with driver mutations; and checkpoint inhibitors where approved.
- Must have documented disease progression on a prior PD-1–pathway tru·geted agent (Expansion Coho1ts A-1, B-1, B-3, B-5, B-7, C-1, C-3, C-5, C-7, and C-9). Progression following cessation of PD-1 pathway–targeted therapy is not sufficient. The baseline scan for the purposes of this snldy may serve as the documentation of progression.

Subjects with recunent (unresectable) or metastatic CRC:

- Histologically or cytologically confi1med adenocru·cinoma of the colon or recnllll.
- Confumed MSS CRC as per local testing.
- Stage IV CRC (according to American Joint Committee on Cancer 7th edition guidelines) who have had disease progression after available therapies for advanced or metastatic disease that are known to confer clinical benefit, been intolerant to treatment, or refused standard treatment.
- Prior systemic regimens must include previously approved therapies, including fluoropyrimidine-, oxaliplatin-, and liinotecan-based chemotherapy; an anti–vasculru endothelial growth factor therapy (if no contraindication); and if negative for KRAS, NRAS, and BRAF mutations and no contraindication, an antipide1mal growth factor receptor therapy; and progressed after the last administration of approved therapy.

Subjects with HNSCC:

- Histologically confumed squamous cell cru·cinoma of the oral cavity, oropharynx, hypophruynx, or lal ynx.
  Note: Cru·cinomas of the nasophruynx, salivruy gland, or nonsquamous cell histology are excluded.
- Must have received prior treatment with a platinum-based therapy. Subjects who relapsed within 6 months of adjuvant therapy, including a platinum-containing regimen, may enroll. Additionally subjects must have had disease progression on a prior PD-1 pathway–tru·geted agent.
- Must have documented hllllllan papilloma viius status.

Subjects with melanoma:

- Histologically or cytologically confmned melanoma.
- Unresectable Stage III or Stage IV melanoma, as per American Joint Committee on Cancer staging s stem not amenable to local thera

- Documentation ofV600-activating BRAF mutation stants or consent to BRAF.
- V600 mutation testing during the screening pe1iod.
- Must not have ocular melanoma.

Subjects with urothelial carcinoma:

- Histologically or cytologically confhmed urothelial carcinoma of the renal pelvis, ureter, urina1y bladder, or urethra that is transitional cell or mixed transitionaVnontransitional (pred01ninantly transitional) cell type.
- Stage IV locally advanced or metastatic urothelial carcinoma (according to American Joint Committee on Cancer 7th edition guidelines) with disease progression during or after PD-1 pathway–targeted therapy.

Key Exclusion Criteria:

- Laborat01y and medical hist01y parameters not within Protocol-defined range. Cycle 1 Day 1 laborat01y assessments for the dete1mination of eligibility do not need to be pe1f01med if the screening labs were pe1fonned within 7 days of Cycle 1 Day 1. If the screening lab assessments were pe1fonned more than 7 days before Cycle 1 Day 1, the hematology, senun chemistiy, and liver chemistiy lab results must be confinned on Cycle 1 Day 1 before treannent initiation.
  - Absolute neun·ophil count < 1.5 x 10^9/L.
  - Platelet count < 100 x 10^9/L.
  - Hemoglobin < 8 g/dL (1ransfusion is acceptable to meet this crite1ion).
  - Senun creatinine1.5 x institutional upper limit of n01mal (ULN) OR measured or calculated creatinine clearance (glomemlar filn·ation rate can also be used in place of creatinine or CrCl) < 50 mL/min for subjects with creatinine levels > 1.5 x institutional ULN).
  - Aspartate aminon·ansferase, alanine aminon·ansferase, and alkaline phosphatase2.5 x ULN.
    Note: Subjects with 1) bone metastases and 2) no hepatic parenchymal metastases on screening radiographic examinations may emoll if the alkaline phosphatase is < 5 x ULN. Subjects with 1) bone metastases and 2) hepatic parenchymal metastases on screening radiographic examinations may enroll if the alkaline phosphatase is < 5 x ULN only with medical monitor approval.
  - Total bilimbin1.2 x ULN are excluded unless direct bilimbin isULN. If there is no institutional ULN, then direct bilimbin must be < 40% of total bilimbin to be eligible.
  - Intemational n01malized ratio or prothrombin time > 1.5 x ULN.
  - Activated pa1tial thromboplastin time > 1.5 x ULN.
  - Senun albmnin < 3 g/dL.
- Receipt of anticancer medications or investigational dmgs within the following interval before the first adminisn·ation of study mug:
  - < 14 days for chemotherapy, targeted small-molecule therapy, or radiation therapy. Subjects must also not require c01ticosteroids and must not have had pnemnonitis as a result ofn·eatment. A 1-week washout is pennitted for palliative radiation to non-central nervous system (CNS) disease with sponsor approval.
    Note: The use of denosumab is pennitted.
  - < 14 days for a prior PD-1 pathway–targeted agent. (If the subject was on pembrolizumab monotherapy, a wash-out is not required.)
  - < 28 days for prior monoclonal antibody used for anticancer therapy with the exception of PD-1 pathway–targeted agents.
  - < 14 days for an immune-suppressive-based treatment for any reason (including chronic use of systemic cOiticosteroid at doses of prednisone equivalent to > 10 mg/day). Use of inhaled or topical steroids or systemic corticosteroids10 mg is pe1mitted. The use of physiologic doses of corticosteroids may be approved after consultation with the sponsor.

- < 28 days or 5 half-lives (whichever is longer) before the first dose for all other investigational study <hugs or devices. For investigational agents with long half-lives (eg, > 5 days), emollment before the fifth half-life requires medical monitor approval.

- Has not recovered from toxic effect(s) of ptior therapy toGrade 1. Any immune-related adverse events (irAEs) from plior immunotherapy must have complete resolution and must have resolved at least 2 weeks before C1Dl.

  Note: Subjects withGrade 2 neuropathy or alopecia are an exception and may emoll. Subjects with immune-related hypothyroidism or a<lrenal insufficiency because of prior immunotherapy who are medically stable and adequately managed on a stable dose of replacement therapy may be emolled.

- Subjects with plior ocular toxicity from plior immune therapy are excluded.

- Subjects who have any active or inactive autoimmune disease or syn<lrome (ie, rheumatoid artluitis, moderate or severe psoriasis, multiple sclerosis, inflammat01y bowel disease) that has required systemic treatment in the past 2 years or who are receiving systemic therapy for an autoimmune or inflammat01y disease (ie, with use of disease modifying agents, c01ticosteroids, or immunosuppressive <hugs).

  Note: Exceptions include subjects with vitiligo or resolved childhood asthma/atopy, hypothyroidism stable on h01mone replacement, controlled asthma, Type I diabetes, Graves' disease, or Hashimoto's disease, or with medical monitor approval.

- Known active CNS metastases and/or carcinomatous meningitis.

  Note: Subjects with previously treated brain metastases may patticipate provided they m·e stable (without evidence of progression by imaging for at least 4 weeks before the flrst dose of study treatment and any neurologic symptoms have retumed to baseline), have no evidence of new or enlarging brain metastases, and have not required steroids for at least 7 days before study treatment.

- Has received a live vaccine within 30 days of planned stmt of study therapy.

  Note: Examples of live vaccines include, but m·e not limited to, the following: measles, mumps, mbella, chicken pox/zoster, yellow fever, rabies, Bacillus Calmette-Guerin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed vims vaccines and m·e allowed; however, intranasal influenza vaccines are live-attenuated vaccines and are not allowed.

- Evidence of interstitial hmg disease or active, noninfectious pneumonitis.

- Inability to swallow food or any condition of the upper gastrointestinal tract that precludes administration of oral medications.

- Subject has a known hist01y of or is positive for hepatitis B (hepatitis B smface antigen reactive or hepatitis B vims DNA detected) or hepatitis C (hepatitis C vims [HCV] antibody positive and/or HCV RNA [qualitative] is detected).

  Note: Hepatitis C antibody–positive subjects who received and completed treatment for HCV that was intended to eradicate the vims may patticipate ifHCV RNA levels m·e undetectable.

  Note: In Patt 2, subjects who m·e immune to hepatitis B (hepatitis B vims [HBV] surface antibody and/or HBV core antibody positive) are allowed (ie, no evidence of active infection).

- Known hist01y of human immunodeficiency vims (HIV; HIV 1/2 antibodies).

- Active infection requiring systemic therapy.

- Prior receipt of an IDO inllibitor.

- Receipt of monoamine oxidase inhibitors (MAOIs) within the 21 days before the flrst dose of study treatment.

- Hist01y of serotonin syn<h·ome after receiving 1 or more serotonergic dmgs.

- Prior receipt of any fonnulation of azacitidine, decitabine, or any other hypomethylating agent (Treatment Group A only).

- Subjects with bleeding associated with tlllnors in proximity to major blood vessels m·e excluded except with medical monitor approval.

- Hist01y of a prior Grade 3 or 4 irAE (Patt 1 dose escalation only).

- Subjects with uncontrolled type I or type II diabetes mellitus (defined as HgbAlc > 8).
- Prior receipt of a BET inhibitor (Treatment Group B only).
- Subjects with a histo1y of bleeding related to cancer under sttldy requiring a medical intervention (eg, embolization procedure, RBC transfusion, or hospitalization) within 30 days of sttldy emollment (Treatment Groups Band Conly).
- Clinically significant bleeding within 14 days of Cycle 1 Day 1 (Treatment Groups Band Conly).
- Subjects cunently receiving warfarin therapy (Treatment Group B only).
- Prior receipt of an LSD1 inhibitor including INCB059872 (Treatment Group Conly).

Epacadostat, Dosage, and Mode of Administration:

Epacadostat will be orally self-administered BID beginning on Cycle 1 Day 1 (or Cycle 2 Day 1 in Treatment Groups Band C) and continuously thereafter in 21-day cycles. All BID doses will be taken in the moming and evening, approximately 12 hours apa1t without regard to food. If a dose is missed by more than 4 hours, then that dose should be skipped, and the next scheduled dose should be taken at the usual time. Details for sttldy dmg administration in the treatment sequencing rumor biopsy coho1ts (Coho1ts A-3 through A-5, B-9 through B-11, and C-11 through C-13) ru·e presented in the Overall Srudy Design section of the Synopsis and in the Protocol.

INCB057643, Dosage, and Mode of Administration:

INCB057643 will be orally self-administered QD beginning on Cycle 1 Day 1 and continuously thereafter in 21-day cycles. All daily doses will be taken in the moming at the same time as the moming dose of epacadostat, approximately 24 ho[redacted] prior and 1 hour following dose administration, except on days when serial srunpling is conducted, then subjects will fast at least 8 hours before and 1 hour after sttldy dmg or as indicated in the Protocol. If a dose is missed by more than 8 hours, then that dose should be skipped, and the next scheduled dose should be taken at the usual time. Details for srudy dmg administration in the treatment sequencing ttimor biopsy coho1ts (Cohorts B-9 through B-11) ru·e presented in the Overall Srudy Design section of the Synopsis and in the Protocol.

INCB059872, Dosage, and Mode of Administration:

INCB059872 (United States sites only) will be orally self-administered either QD or QoD beginning on Cycle 1 Day 1 and continuously thereafter in 21-day cycles. All daily doses will be taken in the moming at the same time as the moming dose of epacadostat, approximately 24 hom
prior and 1 hour following dose administration, except on days when selial
sampling is conducted, then subjects will fast at least 8 hours before and 1 hour after srudy dmg or as indicated in the Protocol. If a dose is missed by more than 8 hours, then that dose should be skipped, and the next scheduled dose should be taken at the usual time. Details for srudy dmg administration in the treatment sequencing ttlmor biopsy coho1ts (Coho1ts C-11 through C-13) are presented in the Overall Srudy Design section of the Synopsis and in the Protocol.

Reference Therapies, Dosage, and Mode of Administration:

Pembrolizumab will be administered as a 200 mg, 30-minute IV infusion Q3W on Day 1 of each 21-day cycle. Details for study dmg administration in the treatment sequencing tumor biopsy coh011s (Coh011s A-3 through A-5, B-9 through B-11, and C-11 through C-13) are presented in the Overall Stttdy Design section in the Synopsis and in the Protocol.

Azacitidine will be administered as a SC injection or IV infusion for 5 days in Cycles 1 through 3 (in the European Union, it will be administered SC only). Details for study dmg administration in the treatment sequencing tumor biopsy cohmts (Cohmts A-3 through A-5) are presented in the Overall Study Design section of the Synopsis and in the Protocol. Subjects who remain on treatment beyond the Week 9 scan should continue to receive azacitidine until the second on-study scan (up to the Week 18 scan, for a maximum of3 additional cycles). Five doses should be administered over the Day 1-7 period.
Re-treatment with azacitidine (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 progressive disease while receiving pembrolizumab and epacadostat with medical monitor approval. Three additional cycles of azacitidine are pennitted.

Study Schedule/Procedures:

Subjects will have regularly scheduled study visits at the clinical site on Day 1 of each cycle. Additional study visits will be required during Cycles 1 through 3 (or Cycle 6 for subjects continuing azacitidine treatment beyond the first scan) while subjects are receiving priining doses of azacitidine, INCB057643, or INCB059872 ted States sites only) and throughout the study to monitor for safety, efficacy, or for [redacted]. Study visits will be as follows:

- Screening: up to 28 days before enrollment. Screening will begin at the time that the subject signs the llfmmed consent fmm and will continue until the date the subject is enrolled in the study (Cycle 1 Day 1 or Day 1 of Week -1 for Expansion Coho1t A-3).
- Treatment (Pa1t 1 Cohotts):
  - Cycle 1 (Treatment Group A): Day 1, 4 additional visits between Day 2 and Day 7, and Day 15 (± 3 days).
  - Cycle 2 (Treatment Group A): Day 1, 4 additional visits between Day 2 and Day 7, and Day 15 (± 3 days).
  - Cycle 1 (Treatment Groups Band C): Days 1, 8 (± 3 days), and 15 (± 3 days).
  - Cycle 2 (Treatment Groups Band C): Days 1, 8 (± 3 days), and 15 (± 3 days). For subjects receiving INCB059872 QoD, an additional visit will be perfmmed on Cycle 2 Day 2 or 4 so that the – and ECG assessments occur on the day ofiNCB059872 administration.
  - All other treatment cycles: Day 1 (± 3 days).

  Note: Visit schedules for the Part 2 Cohmts are specified in the Protocol.
- Efficacy assessments: Eve1y 9 weeks(± 7 days) for 12 months, and then eve1y 12 weeks(± 7 days) thereafter until disease progression is dete1mined.
- End of treatment (+ 5 days).
- Safety follow-up: 42 to 49 days after end of treatment.
- Disease status follow-up: Eve1y 9 weeks (63 ± 7 days) lmtil the sta1t of new antineoplastic therapy, disease progression, death, or the end of the study. Upon implementation of Amendment 4, follow-up for disease status will no longer be required.
- Survival follow-up: Eve1y 12 weeks (+ 7 days) following disease progression or start of new anticancer therapy. Upon implementation of Amendment 4, follow-up for survival stattls will no longer be required.

Estimated Duration of Participation:

Up to 28 days for screening, continuous treatment in consecutive 21-day cycles as long as subjects are receiving benefit and have not met any clitelia for stttdy withdrawal, and 42 to 49 days(+ 7 days) for safety follow-up. A survival follow-up period will continue evety 12 weeks(+ 7 days) after study treatment discontinuation. It is estimated that an individual subject will patticipate for approximately 18 months (screening/study treatment for 6 months and follow-up for an additional12 months). Upon implementation of Amendment 4, survival follow-up will no longer be required.

Estimated Number of Subjects:

Up to approximately 531 subjects will be enrolled in the stttdy:

- Part 1 (Treatment Group A): 15 to 45 subjects.
- Patt 2 (Treatment Group A): 76 to 114 subjects.
- Patt 1 (Treatment Group B): 39 to 57 subjects.
- Patt 2 (Treatment Group B): 0 to 129 subjects.
- Patt 1 (Treatment Group C): 39 to 57 subjects.
- Patt2 0 to 129 subjects.

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

Statistical Methods:

This is an open-label, multicenter, nonrandomized, dose-escalation Phase 1/2 stttdy. In Patt 1, dose escalation (all treatment groups), the primmy objective of the study is to detennine the MTD, maximum tested dose, or PAD ofazacitidine, INCB057643, or INCB059872 administered in combination with pembrolizumab and epacadostat in subjects with advanced or metastatic solid tumors. Dose-escalation will follow a 3 + 3 + 3 design algorithm. The total number of subjects will depend on the frequency of DLTs and the number of dose levels tested before the MTD, maximum tested dose, or PAD is reached. In addition, Pa1t 1 dose expansion coh01ts for Treatment Groups Band C in 5 NSCLC subjects who progressed on a PD-1 pathway–targeted agent and 5 MSS CRC will be opened at each dose level tested that clears the DLT window for signal analysis to guide an RP2D. The safety/efficacy expansion in Pa1t2 will include 2 m 3 treatment groups, 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 coh01ts. The response rates for histolical control *(po),* desired response rates for the combination (p1), number of subjects needed in Stage 1 (n1) and Stage 2 (n2), total number of subjects *(n),* first stage threshold declming coh01t undesirable (n), and the upper lhnit of the number of responses inn subjects such that futility ofthe dmg is concluded (r) me provided in the table below. Detailed calculation is based on a 1-sided Type enor of0.05 and power of 80%.

Simon 2-Stage Design

Cohort	Tumor Type	*Po*	Pt	n1	n2	n	rt	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 Coh01t A-2	MSSCRC	3%	20%	8	19	27	0	2
Expansion Coh01t 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 Coh01t B-8	MSSCRC	3%	20%	8	19	27	0	2
Expansion Coh01t 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 Coh01t C-10	MSSCRC	3%	20%	8	19	27	0	2

In addition to the 6 Simon 2-stage safety/efficacy expansion coho1ts, another 9 treatment sequencing tumor biopsy coho1ts will be emolled to evaluate epigenetic and tumor microenvironment changes. A total of25 subjects will be emolled in each Expansion Cohorts A-3, A-4, B-9 through B-11 and C-11 through C-13, and 10 first-line melanoma subjects will be emolled in Expansion Cohort A-5.

In the Part 2 treatment sequencing tumor biopsy cohorts, 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 Coho1ts 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 Coh01t A-5.

All statistical analyses are descdptive in nature. Descriptive statistics will be dedved where appropriate. Continuous endpoints will be summarized with number of subjects, mean, standard deviation, minimum, median, and maximum for each coho1t. Catego1ical endpoints will be summarized with frequency and percent for each coho1t.

If data wanants, ORR will be estimated with 95% exact confidence interval. Time to event endpoints such as DOR, PFS, and OS will be summarized with Kaplan-Meier estimates by cohort.

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LIST OF ABBREVIATIONS

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

Abbreviation	Definition
ACTH	adrenocorticotropic hormone
[redacted]	[redacted]
AE	adverse event
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AST	aspmtate aminotransferase
[redacted]	[redacted]
[redacted]	[redacted]
BBB	blood-brain bmTier
BCRP	breast cancer resistance protein
BID	twice daily
BET	bromodomain and extra-te1minal protein
BRD	bromodomain-containing protein
BRDT	bromodomain testis-specific protein
[redacted]	[redacted]
CEA	carcinoembryonic antigen
CFR	Code of Federal Regulations
CI	confidence interval
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
c-MYC	cellulm· f01m of a regulator gene that can act as an oncogene (MYC)
c-Myc	transcription factor encoded by the c-MYC gene
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clem·ance
CT	computed tomography

Abbreviation	Definition
CTCAE	Collllllon Te1minology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CTLA	cytotoxic T-lymphocyte antigen
CYP	cytochrome P450
DC	dendlitic cells
DDI	dmg-dmg interaction
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DNMT	deoxyribonucleic acid methyltransferase
DOR	duration of response
ECso	half maximal effective concentration
ECG	electrocardiogram
ECOG	Eastem Cooperative Oncology Group
eCRF	electronic case repo1t f01m
EDso	median effective dose
EDC	electronic data capnlre
EGFR	epide1mal growth factor receptor
EOT	end of treatment
FAD	flavin adenine dinucleotide
FDA	Food and Dmg Administration
[redacted]	[redacted]
FOXP3	forkhead box P3
GCP	Good Clinical Practice
H&E	hematoxylin and eosin
HBV	hepatitis B vims
HCV	hepatitis C vims
HDAC	histone deacetylase
HIPAA	Health Insurance Po1tability and Accountability Act of 1996
HIV	human immunodeficiency vims
HNSCC	head and neck squamous cell carcinoma
IB	Investigator's Brochure
ICso	half maximal inhibito1y concentration
lCgo	concentration that results in 90% inhibition
ICF	info1med consent f01m
ICH	Intemational Conference on Harmonisation
IDO	indoleamine 2,3-dioxygenase

Abbreviation	Definition
IEC	independent ethics cormnittee
IHC	inummohistochemist1y
IL	interleukin
IMP	investigational medicinal product
IN	Investigator Notification
INR	intemational nonnalized ratio
irAE	inununе-related adverse event
IRB	institutional review board
IRT	interactive voice/web response system
IDD	intrauterine device
IDS	intrauterine ho1mone-releasing system
IV	intravenous
JAK	Janus kinase
LFT	liver function test
LSDl	lysine-specific demethylase lA
LSD2	lysine-specific demethylase 2
MAO-A	monoamine oxidase A
MAO-B	monoamine oxidase B
MAOI	monoamine oxidase inhibitor
MCP	methyl-accepting chemotaxis protein
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulato1y Activities
MM	multiple myeloma
MMR	mismatch repair
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MSI	microsatellite instability
MSI-L	microsatellite instability-low
MSI-H	microsatellite instability-high
MSS	microsatellite stable
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSCLC	non–small-cell lung cancer
OAT	organic anion transpo1ter

Abbreviation	Definition
OATP	organic anion t:ransp01ting polypeptide
OCT	organic cation transp01ter
ORR	objective response rate
OS	overall survival
PAD	pharmacologically active dose
PD	progressive disease
PD-1	programmed death receptor-!
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-fi·ee survival
P-gp	P-glycoprotein
PK	pharmacokinetic
PO	orally
PR	pa1tial response
PSA	prostate-specific antigen
PT	prothrombin time
Q3W	evety 3 weeks
Q9W	evety 9 weeks
Q12W	evety 12 weeks
QAM	evety moming
QD	once daily
QoD	evety other day
QPM	evety evening
RCC	renal cell car·cinoma
RECIST	Response Evaluation Critelia in Solid Tumors
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SC	subcutaneous
SCCHN	squamous cell carcinoma of the head and neck
SCLC	small-cell lung cancer
SD	stable disease
SmPC	Summa1y of Product Characteristics
SNRI	serotonin-norepinephrine reuptake inhibitor
SS	serotonin syndrome
SSRI	selective serotonin reuptake inhibitor

Abbreviation	Definition
SUSAR	suspected unexpected serious adverse reaction
[redacted]	[redacted]
TDLN	tumor-draining lymph nodes
TEAE	treatment-emergent adverse event
TGA	Treatment Group A
TGB	Treatment Group B
TGC	Treatment Group C
TGI	tumor growth inhibition
TIL	tumor-infiltrating lymphocyte
TKI	tyrosine kinase inhibitor
Treg	T regulatoly cells
ULN	upper limit of nmmal
VEGF	vascular endothelial growth factor
[redacted]	[redacted]
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman of childbearing potential
[redacted]	[redacted]

1- INTRODUCTION

This is an open-label, multicenter, Phase 1/2 study evaluating the addition of 3 different epigenetic p1iming regimens to an immunotherapy doublet in ·ects with advanced or metastatic solid tumors. This study will use a suite of tissue technologies to evaluate the immune activity of the DNA methyltransferase azacitidine; the bromodomain and extra-terminal (BET) inhibitor, INCB057643; or the lysine-specific demethylase IA (LSDI) inhibitor, INCB059872, in combination with the programmed death receptor-I (PD-1) inhibitor pembrolizumab and the indoleamine 2,3-deoxygenase (IDO) 1 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. Pmt 2 of the study will be an open-label Phase 2 assessment with Simon 2-stage design to evaluate objective response rate (ORR) and tumor-infiltrating lymphocyte (TIL) infiltration in previously treated non-small-celllung cancer (NSCLC) and microsatellite stable (MSS) colorectal cancer (CRC). Separate treatment sequencing tumor biopsy cohorts are also included in the expansion to fmther evaluate epigenetic changes and changes in the tumor microenvironment in subjects with head and neck squamous cell carcinoma (HNSCC), melanoma, urothelial carcinoma, and MSS CRC.

LL Immunotherapy in Cancer

The impmtance of intact immune smveillance in controlling outgrowth of neoplastic transfmmation has been known for decades (Disis 2010). The inability of the immune system to control tumor growth does not appear to result from an inability to recognize the tumor as foreign. Tumor cells have been shown to evade the immune system by exploiting the immune checkpoint pathways that down-regulate the immune response to avoid healthy tissue damage (Davies 2014). Histologic evaluation of many human cancers shows extensive infiltration by inflammatmy and immune cells (Galon et al2006), suggesting that the immune system responds to malignancy, albeit less effectively than needed to eradicate the tumors. The presence ofTILs in cancer tissue among val ious malignancies has been shown to confer a more favorable prognosis (Mei et al2014, Gooden et al2011, Bremnes et al2011, Talmadge 2011). Detailed analysis of CD8+ T cells and the ratio of CD8+ effector T cells/forkhead box P3 (FOXP3)+ T regulatmy cells (Tregs) seem to conelate with improved prognosis and long-te1m smvival in many solid tumors (Nosho et al2010, Chang et al2014, Preston et al2013, Yoon et al2012, Kim et al2013). Although the immune system has been shown to recognize and reject a tumor, many tumors evade immune smveillance or develop mechanisms of resistance.

Immune therapies targeting the immune checkpoint pathways have recently become an important therapeutic strategy for hamessing the immune system's ability to control malignancy. Justification for the blockade of immune inhibitmy pathways is evidenced by the clinical responses obse1ved with antibodies to cytotoxic T-lymphocyte antigen (CTLA)-4 and PD-1/programmed death-ligand 1 (PD-L1). Checkpoint inhibitors including ipilimumab, nivolumab, pembrolizumab, and atezolizumab have shown durable antitumor activity with minimal toxicity in several different tumor types and have been approved as monotherapy or combination treatment in melanoma, NSCLC, renal cell carcinoma, classical Hodgkin lymphoma, urothelial carcinoma, and HNSCC (Opdivo 2017, Keytmda 2017,

Powles et al2014). While great advances have been made, with the exception of melanoma, which has shown the highest response rates in monotherapy, the majority of solid tumors do not respond to checkpoint inhibitors alone. Additionally, the greatest antitumor effect is in patients with the highest expression of the PD-1 ligand, PD-L1, on tumor cells (Brahmer et al2010, Garon et al2015). Multiple immune inhibitmy mechanisms are present concunently within the tumor microenvironment, suggesting that combination therapies may be required for optimal therapeutic effect (Quezada and Peggs 2013). A combination of immunotherapy agents that stimulate an immune response targeted to tumor cells combined with the relief of negative regulation should synergize in allowing the immune system to generate a response leading to enhanced tumor rejection.

One mechanism of inducing tolerance for malignancy is through IDO1 (Godin-Ethier et al2011). Indoleamine 2,3 dioxygenase **1** is a heme-containing, monomeric oxidoreductase that catalyzes the degradation of the essential amino acid tryptophan to N-fmmyl-kynurenine. Indoleamine 2,3-dioxygenase l-d1iven oxidation of tryptophan results in a strong inhibitmy effect on the development ofT-cell-mediated responses by blocking T-cell activation and inducing T-cell apoptosis (Mellor et al2003). Both the reduction in local tryptophan levels and the production of tryptophan catabolites are inhibitmy to T-cell proliferation and contribute to immunosuppressive effects (Fnnnento et al 2002). Indoleamine 2,3-dioxygenase 1 activity also promotes the differentiation of naive T cells to cells with a regulatmy phenotype (Treg; Fallarino et al2006). Since increased Treg activity has been shown to promote tumor growth and Treg depletion has been shown to stimulate an othe lwise ineffectual antitumor immune response (Zou 2006), IDO**1** expansion of Tregs may provide an additional mechanism whereby IDO1 could promote an immunosuppressive environment.

Epigenetic therapies such as DNMT inhibitors, histone deacetylase (HDAC) inhibitors and BET inhibitors have recently become a suggested combination pa1tner for immune therapies. Over the last several decades, there has been a greater understanding of the functional implications of histone modifications and DNA methylation pattems in regards to cell cycle regulation and cancer (Ahuja et al2016). Recent preclinical studies have shown evidence that epigenetic modulators may sensitize tumor-bearing animals to immune therapies including PD-1 blockade. In NSCLC cell lines, azacitidine has been shown to upregulate genes and pathways related to both innate and adaptive immunity as well as genes related to immune evasion. Of particular interest, azacitidine was shown to up-regulate PD-Ll tr·anscripts and protein (Wrangle et al2013). In a recent study, Chiappinelli et al (2015) showed that DNMT inhibitors up-regulated immune signaling in cancer cell lines through a viral defense pathway. In ova1ian cancer, DNTM inhibition u·iggered cytosolic sensing of double-stranded RNA and caused a Type I interferon response and apoptosis.

Early signals of potential efficacy from combined epigenetic agents were obse1ved in solid tumors while evaluating a low dose regimen of the DNMT inhibitor azacitidine with the HDAC inhibitor entinostat. In a heavily pretreated NSCLC population of 45 subjects, objective responses were obse1ved in only 4% of subjects, but 1 subject had a complete response (CR) for a duration of 14 months and a second subject had a pa1tial response (PR) that lasted 8 months. There were 10 subjects who had stable disease (SD) for at least 12 weeks. The clinical responses that were obse lved continued after the discontinuation of the epigenetic modifiers, suggesting a sustained antitumoral effect (Juergens et al2011). Five NSCLC subjects from this epigenetic study went on to receive immune checkpoint therapy in a nivolumab Phase **1** study. All

5 subjects were without progression at 6 months, and 3 of these subjects developed high-grade Response Evaluation C1iteria in Solid Tumors (RECIST) PRs that have been durable for over 2.5 years (Chiappinelli et al2016). As a result of the preclinical and early clinical data, several clinical studies have been initiated in solid tumors to dete1mine whether the combination of an epigenetic modifier with checkpoint inhibitors may increase response rates and prolong duration of response (DOR) in tumor types that are known to respond to PD-1 pathway inhibition (NCT01928576, NCT02512172). There are also investigations unde1way to dete1mine whether adding epigenetic therapy to checkpoint inhibitors can release the immune tolerance and generate responses in leukemia and solid tumors where they have not been shown to be responsive to checkpoint inhibition alone (Murphy et al2016, Daver et al2016). The current study will investigate whether generating an inte1feron response while simultaneously blocking multiple adaptive resistance pathways that are also interferon regulated creates benefit in subjects with solid tumors.

1.2. Overview of Pembrolizumab

Pembrolizumab is a humanized immunoglobulin G4 antibody that blocks the PD-1 receptor expressed by T cells (Hamid et al2013). In a Phase 1 study in subjects with advanced melanoma and NSCLC, pembrolizumab was shown to be generally well-tolerated with no maximum tolerated dose (MTD) identified. Pembrolizumab showed promising antitumor activity in melanoma and NSCLC with ORRs of38% and 19.4%, respectively (Hamid et al2013, Garon et al 2015). A broad development program was initiated in multiple solid tumors and hematological malignancies, and pembrolizumab was first approved by the FDA on 04 SEP 2014 for the treatment of patients with umesectable or metastatic melanoma and disease progression following ipilimumab and, ifBRAF V600 mutation-positive, a BRAF inhibitor. Pembrolizumab has shown broad anticancer activity in a variety of solid tumors and has also been approved in subjects with metastatic NSCLC whose tumors express PD-Ll and had progression on or after platinum-based chemotherapy and in subjects with recunent or metastatic HNSCC that have disease progression on or after platinum-containing chemotherapy (Robe1t et al 2014, Le et al2015, Ribas et al2015, Herbst et al2016, Seiwe1i et al2016).

Refer to the pembrolizumab approved label for fmther preclinical and clinical study data.

1.3. Overview of Epacadostat

Epacadostat represents a novel, potent, and selective inhibitor of the enzyme IDO1. In cell-based assays, epacadostat potently inhibits IDOl in both human tumor cells and human dendritic cells (DCs), resulting in reduced tryptophan to kynurenine conversion (IC_{50} values = 7.1-12.7 nM). Epacadostat does not significantly inhibit other proteins that could affect tryptophan catabolism. In cell culture, epacadostat reverses the strongly inhibitmy effect on the development ofT-cell-mediated responses that IDO1 activity impa1ts, resulting in enhanced T-cell and natural killer cell proliferation, enhanced interferon-y production, reduced Treg differentiation, reduced DC apoptosis, and enhanced expression of DC activation markers. Epacadostat reversal of the IDO1-mediated suppression ofT-cell proliferation is dose-dependent, with a potency consistent with its inhibition of tryptophan to kynurenine conversion (EC_{50} = 17.7 nM). The *in vivo* data demonsti·ate that epacadostat can inhibit IDOl systemically, and impmtantly, in tumors and tumor-draining lymph nodes (TDLN). Epacadostat was

efficacious in mouse models of colon and pancreatic cancer, and its ability to reduce tumor growth was dependent on a functional immune system, which is consistent with its proposed mechanism of action. Moreover, epacadostat enhanced lymphocyte function in tumors and TDLN. The combination of epacadostat and either an antimouse CTLA-4 or an antimouse PD-L1 antibody was also shown to act synergistically in significantly reducing tumor growth in a melanoma xenograft model. Finally, epacadostat improved the tumor growth control of cytotoxic chemotherapy when used in combination. These data support the evaluation of epacadostat in patients with malignant diseases.

As ofSEP 2016, 12 Phase 1, 2, or 3 Incyte-sponsored clinical studies have either been completed or are ongoing. Five investigator-sponsored clinical studies have either been completed or are ongoing. As of 10 JUN 2016, 607 unique subjects have been exposed to epacadostat either as monotherapy (91 subjects) and/or in combination with checkpoint inhibitors (anti-PD-1 targeted therapy: 384 subjects; anti-PD-L1 targeted therapy: 82 subjects; and anti-CTLA-4 targeted therapy: 50 subjects). Epacadostat has been evaluated in a completed Phase 1 study and has several ongoing Phase 1 and 2 studies in combination with immune-targeted agents, such as a small molecule Janus kinase (JAK)-1 inhibitor and anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies. Based off of preliminary data in subjects with melanoma in the Phase 1\2 study evaluating the combination of pembrolizumab and epacadostat (Study INCB 24360-202), a global Phase 3 study has been initiated in first-line metastatic melanoma.

In the Phase 1 clinical study in subjects with refractmy solid tumors (INCB 24360-101), epacadostat was well-tolerated at doses ranging from 50 mg once daily (QD) to 700 mg twice daily (BID). Twenty-five (48.1%) ofthe 52 subjects administered epacadostat repmted a serious adverse event (SAE). The most frequently repmted SAEs were disease progression (4 subjects, 7.7%) followed by abdominal pain, nausea, and hypoxia (3 subjects each, 5.8%). The most commonly repmted treatment-related treatment-emergent adverse events (TEAEs) were fatigue and nausea (25 subjects, 48.1%). Two dose-limiting toxicities (DLTs) occUlTed: 1 DLT of radiation pneumonitis at the 300 mg dose level and 1 DLT of fatigue at the 400 mg BID dose level.

In an ongoing Phase 1 open-label dose-escalation study of epacadostat with ipilimumab (3 mglkg intravenously [IV]), daily doses of epacadostat have been evaluated in 21-day cycles. A total of 48 subjects have been emolled to date in 6 cohmts: 300 mg, 100 mg, 25 mg, and 50 mg BID; 75 mg total daily dose (50 mg evely moming [QAM] and 25 mg evely evening [QPM]); and 50 mg BID intemlittent doses (2 weeks on and 1 week off). The initial evaluation of INCB024360 300 mg BID in combination with ipilimumab was tenninated due to the occunence of Grade 3 or 4 alanine aminotransferase (ALT)/aspaitate aminotransferase (AST) elevations in 5 of7 subjects treated at tills dose. These adverse events (AEs) were reversible in all subjects upon discontinuation of study therapy and institution of corticosteroids based on an established protocol for the management of immune toxicities related to ipilimumab therapy. Emollment was resta1ted at 25 mg BID. Serious AEs were observed in the 300 mg BID, 25 mg BID, 75 mg total daily dose (50 mg QAM and 25 mg QPM), and 50 mg BID inte1mittent dose groups. The system organ class with the most frequently repmted SAEs was gastrointestinal disorders (8 subjects, 16.7%) followed by investigations (6 subjects, 12.5%). Treatment-emergent AEs were repmted in 49 subjects (98.0%). Fatigue was the most frequently repmted TEAE (33 subjects, 66.0%) followed by rash (27 subjects, 54.0%; includes the prefened telms rash, rash generalized, rash macular, rash maculopapular, and rash pmritic). As of European Society

for Medical Oncology 2015, 30 immunotherapy-naive subjects were emolled; 30% of those subjects achieved objective response, and 60% achieved disease control (both assessed by immune-related response c1iteria; Gibney et al2015). INCB024360 at doses up to 50 mg BID with ipilimumab were generally well-tolerated, and immune-related adverse events (irAEs) previously observed with ipilimumab were reversible with approp1iate management. Tumor response and duration data suggest the potential for enhanced melanoma patient outcomes compared with ipilimumab monotherapy. Epacadostat is also being evaluated in 2 clinical studies with the PD-1 inhibitors nivolumab (INCB 24360-204) and pembrolizumab (INCB 24360-202) and 2 studies with anti-PD-Ll inhibitors, atezolizumab (INCB 24360-110) and dmvalumab (INCB 24360-203).

In a current, ongoing study (INCB 24360-202), emollment is complete in the Phase 1 cohmts of epacadostat 25 mg BID, 50 mg BID, 100 mg BID, and 300 mg BID cohmts with pembrolizumab 2 mglkg or 200 mg IV eve1y 3 weeks (Q3W). The Phase 2 pa1t of the study is still ongoing, in which the recommended Phase 2 dose (RP2D) of epacadostat 100 mg BID is being evaluated in combination with the fixed dose ofpembrolizumab 200 mg IV Q3W. As of28 MAR 2016, a total of 181 subjects have been emolled to the study (both Phase 1 and Phase 2). Among the 117 subjects who have received epacadostat 100 mg BID in combination with pembrolizumab, the most frequently reported (;::: 15%) AEs of any grade for all treatment groups combined were fatigue (35.0%), constipation (24.8%), dianhea (20.5%), nausea (20.5%), vomiting (18.8%), pyrexia (16.2%), and dyspnea (15.4%). Fatigue (13.7%) and rash (11.1%; including the prefened tenns rash, rash maculopapular, rash generalized, and rash macular) were the only treatment-related AEs repmted in > 10% of subjects. Treatment-related AEs of rash were only repmted in the Phase 2 group.

The ORR in 19 evaluable subjects with treatment-naive metastatic melanoma was 53% (10119), with disease control rate of74% (14l19). Median progression-free smvival (PFS) has not been reached, and all responses are ongoing with minimum follow-up of 31.7 weeks. Objective responses were also seen in other tumor types emolled in Phase 1 (Gangadhar et al2015). Based off of data in Study INCB 24360-202, a Phase 3 study of epacadostat in combination with pembrolizumab has been initiated in subjects with umesectable or metastatic melanoma.

Refer to the epacadostat Investigator's Brochure **(IB)** for additional preclinical and clinical study data.

1.4. Overview of Azacitidine

Azacitidine is a cytidine nucleoside analog that incorporates with DNA and RNA. Once azacitidine is incorporated in the DNA, this leads to the depletion of DNMTs, hypomethylation of DNA, and the induction of DNA damage (Hollenbach 2010). There are 2 main mechanisms that result in antitumor activity for azacitidine, cytotoxicity, which is the result of its incorporation into RNA and DNA, and DNA hypomethylation, which restores nmmal growth control and the differentiation in hematopoietic cells. Clinical investigation of azacitidine as a standard cytotoxic agent began in the late 1960s and 1970s in various hematologic and solid tumor indications. Early studies evaluated doses ranging from 150 to 750 mg/m^2 and showed activity in myeloid malignancies. In subsequent studies in subjects with relapsed leukemia, an obse1vation was made that higher remission rates occmTed with treatment at lower doses (Vigil et al2010). Azacitidine was evaluated in subjects with myelodysplastic syndrome (MDS)

in a Phase 3 randomized controlled study using a subcutaneous (SC) dose of 75 mg/m^2 for 7 days every 4 weeks. In this study, 60% of patients randomized to azacitidine had a response (7% CR, 16% PR, and 37% had hematologic improvement), compared with 5% improved in the supportive care aim. The median time to leukemic transfmmation or death was 21 months on the azacitidine aim, compared with 13 months on the best suppmtive care aim (Silve1man et al2002). In a separate randomized overall survival (OS) study in high-risk MDS, azacitidine showed a median OS of24.5 months, compared with 15.0 months for subjects receiving conventional care (Fenaux et al2009). Azacitidine was approved by the FDA in 2004 for the treatment MDS, defmed by French-American-British criteria. In the European Union, azacitidine is indicated for the treatment of adult patients who are not eligible for hematopoietic stem cell transplantation with inteimediate-2 and high-1isk MDS according to the Intemational Prognostic Scoring System, chronic myelomonocytic leukemia with 10% to 29% manow blasts without myeloproliferative disorder, acute myeloid leukemia (AML) with 20% to 30% blasts and multilineage dysplasia (according to WHO classification, and AML with > 30% manow blasts according to the WHO classification.

In the United States, azacitidine may be administered by SC injection or IV infusion with a recommended staiting dose of 75 mg/m^2 daily for 7 days. In the European Union, azacitidine is approved with the same dose with administration by the SC route only. Cycles should be repeated every 4 weeks, and after 2 cycles, the dose may be increased to 100 mg/m^2 if no beneficial effect has been observed and no toxicity other than nausea and vomiting has occmTed. By SC injection, azacitidine is rapidly absorbed with a maximum plasma concentration observed at 30 minutes and a mean plasma half-life of approximately 41 minutes. Due to the inconvenience of a 7-day schedule, a randomized study evaluated altemative dose schedules (with a maximum of 5 consecutive days) and showed them to be similarly safe and efficacious compared with the approved regimen. Results suggested that a azacitidine regimen of75 mg/m^2 daily for 5 days may be better tolerated and more convenient (Lyons et al 2009).

Evidence of efficacy from azacitidine treatment in solid tumors has recently been shown in several preclinical and clinical studies (Juergens et al2011, Tsai et al2012, Wrangle et al2013, Li et al2014). When given in low doses, on-target effects have been maintained, and off-target effects have been avoided. In solid tumor cell lines, it has been shown that low doses of azacitidine alter several key pathways related to cancer, including cell cycle and mitotic pathways, mRNA splicing and translation, and transcription and DNA replication. Treatment with azacitidine has shown strong upregulation of immunomodulatmy pathways and suggests the possibility that epigenetic therapy may be able to sensitize patients to immunotherapy (Wrangle et al2013, Li et al2014, Chiappinelli et al2015, Peng et al2015, Chiappinelli et al2016).

Refer to the azacitidine local label for fmther preclinical and clinical study data.

L5- Overview of INCB057643

INCB057643 is a selective inhibitor of BET proteins that is proposed for the treatment of advanced cancer. The BET family ofbromodomain-containing proteins (BRDs) function as transcriptional regulators binding to acetylation marks in chromatin at gene promoter and enhancer elements and recmiting transcription initiation and elongation complexes. In tumor cells, abenant patte1ns of epigenetic marks, including acetylation, underlie abnmmal transcriptional regulation of genes involved in cellular proliferation, smvival, differentiation, and

migration, thereby promoting an oncogenic program. Bromodomain and extra-telminal proteins are essential for the transcription of many of these genes; thus, inhibition of BET binding to chromatin may suppress oncogenic transcription in cancer cells. Suppression of these oncogenic factors has the potential to inhibit the growth of a valiety of tumor cell types and may be effective in the treatment of advanced malignancies.

In vitro, INCB057643 inhibited binding of BET proteins to acetylated histone H4 peptide. The ICso values for BRD4BD1 and BRD4BD2 are 39 ± 6 and 6 ± 1 nM (mean ± standard deviation), respectively. INCB057643 also inhibited BRD2, BRD3, and with lower potency, bromodomain testis-specific protein (BRDT), in biochemical assays. When evaluated against 32 distinct bromodomains from 25 human proteins, INCB057643 exhibited selectivity for BET family BDs. In cellular assays, INCB057643 suppressed the c-MYC protein, a BRD4 target, in KMS12BM multiple myeloma (MM) cells, with an ICso value of 111 ± 41 nM. Many cancer cells derived from hematologic malignancies showed sensitivity to INCB057643 in viability assays, and cells treated with INCB057643 exhibited G1 cell cycle anest and, in some examples, apoptotic cell death. Multiple myeloma and AML cell lines showed the greatest sensitivity, in general, with ICso values for growth inhibition generally < 200 nM. In contrast, INCB057643 inhibited the proliferation of interleukin (IL)-2–stimulated T cells from nmmal donors with a potency of 494 ± 118 nM (mean± standard deviation). The growth of a number of solid tumor cell lines from colon, lung, and breast cancer were also inhibited by INCB057643. In an assay to estimate potency in the presence of human semm proteins, INCB057643 suppressed c-Myc protein levels in myeloma cells spiked into human whole blood, with an ICso value of 55 nM. INCB057643 also suppressed the induction of endogenous methyl-accepting chemotaxis protein (MCP)-1 and MCP-3 from human whole blood that was stimulated *ex vivo* with lipopolysaccharide. The ICso values of 40 nM and 39 nM for MCP-1 and MCP-3, respectively, are similar to the c-Myc whole blood ICso value. These data demonstrate that INCB057643 inhibits BET proteins *in vitro* and in cellular assays, and that inhibition of BET proteins results in the anest and, in some models, death of cancer cells.

In vivo, INCB057643 inhibited the growth of several tumor models in mice at tolerated, oral doses. In the MM1.S model ofMM, a single dose of iNCB057643 suppressed c-Myc protein levels in tumor cells in a dose-dependent manner. Tumor pha1macokinetic (PK)-phaimacodynamic analysis revealed an *in vivo* ICso value of 367 nM for c-Myc suppression in the MM1.S MM model. The growth of established human tumors was suppressed significantly by INCB057643 when administered as a single agent in the MM1.S MM, MOLM-16 AML, WILL2 lymphoma, H526 small-cell lung cancer (SCLC), and RKO colon cancer SC xenograft models in immunocompromised mice at 3 to 20 administered or 1 to 3 mg/kg administered BID orally. [redacted]

The absorption, distiibution, metabolism, and excretion of iNCB057643 have been characterized in rats, dogs, and monkeys. Following IV administration, the systemic clearance was moderate in rats (36% hepatic blood flow) and low in dogs and monkeys (4.1% and 13% of hepatic blood flow, respectively). The steady-state volume of distiibution was moderate in rats and monkeys (2.6 and 2.8 L/kg, respectively), but low in dogs (0.66 L/kg). The te1minal elimination half-life was moderate, estimated to be approximately 4.3 hours in rats, 7.1 hours in dogs, and 7.0 hours in monkeys. INCB057643 has low to moderate renal excretion; the administered dose excreted

in mine as parent varied from 12.5% in monkeys, to 17.6% in rats, and to 26.1% in dogs. After oral administration, oral bioavailability was low in dogs (21%), but moderate in rats (58%) and monkeys (39%-78%). Based on 2-species allometric scaling from rats and monkeys, the temlinal elimination half-life in humans is projected to be approximately 17 hours, and the oral bioavailability is projected to be approximately 40%. At a clinical dose of 12 mg QD, which is expected to provide plasma concentration exceeding ICso (55 nM based on whole blood c-Myc inhibition) for 12 hours, the total steady-state plasma AUCo-24 and Cmax are estimated to be approximately 1.5 JlM·h and 0.1 JlM, respectively.

INCB057643 exhibits low in vitro pe1meability across Caco-2 monolayers and low aqueous solubility. *In vitro* transpmt studies indicate that INCB057643 is a substrate of both P-glycoprotein (P-gp) and breast cancer resistant protein (BCRP) efflux transpmters, and neither efflux transpmter was saturated up to 300 JlM. INCB057643 has limited penetration across the rat blood-brain banier (BBB), with a steady-state brain to plasma concentration ratio of 0.11. *In vitro* human protein binding of INCB057643 was low (unbound fraction of 49.1%), similar to that in preclirucal species.

The interactions of iNCB057643 with uptake and efflux transpmters were evaluated using *in vitro* systems. Though INCB057643 is a moderate inhibitor of P-gp, organic cation transpmter (OCT)2, organic anion transpmter (OAT)3, orgaruc aruon transpmting polypeptide (OATP)1B3, and OATP1B1, no dmg-dmg interactions (DDis) are expected based on the projected steady-state human plasma Cmax and concentrations in the gut. Reaction phenotyping using recombinant human cytochrome P450s (CYPs) indicated that INCB057643 was primarily metabolized by CYP3A4/5, and therefore, it is possible that the PK ofiNCB057643 might be affected by coadministration of potent CYP3A4 inhibitors or inducers. INCB057643 is not an inhibitor of the major CYPs evaluated. The metabolism profiles of iNCB057643 in rat, monkey, and human *in vitro* liver preparations were qualitatively similar. Analysis of plasma samples identified M3 (INCB070378) to be a major metabolite in rats and M2 (INCB057228) to be a major metabolite in monkeys *in vivo*. There was no evidence of a human-specific metabolite. Metabolite M2 (INCB057228) is an active metabolite with an ICso of 29 nM (whole blood c-MYC inhibition) while M3 (INCB070378) was not active. The metabolites observed *in vitro* in human liver microsomes were also observed *in vivo* in preclinical species. No glutathione adducts were detected upon incubation of iNCB057643 in human liver microsomes, suggesting that INCB057643 does not generate any reactive metabolites.

Recent studies have shown that BET protein inhibition may have effects beyond the direct inhibition of malignant cell growth. Using genetic knockdown and small molecule inhibitors, BET protein inhibition altered the expression of pro-inflammatory cytokine genes (Belkina et al2013) and (Ceribelli et al2014). Inhibition of BET protein activity may have utility in a setting where there is an altered expression of growth-promoting, proinflammatory, and survival genes contiibuting to the establishment and persistence of the oncogenic phenotype.

INCB057643 is cunently being evaluated in an ongoing Phase 1 study (INCB 57643-101) in subjects with advanced solid tumors or hematologic malignancies. A total of 32 subjects have been dosed with INCB057643 as of 17 MAY 2017. See Section 1.7.2 for fmther details. For a thorough discussion of the pha1macology of iNCB057643, refer to the INCB057643 Investigator's Brochure (IB).

L6- Overview of INCB059872

INCB059872 is a covalent flavin adenine dinucleotide (FAD)-directed inhibitor ofLSD1 that is proposed for the treatment of advanced malignancies. Lysine-specific demethylase 1 regulates gene expression epigenetically by removing methylation marks from lysine 4 or 9 of histone H3. Target genes of LSD1 are involved in many biological processes including cell growth, survival, differentiation, and stem cell homeostasis. Studies have shown that deregulated LSD1 activity is associated with human diseases, including cancer, where overexpression of LSD1 is frequently associated with poor clinical outcomes. These data suggest that INCB059872 may be therapeutic for the treatment of a variety of malignancies.

In enzyme-based assays, INCB059872 potently inhibited LSD1, with half maximal inhibition (ICso) values of 18 ± 3 nM (mean ± standard deviation), while INCB059872 did not inhibit lysine-specific demethylase 2 (LSD2) and monoamine oxidase *AIB* (MAO-A, MAO-B). Both biochemical and *in vitro* phatmacodynamic assays consistently demonstrated that INCB059872 was a FAD-directed inhibitor ofLSD1. In cellular assays, INCB059872 inhibition resulted in the up-regulated expression of the differentiation markers, CD86 and CD11b, in multiple AML cell lines and human primaty AML cells across the different French-American-British subtypes. Using the human acute monocytic leukemia cell line, THP-1, spiked into human whole blood to estimate potency in the presence of human semm proteins, INCB059872 induced CD86 protein with an ECso value of 23 ± 8 nM. Human AML cell lines showed various degrees of sensitivity to INCB059872 in cell proliferation assays, with ECso values ranging from 17 to 314 nM, and treated cells undetwent G1 cell cycle anest. The antitumor activity of INCB059872 was fmther evaluated in human ptimaty AML cells *ex vivo.* INCB059872 as a single agent or in combination with all-trans retinoic acid induced cellular differentiation (CD86 and CD11b induction) and reduced ptimary AML cell viability *ex vivo.*

The proliferation of a number of SCLC cell lines was also inhibited by INCB059872, with ECso values ranging from 47 to 377 nM. Non-tumorigenic cells, by contrast, were significantly less sensitive to INCB059872, with ICso values > 10 11M in IL-2-stimulated T cells from nmmal donors. INCB059872 also demonstrated no significant effects on cellular proliferation or survival in HEK293 human embtyonic kidney cells at concentrations up to 20 JlM. These data demonstrate that INCB059872 inhibits LSD1 activity *in vitro,* and that inhibition ofLSD1 results in the growth anest and differentiation of cancer cells compared to nmmal cells. *In vitro* phatmacodynamic assays for LSD1 inhibition in AML cells showed that induction of the CD86 myeloid differentiation marker by INCB059872 was sustained for 5 days after removal of INCB059872 in culture. These results confitm that INCB059872 is a covalent FAD-directed inhibitor of LSD1 in cells.

In vivo, oral administration of INCB059872 demonstrated phatmacodynamic activity and efficacy in several models of human and murine AML and in human SCLC xenograft models in mice. Tumor phatmacodynamic analyses conducted in both the Molm-13 human AML systemic xenograft model and the THP-1 human AML SC xenograft model demonstrated induction of CD86 and CD11b expression, consistent with *in vitro* data. In these models, the phatmacodynamic activity ofiNCB059872 was marginal at a dose of0.1 mg/kg and maximal at doses 2:: 0.5 mg/kg, demonstrating an *in vivo* EDso for CD86 induction of approximately 0.3 mg/kg. In addition, tumor phatmacodynamic responses were sustained for over 48 to 72 hours after administration, consistent with the inhibition of LSD1 by covalent modification of

FAD. Consistent with *in vivo* phatmacodynamic studies, QD doses ofiNCB059872 greater than the *in vivo* EDso showed significant and comparable antitumor effects in human AML xenograft models, while doses less than the *in vivo* EDso exhibited either no efficacy or marginal TGI in these tumor xenograft models. Similar effects of QD administration regimens on TGI were observed in human SCLC tumor xenograft models (NCI-H562 and NCI-H1417), with a marked reduction in plasma pro-gastrin-releasing peptide levels in INCB059872-treated NCI-H1417 tumor-bearing mice relative to vehicle controls. Altemative oral administration regimens of INCB059872, including every other day (QoD), generally were comparably efficacious as a QD administration regimen in these AML and SCLC xenograft models, consistent with the prolonged phatmacodynamic effects associated with INCB059872.

In the MLL-AF9 murine leukemia engraftment model in C57BL/6 mice, the median survival of leukemic animals was significantly prolonged in mice receiving doses greater than or equal to a phatmacodynamically active oral dose ofiNCB059872 over a 14-day administration period. These survival effects ofiNCB059872 in the MLL-AF9 murine AML model were associated with an expansion of the percentage of nmmal bone manow cells, a reduction in leukemic stem cells, a decrease in the number of AML blast cells, the induction of myeloid differentiation, and a nmmalization of hematological parameters to those of non-leukemic mice.

The absorption, distiibution, metabolism, and excretion ofiNCB059872, a covalent FAD-directed inhibitor of LSD1, have been characterized in rats, dogs, and monkeys. After IV administi·ation, the systemic clearance was low in monkeys and dogs (23% and 29% of hepatic blood flow, respectively), and moderate in rats (37% of hepatic blood flow). The clearance mechanisms ofiNCB059872 include both CYP-dependent metabolism and non-enzyme dependent catabolism. The administered dose excreted in urine as intact INCB059872 varied from approximately 9.9% in rats to 7.8% in dogs and 3.5% in monkeys, indicating renal clearance as minor elimination pathways. INCB059872 exhibited a moderate steady-state volume of distribution in all3 species (0.9-1.5 L/kg), suggesting moderate disti·ibution. After oral administration, oral bioavailability was moderate in monkeys (37%), but high in rats (70%) and dogs (100%). The tetminal elimination half-life was 1.0 hour in rats, 1.2 hours in dogs, and 3.3 hours in monkeys. Despite a shmt half-life, sustained phatmacological activity was observed *in vitro* and *in vivo,* presumably a result of covalent binding ofFAD, the cofactor ofLSD1 (resulting in LSD1 inhibition, ie, a PK-phatmacodynamic divergence is expected for this mode of inhibition by INCB059872). Based on allometiic scaling, the tetminal elimination half-life in humans is projected to be approximately 3 hours, and the oral bioavailability is projected to be 70%. Significant antitumor effects were observed in mice when peak plasma concentration exceeded the ECso in the whole blood assay with either QD or QoD administi·ation. Based on preclinical PK-phatmacodynamic relationship, the projected clinical dose for efficacy is 2 mg QoD, which is expected to provide plasma concenti·ations exceeding the ECso of0.023 JlM (based on THP-1 spiked whole blood assay with CD86 induction) for 2 hours, the total steady-state plasma AUCo-48 and Cmax are estimated to be approximately 0.2 J.1M·h and 0.05 J.lM, respectively.

INCB059872 exhibits moderate *in vitro* petmeability across Caco-2 monolayers (3.8×10^{-6} em/sec) and high aqueous solubility (20 mg/mL). *In vitro* tt·anspmt studies indicate that INCB059872 is a weak substrate of efflux transpmter P-gp, but not ofBCRP. INCB059872 has limited peneti·ation across the rat BBB, with a steady-state brain to plasma ratio of 0.1.

In vitro human protein binding ofiNCB059872 was low (unbound fraction of73.5%), similar to that in preclinical species.

INCB059872 did not inhibit hepatic uptake transporters (OATP1B1 and OATP1B3). While INCB059872 was a weak inhibitor of renal uptake transpmters (OCT2, OAT1 and OAT3), no DDis are expected based on inhibitmy activities of the INCB059872 uptake transpmter at phatmacologically relevant exposures. Moreover, INCB059872 did not inhibit P-gp or BCRP efflux transpmters. Reaction phenotyping using recombinant human CYPs indicated that INCB059872 was metabolized by CYP2D6 and CYP3A4, and therefore it is possible that the PK of INCB059872 will be affected by co-administration of potent CYP2D6 inhibitors or CYP3A4 inhibitors/inducers. INCB059872 is not an inhibitor of the 6 CYPs evaluated and therefore no DDis are expected based on INCB059872 CYP inhibitmy activities at pha1macologically relevant exposures of INCB059872. The metabolism profile of INCB059872 in rat, dog, monkey, and human *in vitro* liver preparations was qualitatively similar, with M1 (INCB061984) generated at levels greater than 10% ofiNCB059872 across all species. However, M1 was also generated in buffer or buffer fmtified with rat bile, bilimbin and FAD, indicating that nonenzymatic mechanisms are also involved in the fmmation ofM1. There was no evidence of any human specific metabolites. *In vivo,* parent INCB059872 was the most abundant component in rat and dog plasma and M1 (INCB061984) was identified in rat plasma (-4% of INCB059872) and dog plasma (–40% ofiNCB059872).

INCB059872 is cunently being evaluated in an ongoing Phase 1 study (INCB 59872-101) in subjects with advanced solid tumors or hematologic malignancies. A total of 39 patients have been dosed with INCB059872 as of 10 mL 2017. See Section 1.7.2 for further details. For a thorough discussion of the pha1macology ofiNCB059872, refer to the INCB059872 Investigator's Brochure (IB).

L7- Study Rationale

1.7.1. Rationale for Combining Epigenetic Therapy With Immunotherapy

Blockade of immune inhibitmy pathways is emerging as an important therapeutic modality for the treatment of cancer as evidenced by the clinical responses observed with antibodies to CTLA-4 and PD-1/PD-Ll. Pembrolizumab has shown broad antitumor activity and has produced durable objective responses in patients with melanoma, NSCLC, urothelial cancer, gastric cancer, triple-negative breast cancer, and classical Hodgkin lymphoma (Robe1t et al2015, Plimack et al2015, Herbst et al2016, Muro et al2016, Nanda et al 2016, Almand et al 2016). Although checkpoint inhibitors as single agents have significant antitumor activity in several areas of unmet need, there are many patients that do not respond to this immune therapy. Multiple immune inhibitmy mechanisms are present concurrently within the tumor microenvironment, suggesting that combination therapies may be required for optimal therapeutic effect (Quezada and Peggs 2013). There are many clinical studies in all phases of development evaluating checkpoint inhibitors with chemotherapy, radiotherapy, molecularly targeted agents, vaccines, and other novel immunotherapies.

In recent years, there have been many discoveries related to the understanding of the nmmal and cancer "epigenome" and how it is regulated. The knowledgebase of epigenetics continues to expand as more is leamed about the functional significance of histone modifications and DNA

methylation pattems in relation to malignancy (Chiappinelli et al2016). Recent preclinical studies have shown evidence that epigenetic therapy may be able to sensitize tumor-bearing animals to immune therapies including PD-1 blockade. fu NSCLC cell lines, the DNMT inhibitor azacitidine has been shown to upregulate genes and pathways related to both the innate and adaptive immunity as well as genes related to immune evasion. Of particular interest, azacitidine was shown to up-regulate PD-L1 transcripts and protein (Wrangle et al 2013). fu a recent study, Chiappinelli et al (2015) showed that DNMT inhibitors up-regulated immune signaling in cancer cell lines through a viral defense pathway. fu ova1ian cancer, DNTM inhibition triggered cytosolic sensing of double-stranded RNA and caused a Type I interferon response and apoptosis. Early signals of potential efficacy to epigenetic agents were observed in solid tumors while evaluating a low-dose regimen of azacitidine with the HDAC inhibitor entinostat. fu a heavily pretreated NSCLC population of 45 subjects, objective responses were observed in only 4% of subjects, but 1 subject had a CR for a duration of 14 months, and a second subject had aPR that lasted 8 months. There were 10 subjects that had SD for at least 12 weeks. Additionally, the clinical responses that were observed continued after the discontinuation of the epigenetic therapy, suggesting a sustained effect (Juergens et al 2011). Five NSCLC subjects from this epigenetic study went on to receive immune checkpoint therapy in a nivolumab Phase 1 study. All 5 subjects were without progression at 6 months and 3 of these subjects developed high-grade RECIST PRs that have been durable for over 2.5 years (Chiappinelli et al2016).

As noted in Section 1.4, early studies of azacitidine used much higher doses that were associated with more toxicity compared with the cunently approved dose of azacitidine (Vigil et al2010). Lower doses of azacitidine are also required for the induction of DNA hypomethylation compared with direct cytotoxicity (Tsimberidou et al 2015). Utilizing a lower dose of azacitidine should permit hypomethylating and minimize toxicity allowing it to be combined with immune therapies.

Recent studies of BET inhibitors have demonstrated the ability to potently alter the tumor microenvironment resulting in improved tumor immunologic response. fu a syngeneic xenograft mouse model of pancreatic cancer, BET inhibition led to an increase in CD3+, CD4+, and CD8+ T-cells while simultaneously decreasing M2 macrophage infiltration (Koblish et al 2016). fu this same study BET inhibition in combination with either epacadostat or anti-PD-L1 therapy synergistically led to decreased xenograft tumor growth. BET inhibitors were independently shown to decrease expression ofPD-L1 on both tumor cells and DCs with a conesponding increase in number of IFNy- and granzyme B-positive cytolytic T cells in the tumor microenvironment of a syngeneic mouse model of ovarian cancer (Zhu et al2016). fu addition to altering the immune milieu, BET inhibitors have been shown to improve T-cell persistence and anti-tumor effects *in vivo* (Kagoya et al 2016). Fmthe1more, BET inhibition alters the expression ofpro-inflammatmy cytokine genes (Belkina et al2013, Ceribelli et al2014). As such, BET inhibition has the potential to remodel the tumor microenvironment and improve Immune responses.

Multiple recent reports demonstrate a potential role for LSD1 inhibition in checkpoint inhibitor priming strategies. Small interfe1ing RNA inhibition of LSD1 led to an increase in genes associated with interferon signaling as well as major histocompatibility complex Class I expression (Jin et al2017). Fmthe1more, LSD1 inhibition by INCB059872 led to increased effector T-cell and macrophage infiltration and a concomitant decreased myeloid-deprived

suppressor cell infiltration in a 4T1 mouse model (Condamine et al 2017). [redacted]

In summaly, epigenetic priming with DNMT, BET, or LSD1 inhibitors alone or in combination has been shown to alter the expression of growth-promoting, pro-inflammatmy, and survival genes, which contributes to the establishment and persistence of the oncogenic phenotype. Azacitidine, as well as BET or LSD1 inhibition, has the ability to modulate the immune system and may potentially serve as a priming method for immunotherapy combinations. Adding epigenetic p1iming and complimenta1y IDO1 inhibition to checkpoint inhibition may lead to increasing response rates in tumor types that have shown benefit to monotherapy checkpoint inhibition and may sensitize tumors that have been immune tolerant through the expression of silenced genes.

1.7.2. Justification for the Treatment Regimen

The safety and tolerability of the pembrolizumab and epacadostat combination is cunently being evaluated in the ongoing Phase 1/2 INCB 24360-202 study. In Phase 1 of the study, the established regimen of pembrolizumab 2 mglkg Q3W and 200 mg Q3W was evaluated with epacadostat doses ranging from 25 mg BID to 300 mg BID. Prelimina1y data suggest that doses up to 300 mg BID of epacadostat in combination with 2 mglkg or 200 mg IV infusion Q3W are generally well-tolerated. In the Phase 1 portion of the study, the 50 mg BID cohort had 2 DLTs in 18 subjects (Grade 3 rash and Grade 3 arthralgia); the 100 mg BID cohmt had 2 DLTs in 15 subjects (Grade 3 increased AST and Grade 3 nervous system disorder); and the 300 mg BID cohmt had 4 DLTs in 16 subjects (Grade 1 skin e1ythema, 2 Grade 3 rash, and Grade 2 nervous system disorder). The MTD was not exceeded at any dose evaluated. There were no treatment-related Grade 4 AEs or deaths. In a safety-evaluable cohmt of 60 subjects, the most frequent treatment-related AEs were rash (27%), fatigue (23%), and a1thralgia (15%). An epacadostat dose of 100 mg BID with pembrolizumab 200 mg Q3W were selected as the Phase 2 doses (Hamid et al 2015).

The epacadostat sta1ting dose selected for the cunent study was dete1mined on the basis of having a well-tolerated safety profile as monotherapy and in combination with pembrolizumab, as well as providing nearly maximum target inhibition of IDO1. In general, as single agents, epacadostat and pembrolizumab have been well-tolerated in this study population that has significant comorbidities. As monotherapy, maximally effective epacadostat doses in preclinical models result in exposures that are comparable to doses of 50 to 100 mg BID in humans. Doses of epacadostat of up to 700 mg BID as monotherapy have been well-tolerated, and the 100 mg BID dose of epacadostat in combination with pembrolizumab is cunently being evaluated as the RP2D.

Pha1macokinetic and pha1macodynamic obse1vations from Studies INCB 24360-101 and INCB 24360-201 in cancer subjects suppmt the 25 mg BID to 300 mg BID dose levels, which provide a differential pha1macologic effect. Based on a 6-hour obse1vation pe1iod at steady state on Day 15 after administration of epacadostat and using a standardized whole blood assay,

kynurenine levels are incompletely inhibited (66%), compared with baseline levels in subjects treated with 25 mg BID, but are nearly maximally inhibited (89%) in subjects treated with 100 mg BID. Complete inhibition of the IDOl target is not required for maximally effective activity in preclinical models; however, maximally effective doses in nonclinical models result in exposures that are comparable to monotherapy doses of 50 mg BID to 100 mg BID in humans.

Doses of epacadostat of up to 700 mg BID as monotherapy have been well-tolerated, and the 100 mg BID dose as well as 300 mg BID of epacadostat in combination with pembrolizumab and nivolumab is cunently being evaluated in multiple ongoing Phase 2 studies. In Study INCB 24360-101, among 43 subjects treated with epacadostat monotherapy at doses of up to 700 mg BID, there was 1 report of Grade 3 liver function test (LFT) elevations in a subject with bilia1y obstruction from progressive cancer. The initial evaluation of epacadostat 300 mg BID in combination with ipilimumab was terminated because of the occmTence of Grade 3 or 4 ALT/AST elevation in 5 of7 subjects n·eated at this dose level. These AEs were reversible in all subjects upon discontinuation of study therapy and institution of corticosteroids based on an established protocol for the management of immune toxicities related to ipilimumab therapy.

The safety profile for the 300 mg BID dose of epacadostat in combination with pembrolizumab in a Phase 112 study (INCB 24360-202) did not exceed the MTD in that study. While there was a higher incidence of Grade 3 rash in the 300 mg BID cohort compared to the 100 mg BID cohmt, these did not qualify as Protocol-specified DLTs. The dose of epacadostat 300 mg BID in combination with pembrolizumab is cunently under study in other studies of epacadostat plus checkpoint inhibitors.

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

However, in other tumor types that appear to demonst:l·ate more resistance to known immunotherapies, greater target coverage for inhibition of IDO1 may be necessary. Pharmacokinetic/pharmacodynamic modelling suggests that doses of epacadostat 100 mg BID achieve an average ICso at n·ough in most patients. At 300 mg BID, epacadostat achieves target inhibition above the IC9o at trough. Incyte believes that greater target inhibition may be necessary in more resistant tumors, and potentially balances benefit/risk in favor of the higher epacadostat dose combination given that the dose does not exceed the MTD.

The azacitidine sta1ting dose of 75 mg per day on Days 1 to 5 for 2 cycles was selected based off of previous studies evaluating the combination of azacitidine and entinostat as a stand-alone regimen or as a priming regimen before the receipt of nivolumab. In a Phase 1/2 study evaluating azacitidine and entinostat in subjects with recmTent metastatic NSCLC, the combination of 40 mg/m^2 azacitidine administered on Days 1 to 6 and 8 to 10 and 7 mg of entinostat administered on Days 3 and 10 of each cycle was generally well-tolerated and no DLTs were observed (Juergens et al2011). This dose regimen was chosen as RP2D, and a randomized Phase 2 study in subjects with recunent metastatic NSCLC was initiated evaluating

this combination as a priming regimen for 2 cycles before beginning nivolumab monotherapy versus nivolumab without epigenetic p1iming (NCT01928576). For the cunent study, a flat dose of azacitidine has been chosen to be adininistered in the clinic for 5 days per cycle and the starting dose of75 mg for 5 days represents approximately 40% of the dose adininistered per cycle for subjects receiving the MDS approved dose of 75 mg/m^2 for 7 days to be repeated in 28-day cycles. There is 1 planned dose-escalation of azacitidine to 100 mg, and this fmal dose will then be approximately half of the MDS-approved dose, which should minimize hematologic toxicity.

INCB057643 is cunently being evaluated in a Phase 1 dose-escalation and dose-expansion study, INCB 57643-101, in subjects with advanced solid and hematologic malignancies. The first subject was enrolled in this study on 18 MAY 2016. The following data were derived from the clinical database, and ce1tain data were not cleaned or confi1med at the data cutoff date; thus, they should be considered preliininaiy/subject to change.

As of the data cutoff date of 17 MAY 2017, 16 subjects each in Part 1 (solid tumors, n = 13; lymphoma, n = 3) and Pa1t 2 (solid tumors, n = 14; lymphoma, n = 2) have been emolled. Doses of 8, 12, and 16 mg QD were explored in Pmt 1/TGA. Pmt 1/TGB and TGC are cunently open for emollment at 8 mg QD (no subjects have emolled as of the data cutoff date). Pa1t 2/TGA expanded at a sta1ting dose of 12 mg QD.

The emollment sta1ted in Pa1t 1/TGA dose escalation with a 3 + 3 design, using a sta1ting dose of 8 mg QD. Four subjects were emolled in Cohmt 1. During the DLT evaluation period (Cycle 1), no DLTs were observed in Cohmt 1. Cohmt 2 had a sta1ting dose of 16 mg QD. One DLT of increased intemational nmmalized ratio (INR; Grade 3) was observed in Cohmt 2 in the initial3 subjects. Cohmt 2 was then expanded to emoll a total of 6 DLT-evaluable subjects (n = 8; 2 subjects were not evaluable due to early disease progression). Five subjects (5/8) required dose intenuption due to AEs dming Cycle 1 or 2 in Cohmt 2 (due to Grade 3 INR increased, Grade 3 thrombocytopenia, eye pain, Grade 4 hyperglycemia, and Grade 2 total bilimbin increased/Grade 3 direct bilimbin increased, respectively). Even though there was only 1 protocol-defmed DLT in Cohmt 2, because of the extent of dose intenuption due to other Grade 3/4 AEs, 16 mg QD was deemed to be not tolerated by the investigators and the sponsor. Cohmt 3 emolled 4 subjects at the stmting dose of 12 mg QD. Three of the 4 subjects were deemed evaluable, and no DLT was repmted. One subject was not evaluable due to early clinical progression. The MTD was thus dete1mined to be 12 mg QD in Part 1/TGA and was also selected as the RP2D for fmther exploration in Pmt 2/TGA.

As of the data cutoff date, dose levels of 8, 12, and 16 mg QD have been administered over an average of 174.5, 59.5, and 54 days, respectively, in various solid tumors and lymphomas in Pmt 1/TGA.

In Pa1t 1/TGA, there were 5 deaths that occmTed after study dmg discontinuation and during survival follow-up; all of which were caused by disease progression and umelated to study dmg. Of these 5 deaths, 3 were due to fatal AEs (hepatic failure, pneumonia, and new metastasis of the central nervous system [CNS; brain metastasis; n = 1 each]) that occmTed 14, 22, and 0 days post study dmg discontinuation, respectively, and the subjects died 25, 8, and 41 days after the onset of the fatal AE, respectively. All of the fatal AEs were umelated to study treatment based on investigator opinion. All of the 16 subjects (100%) emolled in Pa1t 1/TGA repmted at least 1 TEAE; 10 ofwhich (62.5%) repmted aGrade 3 TEAE. Fomteen of the 16 subjects (88%)

repmted1 treatment-related TEAE, and 4 of those subjects (25%) repmted aGrade 3 treatment-related TEAE. Additionally, 2 treatment-related TEAEs occuned in 1 subject each: Grade 3 increased conjugated bilimbin and Grade 3 increased INR, respectively. Eight subjects (50%) reported SAEs; 2 subjects (12.5%) had SAEs that were considered by the investigator to be treatment-related (Grade 4 hyperglycemia and Grade 3 INR increased, respectively). Treatment-related TEAEs led to dose intenuption in 5 subjects, primarily due to increased conjugated bilimbin, increased INR, thrombocytopenia, decreased appetite, and decreased platelet count (n = 1 each [6%]) and led to dose reduction in 1 subject (increased conjugated bilimbin [6%]). In total, 13 ofthe 16 subjects (81%) have discontinued treatment (4 because of TEAEs [upper abdominal pain and confusional state, perfmmance status decreased, hyperglycemia, and increased INR, respectively], 8 because of progressive disease, and 1lost to follow-up). In Pa1t IITGA, the median exposure of the study dmg was 59.5 days (range, 6-282 days).

In Part IITGA, 11 of the subjects with solid tumors were evaluable for efficacy; 1 subject had SD lasting6 months (cholangiocarcinoma, ongoing at 9 months), 2 subjects had SD lasting < 6 months (discontinued at 3 months due to decreased perfmmance status and progressed at 2 months, respectively), 6 subjects had radiographic progression as best response, and 2 subjects had clinical progression. Two subjects were not evaluable for efficacy (both subjects discontinued treatment due to AEs before the first assessment). The 3 subjects with non-Hodgkin's lymphoma were evaluable for efficacy; 1 subject with follicular lymphoma had a CR (CR based on positron emission tomography [PET], ongoing at 8 months), and 2 subjects had SD lasting < 6 months (ongoing at 5.5 months and progressed at 4 months, respectively).

These data indicate that INCB057643 is safe and well tolerated as a single agent at 8 and 12 mg QD. To mitigate any potential AEs of INCB057643 in combination with epacadostat and pembrolizumab, as well as avoid any potential deleterious cytotoxic effects on effector T-cells, dose escalation ofiNCB057643 will be started at 1 dose level (4 mg QD) below the lowest tested dose in humans, 8 mg QD. Dose escalation will proceed in cohmts including 8 and 12 mg QD until an MTD or maximum tested dose is reached.

INCB059872 is being evaluated in a Phase 1 dose-escalation and dose-expansion study, INCB 59872-101, in subjects with advanced solid tumors and hematological malignancies. Patt 1 (dose escalation) to determine the stalting dose(s) ofiNCB059872 for dose expansion, based on the MTD and/or a tolerated phatmacologically active dose (PAD), has been open and emolling since MAY 2016. Both QoD and QD schedules have been explored to collect safety, PK, and pharmacodynamic data to establish the optimal dose and schedule for subjects with solid tumor and hematological malignancies.

In Part 1, the initial2 mg QoD dose was well-tolerated by subjects in both treatment groups, TGA (AML/MDS) and TGB (solid tumors). As AMLIMDS is a rapidly proliferating disease, it was decided in discussion with the pa1ticipating investigators to use a QD dosing schedule for TGA. A total of 17 subjects have been treated in 4 different cohmts (3 at 2 mg QoD; 6 at 2 mg QD; 5 at 3mg QD; and 3 at 4 mg QD) in TGA. The treatment was generally well-tolerated without any DLTs. 4 mg QD is determined as the monotherapy RP2D for AMLIMDS subjects.

In TGB, a total of22 subjects have been treated in 6 different cohmts. The QoD schedules included 16 of those subjects (3 at 2 mg QoD; 6 at 3 mg QoD; and 7 at 4 mg QoD) in 3 different cohmts. The QoD schedule was generally well-tolerated. There was 1 DLT of Grade 4

thrombocytopenia at 4 mg QoD. Further dose escalation was stopped, and the next lower dose cohmt of 3 mg QoD was expanded to treat a total of 6 subjects. No DLTs or Grade 3/4 thrombocytopenias were reported at 3 mg QoD, and this dose is the RP2D for solid tumors. Dose escalation of the QD schedule in TGB has been halted due to 2 DLTs in the 3 mg QD cohmt and 1 DLT in the 2 mg QD cohmt. A cohmt of 3 subjects has completed emollment, and there were no DLTs seen in the DLT window.

Preliminaly, unaudited data as of 10 JUL 2017 is summarized for 39 subjects who have been treated with INCB059872 doses of 1 mg QD, 2 mg (QoD or QD), 3 mg (QoD or QD), and 4 mg (QoD or QD). Eight subjects were receiving treatment as of the data cutoff date. Of the 39 subjects, 12 subjects have received INCB059872 for > 20 days, 14 subjects have received INCB059872 for > 30 days, and 6 subjects have received INCB059872 for > 90 days.

The most frequent TEAE among all dose cohmts in TGA was fatigue and nausea (6 subjects each). The most frequent TEAE among all dose cohmts in TGB was thrombocytopenia and dysgeusia (9 subjects each).

Based on preclinical data generated to date, there is reason to believe that subjects may develop some level of thrombocytopenia. As of the data cutoff date, 6 DLTs of ≥ Grade 3 thrombocytopenia or platelet count decrease have been repmted in the 2 mg QD, 3 mg QD, and 4 mg QoD cohmts in TGB (1, 2, and 3 DLTs respectively). Treatment intenuption occurred in the subjects with DLTs, and following recovely, 4 of these subjects resumed study treatment at a reduced dose (3 mg QoD).

Four treatment-emergent SAEs resulted in discontinuation of study treatment: thrombocytopenia, bile duct obstmction, epistaxis, and hypotension. With the exception of thrombocytopenia, none of these treatment-emergent SAEs leading to INCB059872 discontinuation were considered related to study treatment. Five treatment-emergent SAEs have resulted in death, none of which were considered related to study treatment by the investigators: leukocytosis, sepsis, pulmonaly alveolar hemonhage, respiratmy failure, and gastrointestinal hemonhage.

These data indicate that INCB059872 is safe and well-tolerated in advanced solid tumors as a single agent at 2 mg QoD, 3 mg QoD, and 1 mg QD. To mitigate any potential AEs of INCB059872 in combination with epacadostat and pembrolizumab, as well as avoid any potential deletelious cytotoxic effects on effector immune cells, dose escalation of INCB059872 will be sta1ted 1 dose level (1 mg QoD) below the lowest tested dose in humans, 2 mg QoD. Dose escalation will proceed in cohmts including 2 mg QoD, 1 mg QD, and 3 mg QoD until an MTD or maximum tested dose is reached.

1.7.3. Rationale for Phase 2 Subject Populations

1.7.3.1. Non-Small Cell Lung Cancer

Lung cancer is the most common cause of death from cancer worldwide, and the majority of subjects present with advanced NSCLC, where the 5-year survival is less than 15% (Siegel et al2016). Non-small cell lung cancer accounts for approximately 80% to 85% of all cases of lung cancer (D'Adda1io et al2010).

The standard of care in first-line for patients with non-oncogenic-driven advanced NSCLC is platinum-based doublet chemotherapy (Rizvi et al2016). Therapy should be individualized based on molecular and histologic features of the tumor. Whenever possible, patients should have tumor tissue assessed for the presence of a driver mutation that stimulates tumor growth. These mutations define subsets of patients likely to respond to specific inhibitors (NCCN Guidelines). Patients with a known driver mutation in the epidetmal growth factor receptor (EGFR) are initially managed with an EGFR tyrosine kinase inhibitor (TKI; Moran and Sequist 2012, Gridelli et al2012). Those with an anaplastic lymphoma kinase (ALK) fusion oncogene in their tumor are preferentially treated with crizotinib (Kwak et al2010, Camidge et al2012, Shaw et al2013). Patients without a driver mutation are generally treated with chemotherapy.

Phase 1 studies of anti–PD-1 agents have demonstrated promising results. In 2015, the FDA granted approval for both pembrolizumab and nivolumab for the treatment of metastatic NSCLC after progression on or after platinum-based chemotherapy. Pembrolizumab was approved for patients whose tumors express PD-L1 as dete1mined by an FDA-approved test and who have disease progression on or after platinum-containing regimens (Garon et al2015). Patients with EGFR or ALK genomic tumor abenations should have disease progression on an FDA-approved therapy for these abenations before receiving pembrolizumab. In the Phase 1 study by Garon et al (2015), an ORR of 19.4% was repmted in the 495 NSCLC patients who received monotherapy pembrolizumab. Median DOR was 12.5 months, median PFS was 3.7 months, and OS was 12 months. Nivolumab was also approved in 2015 for patients with metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should also have disease progression on an FDA-approved therapy for these agents. The Phase 3 study comparing nivolumab to docetaxel resulted in an OS of 12.2 months (95% confidence interval [CI], 9.7 to 15.0) among 292 subjects in the nivolumab group and 9.4 months among the 290 subjects in the docetaxel group (hazard ratio, 0.73; 96% CI, 0.59 to 0.89; p = 0.002). The response rate with nivolumab was 19% as compared with 12% in the docetaxel group (p = 0.02; Borghaei et al2015). Based on results in second-line advanced NSCLC, investigation of PD-1 pathway inhibitors moved to the first-line setting, evaluating PD-1–targeting antibodies as monotherapy as well as in combination with other immunotherapies and chemotherapy (Gettinger et al2016, Rizvi et al2016). On 05 AUG 2016, Bristol-Myers Squibb announced top-line results from the Phase 3 CheckMate-026 study evaluating nivolumab monotherapy versus investigator's choice chemotherapy in a first-line advanced NSCLC population. In the open-label, randomized study, nivolumab did not meet the primaty endpoint of PFS in subjects with at least 5% PD-L1 expression on their tumors (Bristol-Myers Squibb 2016).

While PD-1 inhibition in NSCLC has demonstrated durable antitumor activity that has the potential for long-te1m survival, a significant number of patients do not receive benefit, demonstrated by the failure of nivolumab in the first-line setting. Patients with advanced and metastatic NSCLC represent a population with a large unmet medical need. Therefore, combinations with other immunotherapies, chemotherapy, and targeted agents are being pursued.

1.7.3.2. Microsatellite Stable Colorectal Cancer

Colorectal cancer is the third most common diagnosis worldwide with almost 1.4 million new cases diagnosed in 2012. Survival is highly dependent upon the stage at the time of diagnosis; unfortunately only 40% ofCRC cases have an early stage diagnosis, and approximately 50% of patients who are recently diagnosed will progress to have metastatic disease (Jacobs et al2015). Systemic chemotherapy with fluorop)'limidine-based regimens combined with oxaliplatin or irinotecan is the primary treatment for subjects with metastatic CRC. Targeted therapies are also routinely used to manage metastatic disease. Agents targeting EGFR and vascular endothelial growth factor (VEGF) have become standard of care and have demonstrated survival benefit in combination with chemotherapy (Verdaguer et al2016).

Checkpoint inhibitors have been evaluated across a broad auay of tumor types and have been shown to be effective in several specific tumor types. Many studies have emolled subjects with CRC, and they have been generally umesponsive to anti-PD-1 or anti-PD-L1 therapies (Brahmer et al2010, Topalian et al2012). A subset ofCRC subjects, primarily subjects with microsatellite instability-high (MSI-H) CRC, have been shown to have high expression ofPD-L1 and a high density of tumor-infiltrating immune cells. Therefore, subjects with a MSI-H phenotype have been expected to be responsive to PD-1 targeted therapies (Kim et al2016). A Phase 2 clinical study evaluated pembrolizumab in 41 subjects with treatment refractmy progressive metastatic cancer. Subjects were categorized based on mismatch repair (MMR) status; cohmts were MMR-deficient CRC, MMR-proficient CRC, and cancers of other types who were MMR-deficient. An ORR of 40% was observed in subjects with MMR-deficient CRC and 0% for MMR-proficient CRC. Subjects with other tumor types that were MMR-deficient had similar responses with 5 of7 subjects (71%) responding to pembrolizumab. Whole exome sequences revealed a high number of somatic mutations in MMR-deficient tumors compared with MMR-proficient tumors (Le et al2015).

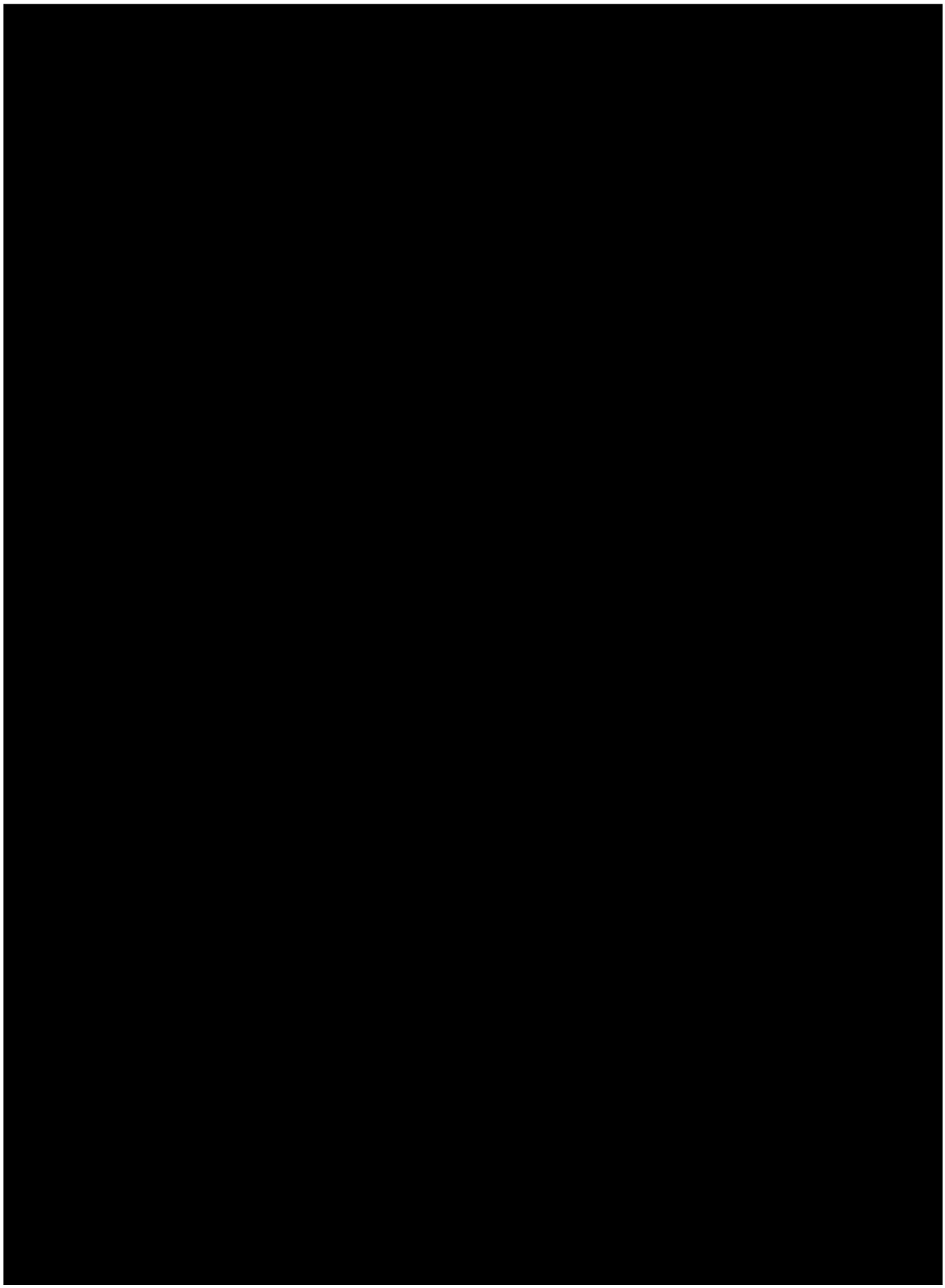
Alterations to the DNA MMR pathway affect 4 key human proteins; MLH1, MSH2, MSH6, and PMS2. This leads to an accumulation of mutations in microsatellite regions of DNA that affect DNA repair, cell signaling, and apoptosis, which leads to the development of malignancy (Lee et al2016). Immunohistochemistry (IHC) and PCR are used to screen patients for MMR or microsatellite instability (MSI), as the fmmer identifies underlying protein abnmmalities and the latter is useful in determining functional abnmmalities in DNA. The 2 testing platfmms are considered complimentary, but PCR is considered the gold standard for identifying CRC subjects with MSI, as it is more reproducible across laboratories, and it can detect nontluncating protein mutations in the 4 MMR proteins that are tested and can also identify MSI caused by other defects. In PCR testing for MSI, subjects who have no sites with MSI are considered MSS, subjects with 1 site are MSI-low (MSI-L), and subjects that have 2 or more sites ofMSI are considered MSI-H (Lee et al 2016). Approximately 15% of subjects with CRC have MSI disease (Vilar and Gruber 2010, Xiao and Freeman 2015), and so a large population of subjects who are MSS are not expected to respond to checkpoint inhibitors alone. Therefore, the evaluation of combined immunotherapy with epigenetic therapy that has the potential to increase the immunogenicity of CRC tumors and synergistically generate an immune response is wauanted in this indication with significant unmet need.

1.7.3.3. Treatment Sequencing Tumor Biopsy Cohort Indications

Subjects with 3 additional tumor types (HNSCC, melanoma, and urothelial carcinoma) will be emolled in the treatment sequencing tumor biopsy cohmts. All 3 tumor types have been demonstrated to be immunotherapy-responsive, and checkpoint inhibitors including ipilimumab, nivolumab, pembrolizumab, atezolizumab, durvalumab, and avelumab have shown durable antitumor activity and have been approved for treatment in either a first-line setting (melanoma) or following progression on chemotherapy (Opdivo 2017, Keytmda 2017, Tecentiiq 2017). While substantial benefit has been observed, the majority of solid tumors do not respond to checkpoint inhibitors alone, and combination therapy with anti-PD-1 agents is being investigated to dete1mine if additional subjects are able to obtain an immune response.

Response data for subjects with metastatic HNSCC, melanoma, NSCLC, renal cell carcinoma (RCC), and urothelial carcinoma from the ongoing Phase 1/2 study INCB 24360-202 (KEYNOTE-037) are encouraging, with high ORRs observed for the pembrolizumab + epacadostat combination that exceed historic monotherapy data with PD-1 and PD-L1 inhibitors. Recently presented data from Phase 1 and Phase 2 subjects showed ORRs and disease contiol rates, respectively, of35% and 63% in 40 NSCLC subjects (Gangadhar et al2017); 33% and 50% in 30 RCC subjects (Lara et al2017); 35% and 53% in 40 urothelial carcinoma subjects (Sinith et al2017); and 34% and 61% in 38 squamous cell carcinoma of the head and neck (SCCHN) subjects (Hamid et al2017a). An update on the melanoma cohort was presented at the European Society for Medical Oncology Annual Meeting 2017. Across all subjects with treatment-naive or treatment-experienced advanced melanoma, an ORR of 56% was observed; median PFS was 12.4 months, with PFS rates of 65% at 6 months, 52% at 12 months, and 49% at 18 months (Hamid et al2017b). Data from the INCB 24360-202 study demonstrate that combination treatment with epacadostat and pembrolizumab across multiple tumor types shows improved response rates and durability compared with pembrolizumab alone, thus wananting finther study in controlled randomized studies. The addition of epigenetic p1iming to the pembrolizumab and epacadostat combination may increase response rates in immunotherapy-sensitive tumor types that have shown benefit from monotherapy and combination therapy checkpoint inhibition. Another focus of the investigation in the ti·eatment sequencing expansion cohmt is to dete1mine whether the addition of epigenetic priining regimens can sensitize tumors that were primarily refractmy to PD-1/PD-L1 inhibition or re-sensitize tumors that were initially sensitive to checkpoint inhibition but progressed while on a PD-11PD-L1 inhibitor.

1.8. Potential Risks and Benefits of the Treatment Regimen



[redacted]

1.8.2. Risks From Pembrolizumab

Potential safety concems and recommended management guidelines regarding pulmonaly toxicity, gastrointestinal toxicity, hepatotoxicity, endocrinopathies, nephritis and renal dysfunction, infusion-related reactions, and other immune-mediated toxicities of concem are summa1ized in the pembrolizumab approved label.

The overall safety experience with pembrolizumab is based on experience in subjects as either a monotherapy or in combination with other therapeutics. In general for monotherapy, the safety profile is similar across tumor types. The 1 exception is AEs of pulmonaty inflammation, which may be numerically greater in subjects with NSCLC, possibly because in some cases it can be difficult to distinguish between pembrolizumab-related and umelated causes of pulmonary symptoms and radiographic changes. The most frequently repmted treatment-related AE is fatigue, which is almost always low grade.

1.8.3. Risks From Azacitidine

Azacitidine is known to be associated to cytopenias including, anemia, neutropenia, and thrombocytopenias. Subjects will have complete blood counts perfmmed at baseline and 2 additional times per cycle in Cycle 1 and 2 in Palt 1 dose escalation. Potential safety concems and recommended management guidelines regarding hematologic toxicities, hepatotoxicity, renal abnmmalities, and other toxicities of concem are summarized in the azacitidine approved label.

1.8.4. Risks From INCB057643

Data from the INCB 57643-101 Phase 1 clinical trial indicate that INCB057643 is overall well-tolerated. Overall, only 1 DLT was noted out of8 subjects repmted at 16mg QD, which is 1 dose level higher than the RP2D of 12 mg QD, the highest dose proposed to be tested in this study. Eight subjects were emolled at 16 mg QD, and 5 of those 8 subjects required dose intenlption due to AEs during Cycle 1 or 2 (due to Grade 3 INR increased, Grade 3 thrombocytopenia, eye pain, Grade 4 hyperglycemia, Grade 2 total bilimbin increased/Grade 3 direct bilirubin increased, respectively). Nine of the 16 subjects (56%) in the dose-expansion cohmt of Study INCB 57643-101 repmted at least 1 treatment-related TEAE. Subjects repmted 4 TEAEs;::: Grade 3 (abdominal pain, appendicitis, sepsis, and thrombocytopenia [n = 1 each [6.3%]); all of which were also repmted as SAEs, and of those, only thrombocytopenia was considered treatment-related by the investigator. Treatment-related TEAEs led to dose intenlption in 2 subjects, p1imarily due to decreased appetite (n = 2 [13%]), and no dose reductions due to treatment-related TEAEs were repmted as of the data cut-off date. Three of the 16 subjects (19%) discontinued treatment (disease progression, n = 2 [13%]; other, n = 1 [6%]).

1.8.5. Risks From INCB059872

Data from the Phase 1 clinical study INCB 59872-101 indicate that INCB059872 is generally well-tolerated. Overall, only 1 DLT was noted in subjects dosed at 4 mg QoD, which is 1 dose level higher than the RP2D of 3 mg QoD, the highest dose proposed to be tested in this study. In the dose-escalation cohort of Study INCB 59872-101, 6 DLTs of 2: Grade 3 thrombocytopenia or platelet count decreased have been reported in the 2 mg QD, 3 mg QD, and 4 mg QoD cohmts in TGB (1, 2, and 3 DLTs respectively), none of which are being evaluated in this study. Treatment intenuption occmTed in the subjects with DLTs, and, following recovery, 4 of these subjects resumed study treatment at a reduced dose (3 mg QoD). Four treatment-emergent SAEs resulted in discontinuation of study treatment: thrombocytopenia, bile duct obstruction, epistaxis, and hypotension. With the exception of thrombocytopenia, none of these treatment-emergent SAEs leading to INCB059872 discontinuation were considered related to study u·eatment. Five treatment-emergent SAEs have resulted in death, none of which were considered related to study treatment by the investigators: leukocytosis, sepsis, pulmonaly alveolar hemonhage, respiratmy failure, and gastr·ointestinal hemonhage.

1.8.6. Risks From Combination Therapy

The combination of the immunotherapies epacadostat and pembrolizumab have the potential to precipitate more frequent, more severe, and/or new immune-related toxicities as compared with each individually. The addition of azacitidine, INCB057643, or INCB059872 to the epacadostat and pembrolizumab regimen may have the potential to increase irAEs due to their ability to re-express and up-regulate genes related to diverse immune pathways. The combination of azacitidine with pembrolizumab and epacadostat has been well-tolerated in Cohmts 1, 2A, 2B, and 3 with no DLTs observed to date in Pa1t 1.

2- STUDY OBJECTIVES AND ENDPOINTS

2-L Study Objectives

2.1.1. Primary Objectives

- Palt 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.
- Palt 2: To evaluate the efficacy of the combinations in subjects with previously treated Stage IV or recunent NSCLC, Stage IV MSS CRC, and select solid tumors by assessing ORR per RECIST v1.1 at the MTD, maximum tested dose, or PAD.

2.1.2. Secondary Objectives

- Palt 1: To evaluate the efficacy of the combinations in subjects with advanced or metastatic solid tumors by assessing ORR per RECIST v1.1 at the MTD, maximum tested dose, or PAD.
- Palt 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.
- Palts 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 recunent NSCLC, and Stage IV MSS CRC.
- Palts 1 and 2: To evaluate the efficacy of the combinations in subjects with advanced or metastatic solid tumors, previously treated Stage IV or recunent NSCLC, and Stage IV MSS CRC by assessing PFS.
- Palts 1 and 2: To evaluate the efficacy of the combinations in subjects with advanced or metastatic solid tumors, previously treated Stage IV or recunent NSCLC, and Stage IV MSS CRC by assessing DOR.

[redacted]

2-2- Study Endpoints

2.2.1. Primary Endpoints

- Pa1t 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 electrocardiograms (ECGs); and through clinicallaboratmy blood and urine sample evaluations.
- Pa1t 2: Objective response rate, defined as the percentage of subjects having a CR or PR, will be dete1mined by investigator assessment of radiographic disease as per RECIST v1.1.

2.2.2. Secondary Endpoints

- Pa1t 1: Objective response rate, defined as the percentage of subjects having a CR or PR, will be dete1mined by investigator assessment of radiographic disease as per RECIST v1.1.
- Pa1t 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 clinicallaboratmy blood and urine sample evaluations.
- Pa1ts 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 dete1mined.
- Pa1ts 1 and 2: Progression-free smvival, defmed as the time from date of first dose of study dmg until the earliest date of disease progression, will be dete1mined by investigator assessment of objective radiographic disease assessments per RECIST v1.1, or death due to any cause, if occmTing sooner than progression.
- Pa1ts 1 and 2: Duration of response dete1mined 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 occmTing sooner than progression, will be dete1mined.

3_ SUBJECT ELIGIBILITY

Deviations from eligibility crite1ia are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatmy acceptability, and/or subject safety. Therefore, adherence to the crite1ia as specified in the Protocol is essential.

3-L Subject Inclusion Criteria

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

Both Part 1 and 2

1. Male or female subjects, age 18 years or older on day of signing consent.
2. Willingness to provide written infmmed consent for the study.
3. Willingness to undergo a pretreatment and on-treatment tumor biopsy to obtain tumor tissue. On-treatment biopsy is optional in Stage 2 of Pa1t2. Two on-treatment biopsies are mandatmy in the Pa1t2 treatment sequencing biopsy expansion cohmts (except for Cohmts B-11 and C-13, which require 1 on-treatment biopsy).

   Note: If a subject is scheduled to have a tumor biopsy for the purposes of this study, and it is subsequently dete1mined that tumor tissue cannot s be then the ect may still emoll in the study. [redacted]

   Note: Care should be taken to biopsy the same lesion for the baseline and on-treatment samples. If a subject has a solitary target lesion, this should not be biopsied. [redacted]
4. Life expectancy >12 weeks.
5. ECOG perfmmance status of 0 to 1.
6. Presence of measureable disease per RECIST v.1.1 as dete1mined by the site study team. Tumor lesions situated in a previously inadiated area are considered measureable if progression has been demonstrated in such lesions. The lesion selected for pre- and/or post-treatment biopsy cannot be the only measurable lesion.
7. Willingness to avoid pregnancy or fathe1ing children based on the c1iteria below:
   a. Woman of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ;::: 12 months of amenonhea and at least 50 years of age.)
   b. Woman of childbearing potential who has a negative semm pregnancy test at screening (must be perfmmed within 72 hours before the first dose of study dmg) and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% ce1tainty) from screening through 120 days after the last dose of study dmg. Pe1mitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confi1med.

c. Man who agrees to take appropriate precautions to avoid fathe1ing children (with at least 99% certainty) from screening through 120 days after the last dose of study dmg. Pe1mitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confi1med.

Part 1 Only

8. Subjects with histologically or cytologically confi1med advanced or metastatic solid tumors that have failed prior standard therapy (disease progression; subject refusal or intolerance is also allowable).

   Note: There is no limit to the number of prior treatment regimens.

Part 2 Only

Note: Subjects must have failed available therapies that are known to confer clinical benefit as indicated below, unless they are ineligible, intolerant, or refused standard treatment.

Subjects with histologically or cytologically confi1med NSCLC:

9. Metastatic (Stage IV) or recunent NSCLC (according to American Joint Committee on Cancer 7th edition guidelines) who have had disease progression after available therapies for advanced or metastatic disease that are known to confer clinical benefit, been intolerant to treatment, or refused standard treatment.
10. Prior systemic regimens must include previously approved therapies, including a platinum-containing chemotherapy regimen; a TKI for tumors with driver mutations; and checkpoint inhibitors where approved.
11. Must have documented disease progression while on a prior PD-1 pathway-targeted agent (Expansion Cohmts A-1, B-1, B-3, B-5, B-7, C-1, C-3, C-5, C-7, and C-9). Progression following cessation of PD-1 pathway-targeted therapy is not sufficient. The baseline scan for the purposes of this study may se1ve as the documentation of progressiOn.

Subjects with recunent (umesectable) or metastatic CRC:

12. Histologically or cytologically confnmed adenocarcinoma of the colon or rectum.
13. Confnmed MSS CRC as per local testing.
14. Stage IV CRC (according to American Joint Committee on Cancer 7th edition guidelines) who have had disease progression after available therapies for advanced or metastatic disease that are known to confer clinical benefit, been intolerant to treatment, or refused standard treatment.
15. Prior systemic regimens must include previously approved therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF therapy (if no contraindication); and if negative for KRAS, NRAS, and BRAF mutations and no contraindication, an anti-EGFR therapy; and progressed after the last administration of approved therapy.

Subjects with HNSCC:

16. Histologically confnmed squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx.

    Note: Carcinomas of the nasopharynx, salivary gland, or nonsquamous cell histology are excluded.

17. Must have received p1ior treatment with a platinum-based therapy. Subjects who relapsed within 6 months of adjuvant therapy, including a platinum-containing regimen, may emoll. Additionally, subjects must have had documented disease progression while on a prior PD-1 pathway-targeted agent. Progression following cessation of PD-1 pathway-targeted therapy is not sufficient.

18. Must have documented human papilloma vims status.

Subjects with melanoma:

19. Histologically or cytologically confnmed melanoma.

20. Umesectable Stage III or Stage IV melanoma, as per American Joint Committee on Cancer staging system not amenable to local therapy.

21. Documentation ofV600-activating BRAF mutation status or consent to BRAF.

22. V600 mutation testing during the screening period.

23. Must not have ocular melanoma.

Subjects with urothelial carcinoma:

24. Histologically or cytologically confnmed urothelial carcinoma of the renal pelvis, ureter, urinaly bladder, or urethra that is transitional cell or mixed transitionaVnontransitional (predominantly transitional) cell type.

25. Stage IV locally advanced or metastatic urothelial carcinoma (according to American Joint Committee on Cancer 7th edition guidelines) with documented disease progression while on a PD-1 pathway-targeted therapy. Progression following cessation of PD-1 pathway-targeted therapy is not sufficient.

3-2- Subject Exclusion Criteria

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

1. Laboratory and medical histmy parameters not within Protocol-defined range. Cycle 1 Day 1 laboratmy assessments for the dete1mination of eligibility do not need to be perfmmed if the screening labs were perfmmed within 7 days of Cycle 1 Day 1. If the screening lab assessments were pe1fmmed more than 7 days before Cycle 1 Day 1, the hematology, semm chemistry, and liver chemistry lab results must be confi1med on Cycle 1 Day 1 before tr·eatment initiation.

    a. Absolute neutr·ophil count $< 1.5 \times 10^9$/L.
    b. Platelet count $< 100 \times 10^9$/L.
    c. Hemoglobin < 8 g/dL (transfusion is acceptable to meet this criterion).

d. Semm creatinine 2:: 1.5 x institutional upper limit of nmmal (ULN) OR measured or calculated creatinine clearance (glomemlar filtration rate can also be used in place of creatinine or CrCl) < 50 mL!min for subjects with creatinine levels > 1.5 x institutional ULN).
e. Aspartate aminotransferase, ALT, and alkaline phosphatase 2::2.5 x ULN.
Note: Subjects with 1) bone metastases and 2) no hepatic parenchymal metastases on screening radiographic examinations may emoll if the alkaline phosphatase is < 5 x ULN. Subjects with 1) bone metastases and 2) hepatic parenchymal metastases on screening radiographic examinations may emoll if the alkaline phosphatase is < 5 x ULN only with medical monitor approval.
f. Total bilimbin 2:: 1.2 x ULN are excluded unless direct bilimbin is:::; ULN. If there is no institutional ULN, then direct bilimbin must be < 40% of total bilimbin to be eligible.
g. Intemational nmmalized ratio or prothrombin time (PT) > 1.5 x ULN.
h. Activated pa1tial thromboplastin time > 1.5 x ULN.
1. Semm albumin < 3 g/dL.

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

a. < 14 days for chemotherapy, targeted small-molecule therapy, or radiation therapy. Subjects must also not require cmticosteroids and must not have had pneumonitis as a result of treatment. A 1-week washout is pe1mitted for palliative radiation to non-CNS disease with sponsor approval.
Note: The use of denosumab is pe1mitted.
b. < 14 days for a p1ior PD-1 pathway-targeted agent. (If the subject was on pembrolizumab monotherapy, a wash-out is not required.)
c. < 28 days for prior monoclonal antibody used for anticancer therapy with the exception of PD-1 pathway-targeted agents.
d. < 14 days for an immune-suppressive-based treatment for any reason (including chronic use of systemic cmticosteroid at doses of prednisone equivalent to > 10 mg/day). Use of inhaled or topical steroids, or systemic cmticosteroids to :::; 10 mg is pe1mitted. The use of physiologic doses of corticosteroids may be approved after consultation with the sponsor.
e. < 28 days or 5 half-lives (whichever is longer) before the first dose for all other investigational study dmgs or devices. For investigational agents with long half-lives (eg, > 5 days), emollment before the fifth half-life requires medical monitor approval.

3. Has not recovered from toxic effect(s) ofp1ior therapy to:::; Grade 1. Any irAEs from prior immunotherapy must have complete resolution and must have resolved at least 2 weeks before Cycle 1 Day 1.

Note: Subjects with:::; Grade 2 neuropathy or alopecia are an exception and may emoll. Subjects with immune-related hypothyroidism or adrenal insufficiency because of prior immunotherapy who are medically stable and adequately managed on a stable dose of replacement therapy may be emolled.

4. Subjects with p1ior ocular toxicity from p1ior immune therapy are excluded.

5. Subjects who have not recovered adequately from toxicity and/or complications from surgical intervention before sta1ting therapy.
6. Subjects who have any active or inactive autoimmune disease or syndrome (ie, rheumatoid arthritis, moderate or severe psmiasis, multiple sclerosis, inflammatmy bowel disease) that has required systemic treatment in the past 2 years or who are receiving systemic therapy for an autoimmune or inflammatmy disease (ie, with use of disease modifying agents, cmticosteroids, or immunosuppressive dmgs).

   Note: Exceptions include subjects with vitiligo or resolved childhood asthma/atopy, hypothyroidism stable on hmmone replacement, controlled asthma, Type I diabetes, Graves' disease, or Hashimoto's disease, or with medical monitor approval.
7. Diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg [> 10 mg] daily of prednisone equivalent) or any other fmm of immunosuppressive therapy within 7 days before the first dose of study treatment. Use of inhaled or topical steroids or systemic cmticosteroids10 mg is pe1mitted.
8. Known active CNS metastases and/or carcinomatous meningitis.

   Note: Subjects with previously treated brain metastases may pa1ticipate provided they are stable (without evidence of progression by imaging for at least 4 weeks before the first dose of study treatment and any neurologic symptoms have retumed to baseline), have no evidence of new or enlarging brain metastases, and have not required steroids for at least 7 days before study treatment.
9. Has received a live vaccine within 30 days of planned sta1t of study therapy.

   Note: Examples of live vaccines include, but are not limited to, the following: measles, mumps, mbella, chicken pox/zoster, yellow fever, rabies, Bacillus Calmette-Guerin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed vims vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMista re live-attenuated vaccines and are not allowed.
10. Evidence of interstitial lung disease or active, noninfectious pneumonitis.
11. Histmy or presence of an abnmmal ECG that, in the investigator's opinion, is clinically meaningful. Screening QTc interval > 480 milliseconds is excluded (corrected by Fridericia). In the event that a single QTc is > 480 milliseconds, the subject may emoll if the average QTc for the 3 ECGs is < 480 milliseconds. For subjects with an intraventricular conduction delay (QRS interval > 120 Insec), the JTc interval may be used in place of the QTc with sponsor approval. The JTc must be < 340 milliseconds if JTc is used in place of the QTc. Subjects with left bundle branch block are excluded.

    Note: QTc prolongation due to pacemaker may enroll if the JT is nmmal or with medical monitor approval.
12. Clinically significant cardiac disease, including unstable angina, acute myocardial infarction within 6 months from Day 1 of study dmg administration, New York Hea1t Association Class III or IV congestive hea1t failure, and arrhythmia requiring therapy.

    Note: A subject with an arrhythmia may emoll if the subject is on anti-arrhythmic medication and is in sinus rhythm on the screening ECG.

13. fuability to swallow food or any condition of the upper gastrointestinal tract that precludes administration of oral medications.
14. Subject has a known histmy of or is positive for hepatitis B (hepatitis B virus [HBV] smface antigen reactive or HBV DNA detected) or hepatitis C (hepatitis C virus [HCV] antibody positive and/or HCV RNA [qualitative] is detected).

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

    Note: fu Patt 2, subjects who are immune to hepatitis B (HBV surface antibody and/or HBV core antibody positive) are allowed (ie, no evidence of active infection).
15. Known histmy of human immunodeficiency virus (HIV; HIV 112 antibodies).
16. Active infection requiring systemic therapy.
17. Known allergy, hypersensitivity, or reaction to any component of the study drugs, fmmulation components, or excipients, including mannitol.
18. Women who are pregnant or breastfeeding.
19. Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, *in situ* cervical cancer, or early stage endometrial cancer.
20. Prior receipt of an IDO inhibitor.
21. Receipt ofMAOis within the 21 days before the first dose of study treatment.
22. Use of any UGT1A9 inhibitor from screening through the safety follow-up period, including the following: diclofenac, imipramine, ketoconazole, mefenamic acid, and probenecid. See Section 5.6.3 for more details.
23. Histmy ofSS after receiving 1 or more serotonergic drugs.
24. fuability or unlikeliness to comply with the dose schedule and study evaluations, in the opinion of the investigator.
25. Any condition that would, in the investigator's judgment, interfere with full patticipation in the study, including administration of study drug and attending required study visits; pose a significant risk to the subject; or interfere with interpretation of study data.
26. Prior receipt of any fmmulation of azacitidine, decitabine, or any other hypomethylating agent (Treatment Group A only).
27. Exclusion criterion removed as of Protocol Amendment 3.
28. Subjects with bleeding associated with tumors in proximity to major blood vessels are excluded except with medical monitor approval.
29. Histmy of a prior Grade 3 or 4 irAE (Part 1 dose escalation only).
30. Subjects with uncontrolled type I or type II diabetes mellitus (defined as HgbA1c > 8).

31. Prior receipt of a BET inhibitor (Treatment Group B only).
32. Subjects with a histmy of bleeding related to cancer under study requiring a medical intervention (eg, embolization procedure, RBC transfusion, or hospitalization) within 30 days of study emollment (Treatment Groups B and C only).
33. Clinically significant bleeding within 14 days of Cycle 1 Day 1 (Treatment Groups B and Conly).
34. Subjects cunently receiving warfarin therapy (Treatment Group B only).
35. Prior receipt of an LSD1 inhibitor, including INCB059872 (Treatment Group Conly).

4- INVESTIGATIONAL PLAN

4-L Overall Study Design

This is an open-label, multicenter, Phase 1/2 study evaluating the addition of 3 different epigenetic p1iming 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 dete1mine 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 cohmts are also included in Pa112 to further evaluate epigenetic changes and changes in the tumor microenvironment in subjects with select solid tumors.

Tumor biopsy samples are required at baseline and on study for subject pa1ticipation in all dose-escalation cohmts and Stage 1 of the Simon 2-stage cohmts. Mandatmy tumor biopsies will be collected at baseline (before Day 1 administration) and while the subject is receiving study treatment as specified below:

- An additional on-treatment biopsy will be required to be collected during Week 5 or Week 6 (Treatment Group A) or Week 8 or Week 9 (Treatment Groups Band C); the on-treatment biopsy is optional for Stage 2 cohmts in Pai12. On-treatment biopsy requirements for the treatment sequencing biopsy cohmts are presented in Table 5, Table 7, and Table 9.
- An additional optional biopsy may be collected once the subject meets the requirements for SD, response, or progression by radiographic disease assessment.

Note: On-treatment biopsies should be collected from the same tumor lesion that was biopsied at baseline.

Note: If a subject is scheduled to have a tumor biopsy for the purposes of this study, and it is subsequently dete1mined that tumor tissue cannot safely be obtained, then the subject may still emoll in the study, and an archived tumor specimen, if available, can be submitted. Such subjects may be replaced.

Note: As a quality control step, prior to submitting the tumor tissue to the centrallaboratmy vendor, all tumor tissue will be fmmalin-fixed and paraffin-embedded locally. A hematoxylin and eosin (H&E) stain will be perfmmed and reviewed by a local pathologist to vetify the adequacy of the tumor biopsy. Additionally, a quality control fmm will be signed and dated by the reviewing pathologist. For the screening biopsy, this fmm will ideally be submitted to the sponsor at the same time that the registration fmm is submitted for emollment.

[redacted] Toxicities will be monitored continuously and will be graded by the NCI CTCAE v4.03.

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 critetia for study withdrawal (except for Expansion Cohmts A-4 and A-5 which, will receive up to 5 cycles). In Pat12 of Treatment Group A will consist of Simon 2-Stage cohmts in previously treated NSCLC and MSS CRC. Separate treatment sequencing tumor biopsy cohmts are also included in Part 2 to finther 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 with medical monitor approval. 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 ofpembrolizumab (approximately 2 years), whichever occurs first. See Figure 1 for study design illustration.

Treatment Groups B and C (NOTE: Upon implementation of Amendment 4, Treatment Groups Band Care no longer applicable.)

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. Pa111 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. Pa111 will also contain dose-expansion cohmts in previously treated NSCLC and MSS CRC. Following emollment of Pai11, there will be an optional study hold for evaluation of safety, efficacy, [redacted] to facilitate a go/no-go decision regarding emollment of Patt 2. and C will consist of Simon 2-Stage cohmts in previously treated NSCLC and MSS CRC. Separate treatment sequencing tumor biopsy cohmts are also included in Part 2 to finther evaluate epigenetic changes and changes in the tumor microenvironment in subjects with select solid tumors. Emollment of the treatment sequencing

tumor biopsy cohmts is contingent upon passing Stage I in I 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 ofpembrolizumab (approximately 2 years), whichever occurs first. See Figure 2 and Figure 3 for study design illustration for Treatment Group B and C.

4.1.1. 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 t1iplet combination of azacitidine, INCB057643, or INCB059872 with pembrolizumab and epacadostat in 2I-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 dete1mined or reached, the dose will be recommended for Pa1t 2. The Pa1t 2 expansion will begin after the dete1mination of the MTD, maximum tested dose, or PAD; however, emollment p1iority will be given to the open Pa1t I dose-escalation cohmt.

A minimum of 3 subjects will initially be emolled in Cohmt I, and each subject will be observed for 2I days from the sta1t of triplet combination therapy before emollment in the next cohmt begins. The dose of azacitidine, INCB057643, or INCB059872 (or epacadostat) will be escalated if 0 of the first 3 evaluable subjects emolled has a DLT. If I of 3 subjects in Cohmt I has a DLT, the cohmt will be expanded to 6 subjects. If I of 6 subjects in Cohmt I has a DLT, a new cohmt of3 subjects will be treated at the next higher dose level (Cohort 2). If2 of 6 subjects in Cohmt I have a DLT, that cohmt will be fu1ther expanded to a total of9 subjects. If ::;; 2/9 subjects have a DLT, 3 subjects will be treated at the next higher dose level. If 2: 2/3, 3/6, or 3/9 subjects have a DLT within a cohmt, dose de-escalation will be required, and Cohmts -I or -2 will be tested. The MTD is defined as the highest dose level at which ::;; I/6 or ::;; 2/9 subjects expe1ience a DLT.

Subjects must have received 2:75% of planned doses of study dmg during the 2I-day DLT (Treatment Group A) or 42-day DLT (Treatment Groups Band C) obse1vation period or have had a DLT to be evaluable for dose tolerability (Treatment Group A: azacitidine [4 doses], epacadostat [32 doses], and pembrolizumab [I dose]; Treatment Group B: INCB057643 [32 doses], epacadostat [32 doses], and pembrolizumab [I dose]; Treatment Group C: INCB059872 [QD dosing, 32 doses; QoD dosing, I6 doses], epacadostat [32 doses], and pembrolizumab [I dose]).

It is recognized that ce1tain toxicities due to the combination agent (eg, including but not limited to gastrointestinal toxicity, including dianhea; renal insufficiency; high-grade laboratory abnmmalities; 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 2: 75% of the prescribed dose during Cycle I. In these cases, the p1incipal investigators and medical monitor may assess subjects who receive dose intensities somewhat below 75% for the dete1mination ofDLTs, and consider in the adjudication process the specific toxicity encountered, the likely cause of the toxicity, and dose intensity and tolerability beyond Cycle I. Additional subjects will be emolled in a cohmt to achieve the minimum of 3 evaluable subjects if dropouts or dose intenuptions/reductions occur that result in a subject being nonevaluable for DLTs.

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

4.1.1.1. Treatment Group A: Azacitidine

Dose escalation will begin with stalting 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 orally (PO) BID continuous dose adininistration. If the staiting dose proves intolerable, then azacitidine 50 mg SC or IV for 5 days, pembrolizurnab 200 mg IV Q3W, and epacadostat 100 mg PO BID will be evaluated. The cohmts and dose levels are shown in Table 1.

Table 1: Dose Levels: Treatment Group A

Cohort	Azacitidine	Pembrolizumab	Epacadostat
-2-	50 mg SC or IV for 5 days (5 doses over Day 1-7 period) in Cycle 1 & 2	200mgiVQ3W	50 mgPOBID
-1"	50 mg SC or IV for 5 days (5 doses over Day 1-7 period) in Cycle 1 & 2	200mgiVQ3W	100mgPOBID
1	75 mg SC or IV for 5 days (5 doses over Day 1-7 period) in Cycle 1& 2	200 mgiVQ3W	100 mg POBID
2Ab	75 mg SC or IV for 5 days (5 doses over Day 1-7 period) in Cycle 1 & 2	200mgiVQ3W	300mgPOBID
2Bb	100 mg SC or IV for 5 days (5 doses over Day 1-7 period) in Cycle 1 & 2	200mgiVQ3W	100mgPOBID
3	100 mg SC or IV for 5 days (5 doses over Day 1-7 period) in Cycle 1 & 2	200mgiVQ3W	300mgPOBID

• If Cohort I proves mtolerable, Coh01t -I may be evaluated. If Cohort -I ts not tolerable, Cohort -2 may be evaluated wtth epacadostat 50 mg PO BID. If a de-escalation cohort is detennined to be safe and tolerable, the dose of azacitidine or epacadostat may be re-escalated in separate, additional coh01ts based on the review of available safety data.

b For Coh01t 2, escalation of azacitidine to I00 mg or epacadostat to 300 mg BID will be dependent on the observation of Grade 3 or greater immtme-related or non– immune-related toxicities in Cohort I (toxicities that were not considered DLTs). If Grade 3 or greater immtme-related toxicities are obsetved in Coh01t I, azacitidine will be escalated first (Cohort 2B). If non– immtme-related Grade 3 or greater toxicities are observed, epacadostat will be preferentially escalated (Coh01t 2A). Dose-escalation Coh01ts 2A and 2B may be opened in parallel if no Grade 3 AEs are observed in Cohort I.

4.1.1.2. Treatment Group B: INCB057643

In Treatment Group B, dose escalation will begin with a sta1ting dose of iNCB057643 of 4 mg PO QD continuous dose adininistration 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 sta1ting dose level proves intolerable, INCB057643 4 mg PO QD in combination with pembrolizurnab 200 mg IV Q3W and epacadostat 50 mg PO BID will be evaluated. The cohmts and dose levels are shown in Table 2.

Table 2: Dose Levels: Treatment Group B

Cohort	INCB057643	Pembrolizumab	Epacadostat
-I"	4mgPOQD beginning C3D1	200mgiVQ3W beginning C2Dl	50 mgPO BID beginning C2D1
1	4 mg PO QD beginning C1D1	200mgiVQ3W beginning C2D1	100 mgPOBID beginning C2D1
2	8mgPOQD beginning C1D1	200mgiVQ3W beginning C2Dl	100mgPOBID beginning C2D1
3	12mgPO QD beginning C1D1	200mgiVQ3W beginning C2Dl	100mgPOBID beginning C2D1

a IfCohort I proves mtolerable, Coh01t -I may be evaluated. If Cohort -I IS not tolerable, lower doses or altemative dose schedules ofiNCB057643 may be tested; however, at this time, 4 mg tablets are the lowest dose fonnulation available. Any dose reduction in INCB057643 would be combined with pembroliztunab 200 mg IV Q3W and epacadostat 50 mg PO BID. If a de-escalation coh01t is detennined 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.

4.1.1.3. Treatment Group C: INCB059872

In Treatment Group C, dose escalation will begin with a stalting 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 stalting 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 cohmts and dose levels are shown in Table 3.

Table 3: Dose Levels: Treatment Group C

Cohort	INCB059872	Pembrolizumab	Epacadostat
-I"	1 mgPO QoD beginning C1D1	200mgiVQ3W beginning C2Dl	50 mgPO BID beginning C2D1
1	1 mgPOQoD beginning C1D1	200mgiVQ3W beginning C2D1	100 mgPOBID beginning C2D1
2Ab	2 mgPO QoD beginning C1D1	200mgiVQ3W beginning C2Dl	100mgPO BID beginning C2D1
2Bb	1 mgPO QD beginning C1D1	200mgiVQ3W beginning C2Dl	100mgPOBID beginning C2D1
3c	3 mgPO QoD beginning C1D1	200mgiVQ3W beginning C2Dl	100mgPO BID beginning C2D1

a IfCohort I proves mtolerable, Coh01t -I may be evaluated. If Cohort -I IS not tolerable, lower doses or altemative dose schedules ofiNCB059872 may be tested. Any dose reduction in INCB059872 would be combined with pembroli.ztunab 200 mg IV Q3W and epacadostat 50 mg PO BID. If a de-escalation cohort is detennined to be safe and tolerable, the dose of INCB059872 or epacadostat may be re-escalated in separate, additional coh01ts based on the review of available safety data.

b Dose-escalation Coh01ts 2A and 2B may be opened in parallel if no Grade 3 AEs are observed in Cohort I.

c Cohort 3 will be enrolled once Coh01t 2A clears the DLT period. Enrollment into Cohort 3 is not dependent upon clearing the DLT period from Cohort 2B.

4.1.2. Dose-Expansion Phase

4.1.2.1. Treatment Group A

Once the safety profile of all doses tested has been characterized and the RP2D of the combination has been defmed, the cohort expansion will be initiated at the RP2D. The doses selected for expansion will not exceed the MTD or maximum tested dose in Pa1t 1.

The purpose of Phase 2 is to gather additional safety, and preliminaly efficacy infmmation 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 cohmt (A-5).

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

Two cohmts will be evaluated as part of the safety/efficacy expansion. The eligible tumor types are NSCLC and MSS CRC. Subjects emolled in the NSCLC tumor cohmt 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 pa1ticular cohmt 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 emolled. If no responses are observed in the NSCLC PD-1 failure and MSS CRC cohmts, the cohmt(s) will be discontinued. If at least 1 response is observed in the NSCLC PD-1 failure or MSS CRC cohmt, 19 additional NSCLC PD-1 failure or MSS CRC subjects will be emolled (Stage 2), for a maximum of27 subjects per cohmt (see Table 4).

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

Cohort	Treatment	Tumor Type (n)
Expansion Coh01t A-1	MTD or maximum tested dose for the azacitidine +pembrolizumab + epacadostat combination.	A maximtun of27 subjects with previously treated Stage IV or recmrent NSCLC with progression on a prior PD-1 pathway-targeted agent.
Expansion Coh01t A-2	MTD or maximum tested dose for the azacitidine +pembrolizumab + epacadostat combination.	A maximum of27 subjects with previously treated Stage IV MSS CRC.

Continuous evaluation of toxicity events will be pe1fmmed throughout the expansion. In the expansion, after the sixth subject in Stage 1 has been emolled, if > 40% of subjects have an AE 2: Grade 3 that is attributable to the investigational agents, further emollment of subjects will be suspended until the sponsor, investigators, and regulatmy authorities (if applicable) have detelmined the appropriate course of action. If an expansion cohmt is discontinued because of toxicity, a new cohmt may be initiated at a previously tested lower dose level.

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

The sequencing biopsy cohmts 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 emolled in Expansion Cohmts A-3 and A-4, and approximately 10 subjects will be emolled in Expansion Cohmt A-5. The eligible tumor types for Expansion Cohmts A-3, A-4, and A-5 are HNSCC, melanoma, urothelial carcinoma, and MSS CRC. In Expansion Cohmts 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 Cohmts A-3 and A-4, and 10 subjects in Expansion Cohmt A-5 will initiate treatment and have tumor biopsies perfmmed 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 Cohort A-3	Azacitidine monotherapy during Week -1 (5 doses), initiate pembrolizmnab and epacadostat on C1D1 (window+ 5 days fi:om the date of the fifth azacitidine dose; should begin 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) Urothelial carcinoma (5-8) MSS CRC (5-8)
Expansion Coh01t A-4	Pembrolizmnab 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 C2Dl (window C1D15 to C2Dl , biopsy before azacitidine administration). Biopsy #3 during Week 8 or 9.	HNSCC (5-8) Melanoma (5-8) Urothelial carcinoma (5-8) MSS CRC (5-8)
Expansion Coh01t A-5	Pembrolizmnab 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 C2Dl (window C1D15 to C2Dl , 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 Cohmts A-4 and A-5 will receive up to 5 cycles of azacitidine. The sponsor will manage emollment 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.

4.1.2.2. Treatment Group B

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

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

The expansion will include:

1. Safety/efficacy cohmts 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 celtain circumstances, as listed below:

1. Cohmts 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, Cohmts B-1 and B-2 will only be emolled if2,_1/3 of the subjects in the dose-escalation cohmt have a 25% drop in platelet count from Cycle 1 Day 1 to Cycle 2 Day 1.

Continuous evaluation of toxicity events will be pe1fmmed throughout the expansion cohmts. After the dose-expansion cohmts have been emolled, beginning with the sixth patient for a specific regimen, if > 40% of subjects have an AE 2: Grade 3 that is attributable to the investigational agents, fmther emollment of subjects will be suspended until the sponsor, investigators, and regulatmy authorities (if applicable) have detelmined the appropriate course of action. If an expansion cohmt is discontinued because of toxicity, a new cohmt may be initiated at a previously tested lower dose level.

Following completed emollmen/efficacy expansion cohmts, there will be an optional 8-week pause to utilize data for RP2D dete1mination. During this time period, no ;ect emollment may be allowed. If there is no evidence of clinical efficacy [redacted] in the dose-expansion cohorts, emollment in the respective treatment group will be stopped prior to Pa.It 2.

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

Following safety, efficacy, evaluation, an RP2D will be determined. A Simon 2-stage design will a stoppmg rule to allow for early termination of a particular cohmt 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 emolled. If no responses are observed in the NSCLC PD-1 failure and MSS CRC cohmts, the cohmt(s) will be discontinued. If at least 1 response is observed in the NSCLC PD-1 failure or MSS CRC cohmt, 19 additional NSCLC PD-1 failure or MSS CRC subjects will be emolled (Stage 2), for a maximum of 27 subjects per cohmt (see Table 6).

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

Cohort	Treatment	Tumor Type (n)
Expansion Coh01t B-7	MTD, maximum tested dose, or PAD for the INCB057643 + pembrolizumab + epacadostat combination.	A maximum of27 subjects with previously treated Stage IV or rectuTent NSCLC with progression on a prior PD-1 pathway-targeted agent.
Expansion Coh01t B-8	MTD, maximum tested dose, or PAD for the INCB057643 + pembrolizumab + epacadostat combination.	A maximum of27 subjects with previously treated Stage IV MSS CRC.

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

The sequencing biopsy cohmts require 3 tumor biopsies (except for Cohmt 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 Cohmt B-7 or C-8, approximately 25 subjects will be emolled in Expansion Cohmts B-9, B-10, and B-11. The eligible tumor types for Expansion Cohmts B-9, B-10, and B-11 are HNSCC, melanoma, urothelial carcinoma, and MSS CRC. In Expansion Cohmts 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 Cohmts B-9, B-10, and B-11 will initiate treatment and have tumor biopsies perfmmed 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 dming 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 dming Week 8 or 9.	HNSCC (5-8) Melanoma (5-8) Urothelial carcinoma (5-8) MSS CRC (5-8)
Expansion Coh01t 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 dming Week 8 or 9.	HNSCC (5-8) Melanoma (5-8) Urothelial carcinoma (5-8) MSS CRC (5-8)
Expansion Coh01t B-11	INCB057643, epacadostat, and pembrolizumab beginning C1.	Biopsy #1 at baseline. Biopsy #2 dming Week *5* or 6.	HNSCC (5-8) Melanoma (5-8) Urothelial carcinoma (5-8) MSS CRC (5-8)

The sponsor will manage emollment 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.

4.1.2.3. Treatment Group C

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

Because higher doses of epigenetic priming regimens may be deleterious to immune function, expansion cohmts at each dose level tested that clear the DLT window will be opened for signal detection analysis to guide an RP2D. Once an RP2D is detennined, this dose will iii iii Simon 2-stage and treatment sequencing tumor biopsy cohmts. During dose expansion, 5 NSCLC subjects who progressed on a PD-1 pathway–targeted agent and 5 MSS CRC subjects will be emolled 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 cohmts 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 celtain circumstances, as listed below:

1. Cohmts 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, Cohmts C-1, C-2, C-5, and C-6 will only be emolled if 1/3 of the subjects in the dose-escalation cohmts have a 25% drop in platelet count from Cycle 1 Day 1 to Cycle 2 Day 1.
2. Cohmts C-3 and C-4 will only be expanded if both of the following occur:
   a. The INCB059872 1 mg QD cohmt does not clear its DLT window or is deemed not tolerated for reasons outside of strict DLT criteria.
   b. The INCB059872 2 mg QoD cohmt clears its DLT window and is deemed to have acceptable tolerability.

Continuous evaluation of toxicity events will be pe1fmmed throughout the expansion cohmts. After the dose-expansion cohorts have been emolled, beginning with the sixth patient for a specific regimen, if > 40% of subjects have an AE 2: Grade 3 that is attributable to the investigational agents, fmther emollment of subjects will be suspended until the sponsor, investigators, and regulatmy authorities (if applicable) have detelmined the appropriate course of action. If an expansion cohmt is discontinued because of toxicity, a new cohmt may be initiated at a previously tested lower dose level.

Following completed emollment of the safety/efficacy expansion cohmts, there will be an optional 8-week pause to utilize data for RP2D dete1mination. During this time period, no ject emollment nd. If there is no evidence of clinical efficacy [redacted] in the dose-expansion cohmts, emollment in the respective treatment group will be stopped pnor to Part 2.

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

Following safety, efficacy, data evaluation, an RP2D will be dete1mined. A Simon 2-stage design will a stopping mle to allow for early te1mination of a palticular cohmt 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 emolled. If no responses are observed in the NSCLC PD-1 failure and MSS CRC cohmts, the cohmt(s) will be discontinued. If at least 1 response is observed in the NSCLC PD-1 failure or MSS CRC cohmt, 19 additional NSCLC PD-1 failure or MSS CRC subjects will be emolled (Stage 2), for a maximum of 27 subjects per cohmt (see Table 8).

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

Cohort	Treatment	Tumor Type (n)
Expansion Coh01t 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 rectuTent NSCLC with progression on a prior PD-1 pathway-targeted agent.
Expansion Coh01t 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.

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

The sequencing biopsy cohmts require 3 tumor biopsies (except for Cohmt 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 Cohmt C-9 or C-10, approximately 25 subjects will be emolled in Expansion Cohmts C-11, C-12, and C-13. The eligible tumor types for Expansion Cohmts C-11, C-12, and C-13 are HNSCC, melanoma, urothelial carcinoma, and MSS CRC. In Expansion Cohmts 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 Cohmts C-11, C-12, and C-13 will initiate treatment and have tumor biopsies perfmmed as indicated in Table 9.

Table 9: Treatment Group C Treatment Sequencing Tumor Biopsy Cohorts

Cohort	Treatment Sequence	Biopsy Sequence	Tumor Type (n)
Expansion Coh01t C-11	INCB059872 continuous monotherapy dming 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 dming Week 8 or 9.	HNSCC (5-8) Melanoma (5-8) Urothelial carcinoma (5-8) MSS CRC (5-8)
Expansion Coh01t 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 dming Week 8 or 9.	HNSCC (5-8) Melanoma (5-8) Urothelial carcinoma (5-8) MSS CRC (5-8)
Expansion Coh01t C-13	INCB059872, epacadostat and pembrolizumab beginning C1.	Biopsy #1 at baseline. Biopsy #2 dming Week 5 or 6	HNSCC (5-8) Melanoma (5-8) Urothelial carcinoma (5-8) MSS CRC (5-8)

The sponsor will manage emollment 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.

Figure 1: Study Design: Treatment Group A

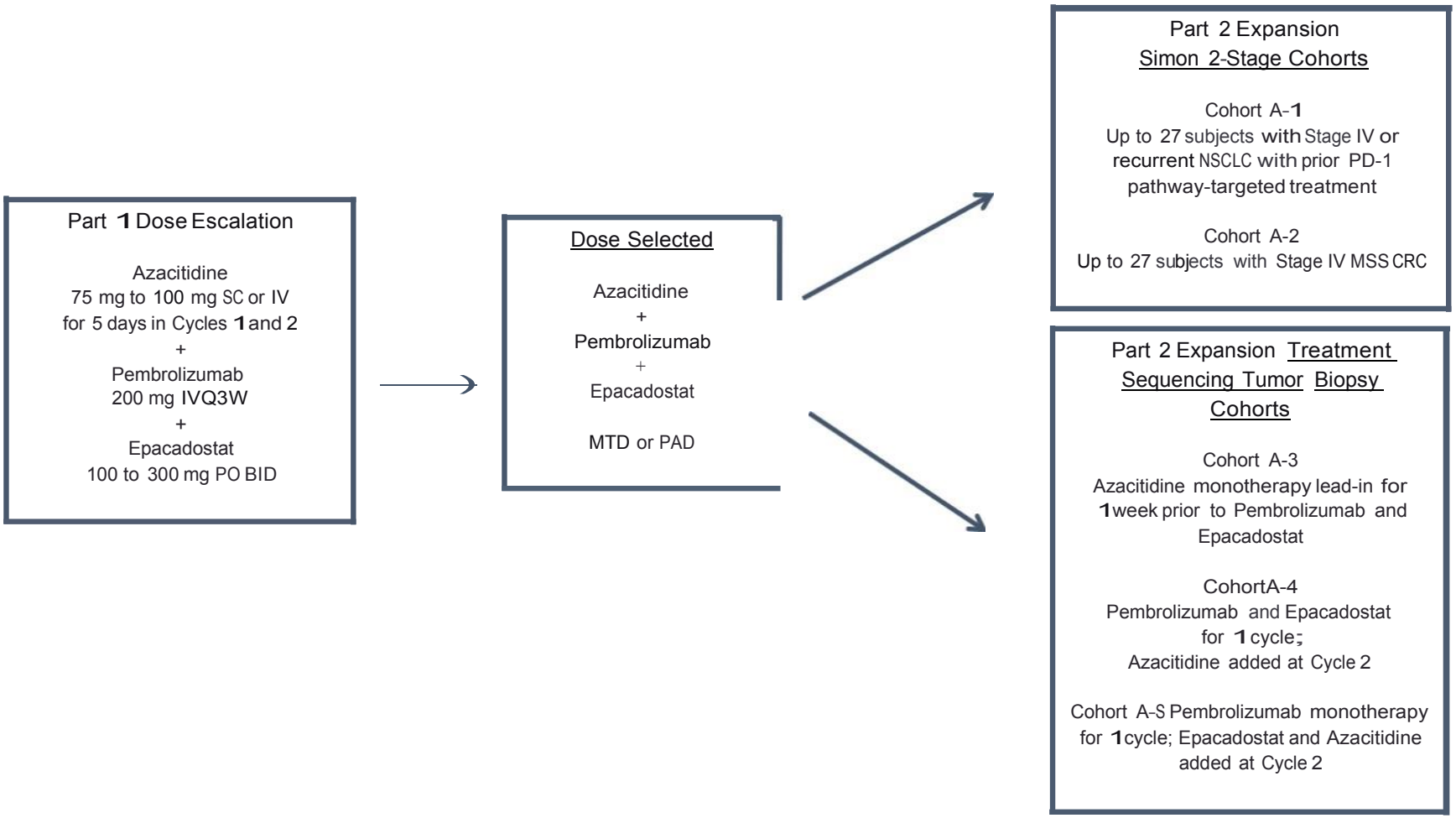


Figure 2: Study Design: Treatment Group B

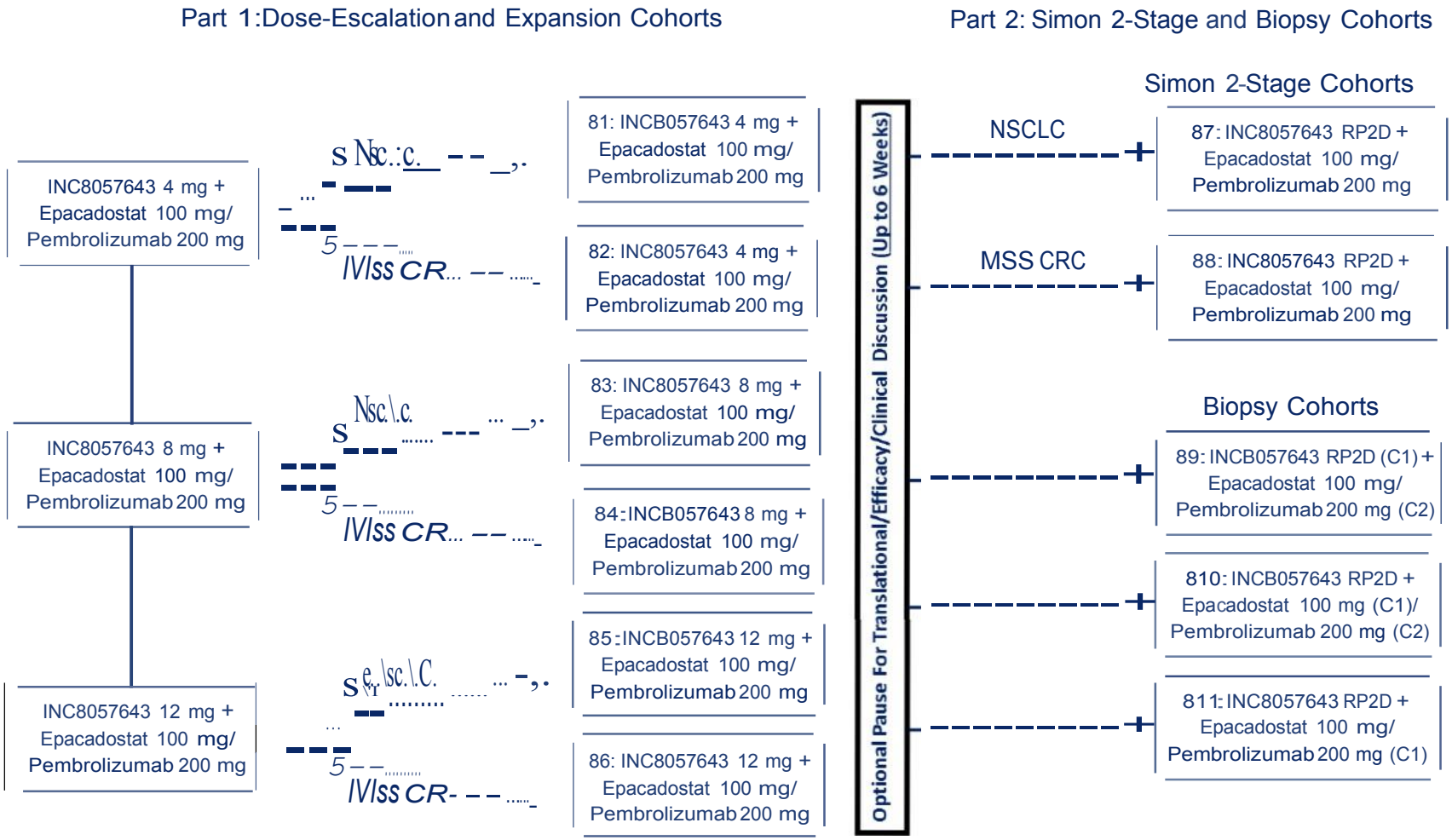
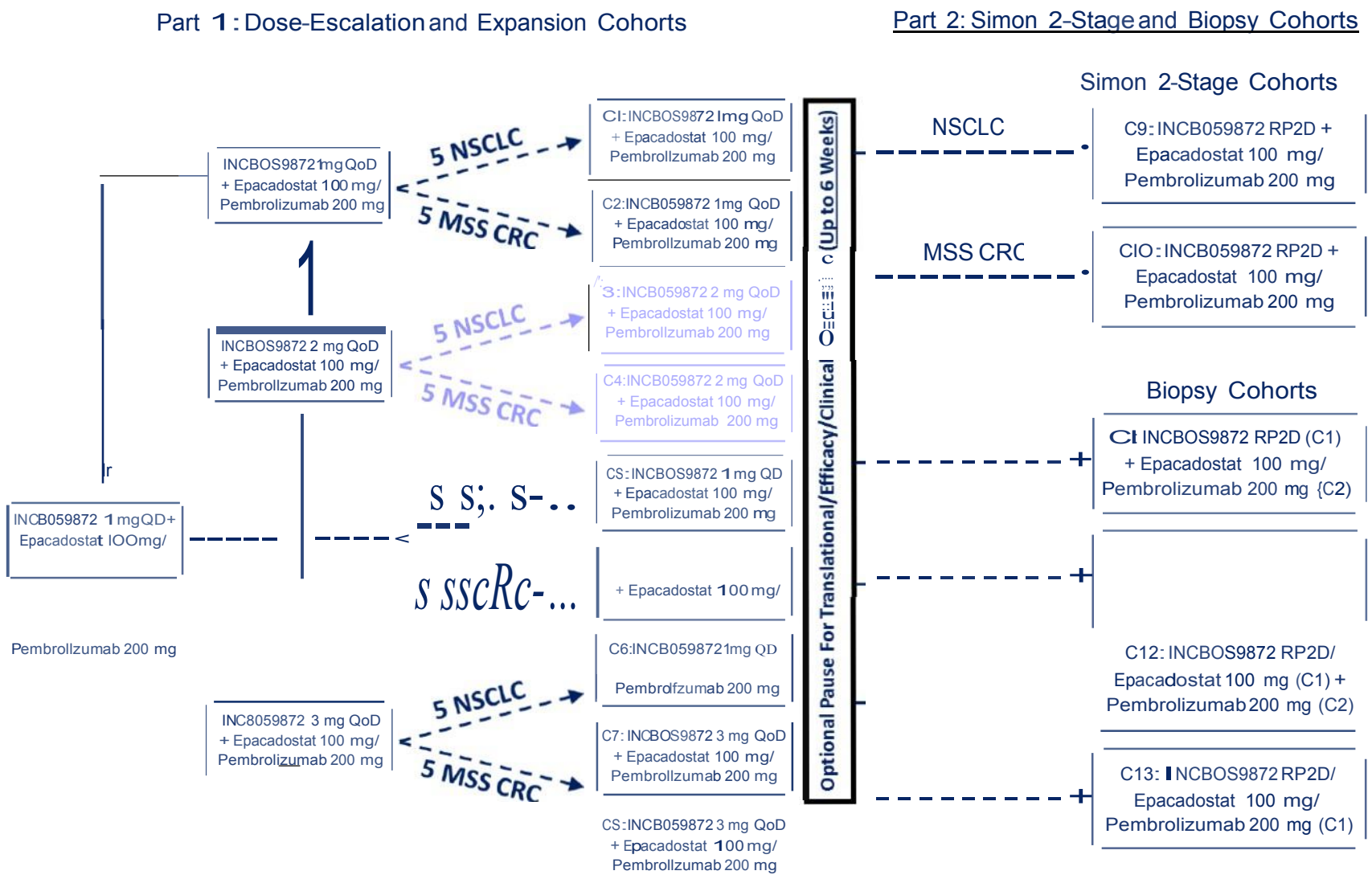


Figure 3: Study Design: Treatment Group C



4-2- Measures Taken to Avoid Bias

Assessments of safety and efficacy are objective measurements.

4_3_ Number of Subjects

4.3.1. Planned Number of Subjects

Up to approximately 531 subjects will be emolled in the study. In Treatment Group A, approximately 15 to 45 subjects will be emolled in Pa1t 1 (Dose Escalation), and approximately 76 to 114 subjects will be emolled in Pa1t 2 (up to 16 subjects in Stage 1 and up to 38 additional subjects in Stage 2; 60 subjects planned in the sequencing tumor biopsy cohmts). In Treatment Group B, up to approximately 186 subjects will be emolled; approximately 39 to 57 subjects will be emolled in Pa1t 1, and up to approximately 129 subjects will be emolled in Pa1t 2. In Treatment Group C, up to approximately 186 subjects will be emolled; approximately 39 to 57 subjects will be emolled in Pa1t 1, and up to approximately 129 subjects will be emolled in Part 2.

4.3.2. Replacement of Subjects

Subjects may be replaced for any of the following reasons:

- Subject is not evaluable for DLTs (see Section 5.4.1.1).
- In Pa1t 1, Stage 1 of Pa1t 2, and the treatment sequencing tumor biopsy cohmts, subject has not met the biopsy requirements for the study (ie, pre- and on-treatment samples).
- Subject does not meet the eligibility requirements of the study (eg, accidental emollment).

4.4. Duration of Treatment and Subject Participation

After signing the infmmed consent fmm (ICF), screening assessments may be completed over a period of up to 28 days. Each subject emolled in the study may continue to receive study treatment in continuous 21-day cycles if, in the judgment of the treating physician, the subject is deriving benefit from treatment and has not met any crite1ia for study withdrawal, or until the subject has received 35 administrations ofpembrolizumab (approximately 2 years). Subjects who achieve a CR may discontinue therapy after 2 cycles upon consultation with the medical monitor. Subjects who achieve aPR or SD should remain on study treatment. Re-treatment with azacitidine 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 progressive disease (PD) while receiving pembrolizumab and epacadostat with medical monitor approval. Three additional cycles of azacitidine are pe1mitted.

Once it is dete1mined that a subject will not continue on study treatment, the subject will enter the follow-up period (see Section 6.4). Study pa1ticipation is expected to average approximately 18 months per individual subject (screening/study treatment for 6 months and follow-up for an additional12 months). Upon implementation of Amendment 4, the follow-up period will end with the safety follow-up visit (42-49 days after EOT).

4.5. Overall Study Duration

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

If there have been:::; 5 subjects on study for more than 6 months, a database lock of the study may occur to allow the analysis of the study data. Any remaining subjects may continue to receive study treatment and be seen by the investigator per protocol. The investigator will be expected to monitor for and repmt any SAEs, AEs of special interest, and pregnancies, as detailed in Section 8. The remaining subjects are considered to be on study until a discontinuation criterion is met and written notification is provided to the sponsor.

4.6. Study Termination

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

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

5. TREATMENT

5.1. Treatment Assignment

5.1.1. Subject Numbering and Treatment Assignment

Study sites will enter subject demographic and baseline data into the interactive voice/web response system (IRT) in order to receive a subject number and treatment allocation.

All subject numbers will be 6 digits; the first 3 digits will be the site number and the last 3 digits will be the subject's number. This subject number will be maintained throughout the study and will not be reassigned. Subjects who withdraw consent or discontinue from the study after being assigned a subject number will retain their initial number.

Site staff will contact the IRT to obtain the initial study drug assignment. The investigator or designee will select the assigned bottles of study drug from their stock that conespond to the number provided by the IRT and dispense the study drug to the subject. All subsequent dispensing of study drug should follow this process. Refer to the IRT manual for detailed infmmation.

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

For subjects who signed an ICF but are not allocated and for subjects who are allocated but were not treated, refer to the electronic case repmt fmm (eCRF) Completion Guidelines for instruction on which eCRFs to complete.

5.1.2. Randomization and Blinding

Not applicable.

5.2. Study Drugs

5.2.1. Epacadostat

5.2.1.1. Description and Administration

Epacadostat will be available as 25 or 100 mg tablets to be administered in a BID administration schedule. All BID doses of epacadostat will be taken PO in the moming and evening, approximately 12 hours apa1t without regard to food. If the moming or evening dose is missed by more than 4 hours, then that dose should be skipped, and the next scheduled dose should be taken at the usual time. Doses of epacadostat will be self-administered except on the days scheduled to be given at the study clinic (see Section 6).

Subjects should be counseled by the investigator to maintain str·ict adherence to the study regimen as prescribed and to keep a record of any missed doses. The subject will be instmcted to bring all unopened, empty, and opened/pa1tially used bottles of study dmg at Day 1 study visits, at which time compliance will be assessed.

5.2.1.2. Supply, Packaging, and Labeling

Study dmg tablets are packaged in high-density polyethylene bottles; no preparation is required. All Incyte study dmgs will be color coded to avoid erTor.

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

5.2.1.3. Storage

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

5.2.1.4. Instruction to Subjects for Handling Epacadostat

The subject must be instructed in the handling of study dmg as follows:

- To store the study dmg at room temperature.
- To only remove from the study dmg bottle/kit the number of tablets needed at the time of administr·ation.
- Not to remove doses in advance of the next scheduled administration.
- To make every effmt to take doses on schedule.
- To repmt any missed doses.

- If the subject vomits after taking study dmg, the subject should not take another dose.
- If the moming or evening dose of epacadostat is missed by more than 4 hours, then that dose should be skipped, and the next scheduled dose should be taken at the usual time.
- To keep study dmg in a safe place and out of reach and sight of children.
- To bring all used and unused study dmg kits to the site at each visit.

5.2.2. Pembrolizumab

5.2.2.1. Description and Administration

Pembrolizumab is available in single dose vials as a 100 mg/4 mL solution and 50 mg powder for injection. All subjects will receive pembrolizumab 200 mg via a 30-minute IV infusion Q3W on Day 1 of each 21-day cycle. Sites should make every effmt to target infusion timing to be as close to 30 minutes as possible. At the end of the infusion, the line should be flushed with a sufficient quantity of normal saline. On days when epacadostat and azacitidine is administered in the clinic, epacadostat and azacitidine should be administered just before beginning the infusion of pembrolizumab.

Subjects may be administered pembrolizumab no less than 18 days between doses and no more than 3 days after the scheduled administration date. Doses given after the 3-day window are considered a dose delay. A maximum delay of 42 days between doses is allowed. If the delay is greater than 14 days, this must be discussed with medical monitor.

5.2.2.2. Supply, Packaging, and Labeling

Pembrolizumab vials will be affixed with a clinical label in accordance with regulatory requirements.

5.2.2.3. Storage

Pembrolizumab should be stored under refrigeration at 2°C to 8°C (36°F-46°F) and protected from light by stming it in the original package until time of use. Pembrolizumab should not be frozen or shaken.

5.2.3. Azacitidine

5.2.3.1. Description and Administration

Azacitidine is provided as a lyophilized powder in 100 mg single-use vials to be administered by SC injection or IV infusion. In the European Union, azacitidine will be administered SC only.

Five doses of azacitidine will be administered in the clinic during Cycles 1 through 3. Details for study dmg administration in the treatment sequencing tumor biopsy cohmts (Cohmts A-3 through A-5) are presented in Table 5 and the study assessments tables (see Section 6). Subjects who remain on treatment beyond the Week 9 scan should continue to receive azacitidine until the second on-study scan (up to the Week 18 scan, for a maximum of 3 additional cycles) and then continue pembrolizumab and epacadostat as long as there is benefit. The 5 doses should be administered over the Day 1 to 7 period. Re-treatment with azacitidine (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 with medical monitor approval. Three additional cycles of azacitidine are pennitted.

5.2.3.2. Supply, Packaging, and Labeling

Azacitidine vials will be affixed with a clinical label in accordance with regulatmy requirements.

5.2.3.3. Storage

Umeconstituted vials of azacitidine should be stored at 25°C (77°F); excursions are pelmitted to 15°C to 30°C (59°F-86°F).

5.2.4. INCB057643

5.2.4.1. Description and Administration

Physical and chemical properties of iNCB057643 are summarized in the INCB057643 IB. INCB057643 is fmmulated as 4 mg immediate-release tablets. The tablet is round and white to off-white and contains the active dmg substance along with compendia!grade excipients lactose monohydrate, sodium starch glycolate, and magnesium stearate.

Subjects will self-administer INCB057643 orally QD, as instmcted by the investigator. It will be administered in the clinic on the schedule outlined in Section 6. The starting dose in Part 1 is 4 mg. INCB057643 doses should be taken in the moming on an empty stomach when possible. Subjects should fast for approximately 2 hours before and 1 hour after INCB057643 administration, except on days when serial sampling is conducted, then subjects will fast at least 8 hours before or as indicated in Section 7.8. If a dose is missed by more than 8 hours, then the subject should skip that dose and take the next scheduled dose at the usual time. The sponsor may implement altemate administrat· such as intelmediate doses, altemate dosing schedules, or altemate fmmulations, depending on [redacted] safety results.

5.2.4.2. Supply, Packaging, and Labeling

INCB057643 will be provided as 4 mg tablets packaged in high-density polyethylene bottles. No preparation is required. The investigational product labels will be in the local language and will comply with the legal requirements of each countly.

5.2.4.3. Storage

INCB057643 dmg product should be stored at ambient conditions (15°C-30°C or 59°F-86°F).

5.2.4.4. Instruction to Subjects for Handling INCB057643

The subject must be instructed in the handling ofiNCB057643 as follows:

- To store INCB057643 at room temperature.
- To only remove from the study dmg bottle the number of tablets needed at the time of administr·ation.
- Not to remove doses in advance of the next scheduled administration.
- To make every effort to take doses on schedule.
- To fast for approximately 2 hours before and 1 hour after INCB057643 administr·ation.
- If a dose is missed by more than 8 hours, then the subject should skip that dose and take next scheduled dose at the usual time.
- To report any missed doses.
- If the subject vomits after taking study dmg, the subject should not take another dose; dosing should be resumed at the next scheduled dose.
- To keep study dmg in a safe place and out of reach of children.
- To bring all used and unused study dmg bottles to the site at each visit.

5.2.5. INCB059872

5.2.5.1. Description and Administration

Physical and chemical properties of INCB059872 are summarized in the INCB059872 IB. INCB059872 is formulated as 1 mg tablets.

INCB059872 is only for use in the United States. Subjects will self-administer INCB059872 orally QD or QoD as instructed by the investigator. It will be administered in the clinic on the schedule outlined in Section 6. The statting dose in Patt 1 is 1 mg QoD. INCB059872 doses should be taken in the moming on an empty stomach when possible. Subjects should fast for a01::•rmm·mateJ 2 hours before and 1 hour after INCB059872 administration, except on days when serial [redacted] sampling is conducted, then subjects will fast at least 8 hours before or as indicated in Section 7.8. If a dose is missed by more than 8 hours, then the subject should skip that dose and take next scheduled dose at the usual time. The sponsor may implement altemate such as intetmediate altemate dosing schedules, or altemate formulations, depending on safety results.

5.2.5.2. Supply, Packaging, and Labeling

INCB059872 will be provided as 1 mg tablets packaged in high-density polyethylene bottles. No preparation is required. The investigational product labels will state "Caution: New Dmg-Limited by Federal (or United States) law to investigational use."

5.2.5.3. Storage

Bottles of tablets should be stored in a refrigerator and maintained at a temperature between 2°C and 8°C (36°F-46°F).

5.2.5.4. Instruction to Subjects for Handling INCB059872

The subject must be instructed in the handling ofiNCB059872 as follows:

- To store INCB059872 in a refrigerator.
- To only remove from the study dmg bottle the number of tablets needed at the time of administration.
- Not to remove doses in advance of the next scheduled administration.
- To make every effort to take doses on schedule.
- To fast for approximately 2 hours before and 1 hour after INCB059872 administration.
- If a dose is missed by more than 8 hours, then the subject should skip that dose and take next scheduled dose at the usual time.
- To report any missed doses.
- If the subject vomits after taking study dmg, the subject should not take another dose; dosing should be resumed at the next scheduled dose.
- To keep study dmg in a safe place and out of reach of children.
- To bring all used and unused study dmg bottles to the site at each visit.

5.3. Treatment Compliance

Compliance with all study-related treatments should be emphasized to the subject by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance with epacadostat, INCB057643, and INCB059872 will be calculated by the sponsor based on the dmg accountability documented by the site staff and monitored by the sponsor/designee (tablet counts). Subjects will be instructed to bring all study dmgs with them to the study visits in order for site personnel to conduct tablet counts to assess study dmg accountability. The dmg accountability documentation will be used by the sponsor to calculate treatment compliance.

Pembrolizumab and azacitidine are administered as either IV or SC infusions by the site personnel. Receipt of infusions will be documented by the site staff and monitored by the sponsor or the sponsor's designee.

5-4_ Treatment Interruptions and Adjustments

5.4.1. Dose Modifications

Selections and modifications to the study dmg regimen are plaillled for dose-escalation cohmts. Dose intenuptions and modifications also may occur for individual study subjects. The identification ofDLTs will define the doses used in Phase 2. Fmther, the occunence ofDLTs and other toxicities (related or unrelated to study dmg) will guide decisions for treatment inten11ptions and discontinuation for individual subjects.

Intrasubject dose escalation will not be pe1mitted.

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

A DLT will be defined as the occmTence of any of the toxicities in Table 10 occmTing up to and including Day 21 for Treatment Group A or Day 42 for Treatment Groups Band C. Only toxicities with a clear altemative explanation (eg, due to disease progression), transient (72 hours) abnmmallaboratmy values without associated clinically significant signs or symptoms based on investigator dete1mination, iiAEs of Grade 3 or higher that improve to Grade 1 or lower in < 5 days by appropriate care or with cmticosteroid therapy can be deemed a non-DLT. All DLTs will be assessed by the investigator using the cmTent CTCAE v4.03 crite1ia. Subjects who receive 2: 75% doses of study dmg (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]) at the level assigned or have a DLT will be considered evaluable for dete1mining tolerability of the dose.

Individual subject dose reductions may be made based on events observed at any time dming treatment with study dmg; however, for the purposes of dose cohmt escalation/de-escalation, expanding a dose cohmt, and dete1mining the MTD of the study drugs, decisions will be made based on events that are observed from the first day of study dmg administration through and including the final day of Cycle 1 (Day 21) for Treatment Group A or Cycle 2 (Day 42) for Treatment Groups B and C. A lower MTD may subsequently be dete1mined based on relevant toxicities that become evident after Day 21 (Treatment Group A) or Day 42 (Treatment Groups Band C).

Table 10: Definition of Dose-Limiting Toxicity

Toxicity
o!Unennatologic
• Grade 4 (life-threatening) vomiting or diarrhea • Grade 4 electrolyte abnormality • Grade 4 systemic reaction • Any 2:: Grade 3 no!Unematologic toxicity EXCEPT the following: – Transient(72 hours) abno1mal laboratory values without associated clinically significant signs or symptoms. – ausea, vomiting, and diarrhea adequately controlled with medical therapy within 48 hours. – Grade 3 rash in the absence of desquamation, with no mucosal involvement, that does not require systemic steroids, and that resolves to Grade 1 within 14 days. – An event clearly associated with the underlying disease, disease progression, a concomitant medication, or comorbidity. – Asymptonnatic changes in lipid profiles. – Singular or nonfasting elevations in blood glucose (ie, blood glucose excursions will be considered toxicities if fasting blood glucose is elevated on 2 separate occasions). – lmmtme-related adverse events of Grade 3 or higher that improve toGrade 1 in < 5 days by appropriate care or with corticosteroid therapy.
Hennatologic
• 2:: Grade 3 thrombocytopenia with clinically significant bleeding (requires hospitalization, transfusion of blood products, or other urgent medical intervention). • Grade 4 thrombocytopenia of any duration • Grade 4 neutropenia lasting > 3 days • 2:: Grade 3 febrile neutropenia (absolute neutrophil cotmt < 1.0 x 10^9/L and fever > 101°F/38.5°C). • Grade 4 neutropenia that does not recover toGrade 2 in3 days after intemlpting study dmg. • Grade 4 anemia not explained by underlying disease or some other concomitant disorder.
General
• Subjects being unable to receive 2:: 75% of study dmg doses during the DLT observation period because of toxicity, even if the toxicity does not meet DLT criteria defined above. ote:Exceptions include the DLT exclusions mentioned above.
MTD
• 1 dose level below that at which 2:: one-third of subjects in a palticular cohort has DLTs. Dose-limiting toxicity will be defined as the occull'ence of any of the toxicities in *this table* occUlTing up to and including study Day 21.

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

In all cases, investigators may employ any measures or concomitant medications, after discussion with the sponsor (whenever possible), necessa1y to optimally treat the subject.

5.4.1.1.2. Follow-Up of Dose-Limiting Toxicities

Any DLT should be followed until it resolves to baseline or appears to have stabilized for a minimum of 4 weeks. During follow-up, subjects should be seen as often as medically indicated to assure safety.

5.4.1.1.3. Procedures for Cohort Review and Dose Escalation

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

5.4.1.2. Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug

Treatment with study dmg may be delayed up to 2 weeks (14 days) to allow for resolution of toxicity. If only 1 of the 2 agents is suspected to be responsible for the toxicity, only the suspected agent should be held (while the other treatment continues). In some circumstances, it may be necessa1y to temporarily inten11pt the combination as a result of AEs that may not have a cause attributable to a single dmg or that may be the result of combined toxicity.

Subjects may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make fmther pmticipation in the study unsuitable. The treating investigator should contact the sponsor to discuss the case of any subject whose treatment has been delayed for more than 14 days before resta1ting treatment with the study dmgs.

Because subjects may enter the study with extensive pretreatment and/or severe bone manow infiltration by the prima1y disease, these dose reduction mles are provided as guidelines (see Table 15 through Table 17). Individual decisions regarding dose reduction should be made using clinical judgment and in consultation with the sponsor's medical monitor, taking into account relatedness of the AE to the study dmg and the subject's underlying condition. Adverse events that have a clear altemative explanation or transient (:S 72 hours) abnmmallaboratmy values without associated clinically significant signs or symptmns may be exempt from dose-reduction mles.

5.4.1.2.1. Pembrolizumab Dose Modifications

There will be no dose reductions of pembrolizumab allowed for the management of toxicities of individual subjects. Doses of pembrolizumab may be delayed for toxicity management.

5.4.1.2.2. Epacadostat Dose Modifications

Table 11 describes epacadostat dose reductions that may occur due to any related AEs. Dose reductions should occur in a step-wise fashion from the initial sta1ting dose of the cohmt, and a maximum of 2 dose reductions of epacadostat are allowed for the management of an AE, regardless of the initial sta1ting dose. If an AE recurs/does not retum to baseline after the second

dose reduction of epacadostat, then the subject must pe1manently discontinue epacadostat. The lowest pe1missible dose of epacadostat is 25 mg BID. If a subject does not tolerate 25 mg BID, then the subject must pe1manently discontinue epacadostat.

Table 11: Epacadostat Dose Reductions

Dose Level
300mgBID
lOOmgBID
50mgBID
25 mgBID

5.4.1.2.3. Azacitidine Dose Modifications

Table 12 describes azacitidine dose reductions that may occur due to any related AEs. Dose reductions should occur in a step-wise fashion from the initial starting dose of the cohmt, and a maximum of 2 dose reductions of azacitidine are allowed for the management of an AE, regardless of the initial starting dose. If an AE recurs/does not retum to baseline after the second dose reduction of azacitidine, then the subject must pe1manently discontinue azacitidine. The lowest pe1missible dose of azacitidine is 50 mg. If a subject does not tolerate 50 mg, then the subject must pe1manently discontinue azacitidine.

Table 12: Azacitidine Dose Reductions

Dose Level
lOOmg
75mg
50mg

5.4.1.2.4. INCB057643 Dose Modifications

Table 13 describes INCB057643 dose reductions that may occur due to any related AEs. Dose reductions should occur in a step-wise fashion from the initial starting dose of the cohmt, and a maximum of 2 dose reductions of INCB057643 are allowed for the management of an AE, regardless of the initial starting dose. If an AE recurs/does not retum to baseline after the second dose reduction ofiNCB057643, then the subject must pe1manently discontinue INCB057643. The lowest pe1missible dose of INCB057643 is 4 mg. If a subject does not tolerate 4 mg, altemative dose schedules may be evaluated.

Table 13: INCB057643 Dose Reductions

Dose Level
12mgQD
8mgQD
4mgQD

5.4.1.2.5. INCB059872 Dose Modifications

Table 14 describes INCB059872 dose reductions that may occur due to any related AEs. Dose reductions should occur in a step-wise fashion from the initial starting dose of the cohmt, and a maximum of 2 dose reductions of INCB059872 are allowed for the management of an AE, regardless of the initial sta lting dose. If an AE recurs/does not retum to baseline after the second dose reduction ofiNCB059872, then the subject must pe1manently discontinue INCB057643. The lowest pe1missible dose ofiNCB059872 is 1 mg QoD. If a subject does not tolerate 1 mg QoD, altemative dose schedules may be evaluated.

Table 14: INCB059872 Dose Reductions

Dose Level
3 mgQoD
2 mg QoD/1 mg QD[a]
1 mgQoD

Table 15: Dose Modification Guidelines for Drug-Related Adverse Events (Treatment Group A)

Toxicity	Grade	Hold Treatment (YIN)	Timing for Treatment Restat1	Dose/Schedule for Treatment Restat1			Discontinue Subject (After Medical Monitor Consultation)
				Azacitidine	Epacadostat	Pembrolizumab	
Hematologic toxicity	1, 2	No	N/A	NIA	N/A	N/A	N/A
	3	Hold azacitidine	Toxicity resolves to Grade 1 or baseline.	Restart at same dose if the toxicity resolves within 7 days.	N/A	N/A	N/A
	4	Yes	Toxicity resolves to Grade 1 or baseline.	Restart at 1 dose level lower if the toxicity resolves within 7 days.	Reduce dose by 1 dose level.	Restrut at srune dose for the following events: Grade 4 neutropenia lasting7 days, Grade 4 lymphopenia or leukopenia. For all other Grade 4 hematologic toxicities, treatment with pembroliztunab tnay not be restarted.	Toxicity does not resolve within 6 weeks of last infusion. Pennanent discontinuation should be considered for any severe or life-tlu·eatening event.
Nonhetnatologic toxicity Note: Exception to be treated to similar Grade 1 toxicity: - Grade 2 alopecia - Grade 2 fatigue - Grade 3 rash in the absence of desqurunation, without mucosal involvement, not requiring systemic steroids, and that resolves to Grade 1 within 14 days. For additional infonnation regarding AE with potential imnume etiology, see Section 5.4.1.3.	1	No	N/A	NIA	N/A	N/A	N/A
	2	Consider holding for persistent symptoms	Toxicity resolves to Grade 1 or baseline.	Restart at same dose.	Restart at same dose.	Restrut at srune dose.	Toxicity does not resolve within 6 weeks of last infusion.
	3.	Yes•	Toxicity resolves to Grade 1 or baseline.	Restart at same dose.	Restart at 1 dose level lower.	Restrut at srune dose.•	Toxicity does not resolve within 6 weeks of last infusion. Pennanent discontinuation should be considered for any severe or life-tlu·eatening event.
	4	Yes	Toxicity resolves to Grade 1 or baseline.	Restart at 1 dose level lower.	Restart at 1 dose level lower.	Restrut only pennitted only as noted.b For all other Grade 4 nonhematologic toxicities, treatment with pembroliztuna.b may not be restruted.	Toxicity does not resolve within 6 weeks of last infusion. Pennanent discontinuation should be considered for any severe or life-tlu·eatening event.

Note: SubJects who expenence a rectuTence of the srune severe or hfe-threatenmg AE at the srune grade or greater treatment should be dtscontmued from study treatment.

• The following exceptions for asympt01natic amylase or lipase do not require a dose delay: Grade 3 amylase or lipase abnonnalities that are not associated with symptotns or clinical manifestations of pancreatitis. It is recommended to consult with the medical monitor for Grade 3 runylase or lipase abnonna.lities.

b Isolated Grade 4 lipase or runylase abnonnalities not associated witl1 symptoms or clinical manifestations of pancreatitis. Medical monitor should be consulted for any Grade 4 amylase or lipase abnonna.lity.

Table 16: Dose Modification Guidelines for Drug-Related Adverse Events (Treatment Group B)

Toxicity	Grade	Hold Treatment (YIN)	Timing for Treatment Restat1	Dose/Schedule for Treatment Restat1			Discontinue Subject (After Medical Monitor Consultation)
				INCB057643	Epacadostat	Pembrolizumab	
Hematologic toxicity	1, 2	No	NA	NA	N/A	NA	NA
	3	Hold INCB057643	Toxicity resolves to Grade 1 or baseline.	Restart at 1 dose level lower if the toxicity resolves within 7 days.	N/A	NA	NA
	4	Yes	Toxicity resolves to Grade 1 or baseline.	Restart at 1 dose level lower if the toxicity resolves within 7 days. If already at lowest dose, discontinue. If evidence of bleeding, patient should pennanently discontinue.	Reduce dose by 1 dose level. If already at lowest dose, discontinue	Restart at same dose.	Toxicity does not resolve within 6 weeks oflast infhsion. Permanent discontinuation should be considered for any severe or life-threatening event.

Table 16: Dose Modification Guidelines for Drug-Related Adverse Events (Treatment Group B) (Continued)

Toxicity	Grade	Hold Treatment (YIN)	Timing for Treatment Restat1	Dose/Schedule for Treatment Restat1			Discontinue Subject (After Medical Monitor Consultation)
				INCB057643	Epacadostat	Pembrolizumab	
Nonhematologic toxicity	1	No	NA	NA	NA	NA	NA
Note: Exception to be treated to similar Grade 1 toxicity: - Grade 2 alopecia - Grade 2 fatigue - Grade 3 rash in the absence of desquruuation, without mucosal involvement, not requiring systemic steroids, and that resolves to Grade 1 within 14 days. For additional information regarding AE with potential inumme etiology, see Section 5.4.1.3.	2	Consider holding for persistent symptoms	Toxicity resolves to Grade 1 or baseline.	Restart at same dose.	Restart at same dose.	Restart at same dose.	Toxicity does not resolve within 6 weeks oflast infhsion.
	3.	Yes•	Toxicity resolves to Grade 1 or baseline.	Restart at same dose.	Restrut at 1 dose level lower.	Restart at same dose.•	Toxicity does not resolve within 6 weeks oflast infhsion. Permanent discontinuation should be considered for any severe or life-tlu-eatening event.
	4	Yes	Toxicity resolves to Grade 1 or baseline.	Restart at 1 dose level lower. If already at lowest dose, discontinue.	Restart at 1 dose level lower. If already at lowest dose, discontinue.	Restart only permitted only as noted.b For all other Grade 4 nonhetuatologic toxicities, treatment with pembroliztuuab may not be restarted.	Toxicity does not resolve within 6 weeks of last infhsion. Permanent discontinuation should be considered for any severe or life-tlu-eatening event.

Note: SubJects who expenence a rectuTence of the srune severe or hfe-threatenmg AE at the srune grade or greater treatment should be dtscontmued from study treatment.

• The following exceptions for asympt0luatic amylase or lipase do not require a dose delay: Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. It is reconllllended to consult with the medical monitor for Grade 3 runylase or lipase abnonnalities.

b Isolated Grade 4 lipase or runylase abnonualities not associated with symptoms or clinical manifestations of pancreatitis. Medical monitor should be consulted for any Grade 4 amylase or lipase abnonnality.

Table 17: Dose Modification Guidelines for Drug-Related Adverse Events (Treatment Group C)

Toxicity	Grade	Hold Treatment (YIN)	Timing for Treatment Restat1	Dose/Schedule for Treatment Restat1			Discontinue Subject (After Medical Monitor Consultation)
				INCB059872	Epacadostat	Pembrolizumab	
Hematologic toxicity	1, 2	No	NA	NA	NA	NA	NA
	3	Hold INCB059872	Toxicity resolves to Grade 1 or baseline.	Restart at 1 dose level lower if the toxicity resolves within 7 days.	NA	NA	NA
	4	Yes	Toxicity resolves to Grade 1 or baseline.	Restart at 1 dose level lower if the toxicity resolves within 7 days. If already at lowest dose, discontinue. If evidence of bleeding, patient should pennanently discontinue.	Reduce dose by 1 dose level. If already at lowest dose, discontinue	Restart at same dose.	Toxicity does not resolve within 6 weeks oflast infhsion. Permanent discontinuation should be considered for any severe or life-tlu-eatening event.

Table 17: Dose Modification Guidelines for Drug-Related Adverse Events (Treatment Group C) (Continued)

Toxicity	Grade	Hold Treatment (YIN)	Timing for Treatment Restat1	Dose/Schedule for Treatment Restat1			Discontinue Subject (After Medical Monitor Consultation)
				INCB059872	Epacadostat	Pembrolizumab	
Nonhematologic toxicity	1	No	NA	NA	NA	NA	NA
Note: Exception to be treated to similar Grade 1 toxicity: - Grade 2 alopecia - Grade 2 fatigue - Grade 3 rash in the absence of desquruuation, without mucosal involvement, not requiring systemic steroids, and that resolves to Grade 1 within 14 days. For additional information regarding AE with potential inumme etiology, see Section 5.4.1.3.	2	Consider holding for persistent symptoms	Toxicity resolves to Grade 1 or baseline.	Restart at same dose.	Restart at same dose.	Restart at same dose.	Toxicity does not resolve within 6 weeks oflast infhsion.
	3.	Yes•	Toxicity resolves to Grade 1 or baseline.	Restart at same dose.	Restrut at 1 dose level lower.	Restart at same dose.•	Toxicity does not resolve within 6 weeks oflast infhsion. Permanent discontinuation should be considered for any severe or life-tlu-eatening event.
	4	Yes	Toxicity resolves to Grade 1 or baseline.	Restart at 1 dose level lower. If already at lowest dose, discontinue.	Restart at 1 dose level lower. If already at lowest dose, discontinue.	Restart only permitted only as noted.b For all other Grade 4 nonhetuatologic toxicities, treatment with pembroliztuuab may not be restarted.	Toxicity does not resolve within 6 weeks of last infhsion. Permanent discontinuation should be considered for any severe or life-tlu-eatening event.

Note: SubJects who expenence a rectuTence of the srune severe or hfe-threatenmg AE at the srune grade or greater treatment should be dtscontmued from study treatment.

• The following exceptions for asymptomatic amylase or lipase do not require a dose delay: Grade 3 runylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. It is recommended to consult with the medical monitor for Grade 3 runylase or lipase abnonnalities.

b Isolated Grade 4 lipase or runylase abnonualities not associated with symptoms or clinical manifestations of pancreatitis. Medical monitor should be consulted for any Grade 4 amylase or lipase abnonnality.

5.4.1.3. Procedures for Subjects Exhibiting Immune-Related Adverse Events

This section is meant to apply to suspected irAEs from epacadostat, pembrolizumab, or the combination.

Immune-related AEs may be defmed as an AE of unknown etiology, associated with dmg exposure and consistent with an immune phenomenon. Immune-related AEs may be predicted based on the nature of the pembrolizumab or epacadostat compounds, their mechanism of action, and repmted experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shmtly after the first dose or several months after the last dose of treatment.

If an irAE is suspected, effmts should be made to mle out neoplastic, infectious, metabolic, toxin or other etiologic causes before labeling an AE as an irAE. Subjects who develop aGrade 2 irAE should be discussed immediately with the sponsor.

General recommendations to managing irAEs not detailed elsewhere in the Protocol are detailed in Table 18. Recommendations for management of specific immune-mediated AEs such as pneumonitis (Section 5.4.1.3.1), enterocolitis (Section 5.4.1.3.2), hepatitis (Section 5.4.1.3.3), delmatitis (Section 5.4.1.3.4), neuropathies (Section 5.4.1.3.5), endocrinopathies (Section 5.4.1.3.6), myocarditis (Section 5.4.1.3.7), and other immune-mediated AEs (Section 5.4.1.3.8) are detailed in the sections below.

Table 18: General Approach to Handling Immune-Related Adverse Events

irAE	Withhold/Discontinue Pembrolizumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 1	No action.	Not applicable.	Provide symptomatic treatment.
Grade 2	May withhold pembrolizumab and epacadostat per investigator's discretion.	May retum to treatment if improves to Grade 1 or resolves within 6 weeks. If AE resolves within 4 weeks, subject may restrut at the same dose and schedule for both pembrolizumab and epacadostat. For an AE that does not resolve within 4 weeks, epacadostat should be reduced 1 dose level, but pembrolizumab may be restruted at the same dose and schedule. If AE does not resolve within 6 weeks, sntdy treatment with both study dmgs should be discontinued or discussed with medical monitor.	Consider systemic c0 lticosteroids in addition to appropriate symptomatic treatment.

Table 18: General Approach to Handling Immune-Related Adverse Events (Continued)

irAE	Withhold/Discontinue Pembrolizumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 3	Withhold or discontinue pembrolizumab and epacadostat. Discontinue if Imable to reduce corticosteroid dose to < 10 mglday of prednisone or equivalent within 6 weeks of toxicity.	Any restrut of study treatment must be discussed with medical monitor before restruting treatment.	Systemic corticosteroids rue indicated in addition to appropriate symptomatic treatment. May use 1 to 2 mglkg of prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to Grade 1 and tapered over at least 4 weeks in most cases.
Grade4	Discontinue pembrolizumab and epacadostat.	Not applicable. Any exceptions require medical monitor approval.	Systemic corticosteroids rue indicated in addition to appropriate symptomatic treatment. May use 1 to 2 mglkg of prednisone or equivalent per day.

5.41.3.1. Procedu res and Guidelines for Pneumonitis

Subjects with symptomatic pneumonitis should immediately stop receiving pembrolizumab and epacadostat and have an evaluation. The evaluation may include bronchoscopy to mle out other causes such as infection. If the subject is detelmined to have study dmg-associated pneumonitis, the suggested treatment plan is detailed in Table 19.

Table 19: Recommended Approach for Handling Noninfectious Pneumonitis

Study Drug(s) Associated Pnemnonitis	Withhold/Discontinue Pembrolizumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 1 (asymptomatic)	No action.	Not applicable.	Intervention not indicated.
Grade 2	Withhold pembrolizumab and epacadostat.	First episode of pneumonitis: If improves to near baseline: Decrease the dose of epacadostat by 1 dose level, and for pembrolizumab, restrut at same dose and schedule subsequent cycles. If not improved after 2 weeks or worsening, pe1manently discontinue pembrolizumab. Discuss with medical monitor if restrut with epacadostat is pennitted. Second episode of pneumonitis: Pe1manently discontinue pembrolizumab and epacadostat if upon rechallenge subject develops pneumonitisGrade 2.	Systemic corticosteroids are indicated. Taper if necessruy.
Grades 3 and 4	Discontinue pembrolizumab and epacadostat.	Not applicable. Any exceptions require medical monitor approval.	Systelnic cmticosteroids rn·e indicated. The use of infliximab may be indicated as appropriate.

5.4.1.32. Procedures and Guidance for Enterocolitis

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as dianhea, abdominal pain, mucus or blood in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic subjects, infectious etiologies should be mled out, and endoscopic evaluation should be considered for persistent or severe symptoms. Recommendations for management of enterocolitis are shown in Table 20.

Table 20: Recommended Approach for Handling Enterocolitis

Study Drug(s) Associated Enterocolitis	Withhold/Discontinue Pembrolizumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 1	No action.	Not applicable.	All subjects who experience dianhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infhsion. An antidianheal can be statted.
Grade 2	Withhold pembrolizumab and epacadostat.	May renun to treatment if improves to Grade 1. If AE resolves within 4 weeks, subject may resta1t at the same dose and schedule for both pembrolizumab and epacadostat. For an AE that does not resolve within 4 weeks, epacadostat should be reduced 1 dose level, but pembrolizmnab may be restaited at the same dose and schedule. If AE does not resolve within 6 weeks, study treatment with both study dmgs should be discontinued or discussed with medical monitor.	An antidianheal should be statted. If symptoms are persistent for > 1 week, systemic c01ticosteroids should be initiated (eg, 0.5-1 mglkg per day of prednisone or equivalent). When symptoms improve toGrade 1, corticosteroid taper should be staited and continued over at least 1 month.
Grades 3 and4	Discontinue pembrolizumab and epacadostat.	Not applicable. Any exceptions require medical monitor approval.	Treatment with systemic cOiticosteroids should be initiated at a dose of 1 to 2 mglkg per day of prednisone or equivalent. Systemic c01ticosteroids are indicated. The use of infliximab may be indicated as appropriate. When sympt01ns improve toGrade 1, cOiticosteroid taper should be staited and continued over at least 1 month.

5.4.1.33. Procedu res and Guidance for Hepatitis

Liver chemistry tests (hepatic transaminase and bilimbin levels) should be monitored and signs and symptoms of hepatotoxicity should be assessed before each dose of pembrolizumab and epacadostat. In subjects with hepatotoxicity, infectious or malignant causes should be mled out, and frequency of LFT monitming should be increased until resolution. Recommendations for managing hepatitis are shown in Table 21.

Table 21: Recommended Approach for Handling Hepatitis

Study Drug(s) Associated Hepatitis	Withhold/Discontinue Pembrolizumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Ca re
Grade 1	No action.	Not applicable.	Increase frequency of LFT monitoring to twice per week lmtil LFTs retum to baseline.
Grade 2	Withhold pembrolizmnab and epacadostat.	If AE resolves toGrade 1 or baseline within 4 weeks, subject may resta1t at the same dose and schedule for both pembrolizumab and epacadostat. For an AE that does not resolve within 4 weeks, epacadostat should be reduced 1 dose level but pembrolizumab may be restalted at the same dose and schedule. If AE does not resolve within 6 weeks, study treatment with both study drugs should be discontinued.	Increase frequency of LFT monitoring to twice per week until LFTs retllln to baseline. If elevation persists for > 1 week, systemic c01ticosteroids should be initiated (eg, 0.5 mglkg per day of prednisone or equivalent). When symptoms improve to Grade 1, c01ticosteroid taper should be stalted and continued over at least 1 month.
Grades 3 and4	Discontinue pembrolizumab and epacadostat.	Not applicable. Any exceptions require medical monitor approval.	Increase frequency of LFT monitoring to eve1y 1-2 days. Treatment with systemic c01ticosteroids should be initiated at a dose of 1 to 2 mg/kg per day of prednisone or equivalent. When sympt01ns improve to Grade 1, c01ticosteroid taper should be stalted and continued over at least 1 month.

5.4.1.3.4. Procedures for Immune-Mediated Dermatitis

Monitor subjects for signs and symptoms of dermatitis such as rash and pruritus. Unless an alternate etiology has been identified, signs or symptoms of dermatitis should be considered immune-mediated. Recommendations for management of dermatitis are shown in Table 22.

Table 22: Recommended Approach for Handling Dermatitis

irAE	Withhold/Discontinue Pembrolizumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 1	No action.	Not applicable.	For mild to moderate dermatitis, such as localized rash and pruritus, treat symptomatically. Administer topical or systemic corticosteroids if there is no improvement of symptoms within 1 week.
Grade 2	No action.	Not applicable.	For mild to moderate dermatitis, such as localized rash and pruritus, treat symptomatically. Administer topical or systemic corticosteroids if there is no improvement of symptoms within 1 week.
Grades 3 and4	Withhold epacadostat and pembrolizumab in subjects with moderate to severe signs and symptoms of rash. Permanently discontinue epacadostat and pembrolizumab in subjects with Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration or by necrotic, bullous, or hemorrhagic manifestations.	If AE resolves to baseline within 4 weeks, subject may restart at the same dose and schedule for both pembrolizumab and epacadostat. For an AE that does not resolve within 4 weeks, epacadostat should be reduced 1 dose level, but pembrolizumab may be restarted at the same dose and schedule. If AE does not resolve within 6 weeks, study treatment with both study drugs should be discontinued or discussed with medical monitor.	Administer systemic corticosteroids at a dose of 1 to 2 mg/kg per day of prednisone or equivalent. When dermatitis is controlled, corticosteroid tapering should occur over a period of at least 1 month.

5.4.1.3.5. Procedures for Immune-Mediated Neuropathies

Subjects should be monitored for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. Recommendations for management of neuropathies are shown in Table 23.

Table 23: Recommended Approach for Handling Neuropathies

irAE	Withhold/Discontinue Pembrolizumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 1	No action.	Not applicable.	Provide symptomatic treatment.
Grade 2	May withhold pembrolizmnab and epacadostat.	If AE resolves to Grade 1 or baseline within 4 weeks, subject may resta1t at the same dose and schedule for both pembrolizumab and epacadostat. For an AE that does not resolve within 4 weeks, epacadostat should be reduced 1 dose level but pembrolizumab may be restruted at the same dose and schedule. If AE does not resolve within 6 weeks, sntdy treatment with both sntdy dmgs should be discontinued or discussed with medical monitor.	Consider systemic c01ticosteroids in addition to appropriate symptomatic treatment.
Grades 3 and4	Discontinue pembrolizumab and epacadostat.	Not applicable. Any exceptions require medical monitor approval.	Consider initiation of systemic c01ticosteroids at a dose of 1 to 2 mg/kg per day prednisone or equivalent for severe nemopathies. Institute medical intervention as appropriate for management of severe nemopathy.

5.4.1.3.6. Procedures for Immune-Mediated Endocrinopathies

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

Thyroid function tests and clinical chemistries should be monitored at the statt of treatment, before each dose and as clinically indicated based on symptoms. fu a limited number of subjects, hypophysitis was diagnosed by imaging studies through enlargement of the pituitaty gland. Recommendations for management of endocrinopathies are shown in Table 24.

Table 24: Recommended Approach for Handling Endocrinopathies

irAE	Withhold/Discontinue Pembrolizumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 1	No action.	Not applicable.	Provide symptomatic treatment.
Grade 2	May withhold pembrolizumab and epacadostat.	If AE resolves within 4 weeks, subject may restalt at the same dose and schedule for both pembrolizumab and epacadostat. For an AE that does not resolve within 4 weeks, epacadostat should be reduced 1 dose level, but pembrolizumab may be resta1ted at the same dose and schedule. If AE does not resolve within 6 weeks, study treatment with both sn1dy d!ugs should be discontinued.	Initiate systemic c01ticosteroids treatment at a dose of 1 to 2 mg/kg per day of prednisone or equivalent, and initiate appropriate ho1mone replacement therapy.
Grade 3	Withhold or discontinue both pembrolizumab and epacadostat.	If AE resolves or is controlled within 4 weeks, subject may resta1t at the same dose and schedule for both pembrolizumab and epacadostat. For an AE that does not resolve within 4 weeks, epacadostat should be reduced 1 dose level, but pembrolizumab may be restalted at the same dose and schedule. If AE does not resolve within 6 weeks, sn1dy treatment with both sn1dy dmgs should be discontinued or discussed with medical monitor	Consider initiating systemic c01ticosteroids treatment at a dose of 1 to 2 mg/kg per day of prednisone or equivalent, and initiate appropriate ho1mone replacement therapy.
Grade4	Discontinue both pembrolizumab and epacadostat.	Not applicable. Any exceptions require medical monitor approval.	Consider initiation of syste1nic c01ticosteroids at a dose of 1 to 2 mg/kg per day of prednisone or equivalent, and initiate appropriate ho1mone replacement therapy.

5.4.1.3.7. Procedures for Immune-Mediated Myocarditis

Subjects should be monitored for clinical signs and symptoms of myocarditis. Subjects may have fatigue, chest pain, decreased exercise capacity, increased jugular venous pressure, hepatomegaly, dyspnea, orthopnea, pulmonary rales, pulmonary edema, heart failure, or cardiogenic shock. Unless an altemate etiology has been identified, signs or symptoms of

myocarditis should be considered immune-mediated. Recommendations for management of myocarditis are shown in Table 25.

Table 25: Recommended Approach for Handling Myocarditis

irAE	Withhold/Discontinue Pembrolizumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 1 and 2	Withhold pembrolizumab and epacadostat.	Withhold both epacadostat and pembrolizumab until Grade 0. May resta1t at same dose level.	Based on severity of AE administer c01ticosteroids.
Grade 3 and4	Withhold pembrolizumab and epacadostat.	Pe1manently discontinue.	

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

Epacadostat and pembrolizumab should be petmanently discontinued for severe immune-mediated adverse reactions. Systemic cmticosteroids treatment should be initiated at a dose of 1 to 2 mg/kg per day of prednisone or equivalent for severe immune-mediated adverse reactions.

Cmticosteroid eye drops should be administered to subjects who develop uveitis, iritis, or episcletitis. Epacadostat and pembrolizumab should be petmanently discontinued for immune-mediated ocular disease that is umesponsive to local immunosuppressive therapy.

5.4.2. Treatment After Initial Evidence of Radiographic Disease Progression

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

If radiographic imaging shows PD, tumor assessment should be repeated 2:: 4 weeks and no later than 8 weeks after the initial assessment to confi1m PD, with the option of continuing treatment as outlined below, while awaiting radiographic confnmation of progression. If repeat imaging shows a reduction in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued as per treatment calendar. If repeat imaging confnms PD, subjects will be discontinued from study therapy. In dete1mining whether the tumor burden has increased or decreased, investigators should consider all target lesions as well as nontarget lesions.

When feasible, subjects should not be discontinued until progression is confiimed; however, the decision to continue study treatment after the first evidence of disease progression is at the investigator's discretion based on the clinical status of the subject as described in Table 26.

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

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

Table 26: Imaging and Treatment After First Radiographic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	Treatment	Imaging	Treatment
First radiographic evidence of PD	Repeat imaging at 4 and8 weeks to confum PD	May continue study treatment at the investigator's discretion while awaiting confmnat01y scan	Repeat imaging at 4 and8 weeks to confmn PD if possible	Discontinue treatment
Repeat scan at 4 and8 weeks confums PD	No additional imaging required	Discontinue treatment	No additional imaging required	*NIA*
Repeat scan at 4 and8 weeks shows SD, PR, or CR	Continue regularly scheduled imaging assessments eve1y 9 weeks	Continue study treatment at the investigator's discretion	Continue regularly scheduled imaging assessments eve1y 9 weeks	May restait study treatment if condition has improved and/or clinically stable per investigator's discretion

543. Procedu res for Subjects Exhibiting Serotonin Syndrome

As noted in Section 1.8.1, there is a rare possibility that epacadostat could cause an increase in serotonin levels in the brain that might tligger SS (Boyer and Shannon 2005) when administered in combination with other serotonergic agents. This syndrome has been most closely associated with the use of MAOis, meperidine, tramadol, linezolid, or methylene blue; all of these agents are prohibited during the study. Selective SSRis and serotonin-norepinephrine reuptake inhibitors (SNRis) are pe1mitted during the study. The following procedures will be implemented if subjects exhibit the signs/symptoms of SS (Table 27), including tremor, hypeneflexia, spontaneous, ocular, or inducible clonus together with agitation, fever, diaphoresis, or muscle 1igidity:

- Immediately inten1lpt epacadostat administration.
- Immediately inten1lpt any SSRI or SNRI administration.

- Provide appropriate medical management of the subject until all signs/symptoms are resolved (eg, IV fluids and/or sympathomimetic amines for hypotension, benzodiazepines for agitation, administration of 5-hydroxytryptamine antagonists such as cyproheptadine).
- If the subject chooses to remain in the study, resta1t treatment with epacadostat after the SSRI or SNRI has been discontinued no sooner than 5 half-lives have elapsed for the specific SSRI or SNRI in question and after resolution of signs/symptoms of SS. The SSRI or SNRI dosing MAY NOT be restarted.
- If the subject chooses to discontinue the study or must resta1t treatment with SSRI or SNRI, the subject should be scheduled for a follow-up visit. Selective serotonin reuptake inhibitor or SNRI treatment may be initiated 2 weeks after resolution of signs and symptoms of SS.

Table 27: **Signs and Symptoms of Serotonin Syndrome**

Tremor and hypeneflexia
Spontaneous clonus
Muscle rigidity, temperature > 38°C (100.4°F), and either ocular clonus or inducible clonus
Ocular clonus and either agitation or diaphoresis
Inducible clonus and either agitation or diaphoresis

5.4.4. Criteria for Permanent Discontinuation of Study Drug

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

- Occunence of an AE that is related to treatment with the study dmg that, in the judgment of the investigator or the sponsor's medical monitor, compromises the subject's ability to continue study-specific procedures or is considered to not be in the subject's best interest.
- An AE requiring more than 2 dose reductions.
- Persistent AE requiring a delay of therapy for more than 2 weeks (14 days) unless a greater delay has been approved by the sponsor.
- Concunent elevation of ALT > 3 x ULN and total bilimbin > 2 x ULN in subjects who do not have evidence of bilialy obstruction or other causes that can reasonably explain the concunent elevations.

If study dmg is pe1manently discontinued, see Sections 6.3 and 6.4 for follow-up assessments.

5.5. Withdrawal of Subjects From Study Treatment

5.5.1. Withdrawal Criteria

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

- The subject becomes pregnant.
- Consent is withdrawn.
- Further participation would be injurious to the subject's health or well-being, in the investigator's medical judgment.
- The study is tenninated by the sponsor.
- The study is tenninated by the local health authority, IRB, or IEC.
- Unacceptable toxicity has occmTed.
- Confilmed radiographic progression of disease per RECIST v1.1 (Eisenhauer et al2009). See Section 5.4.2.
  - Note: For unconfilmed radiographic disease progression, see Section 5.4.2.
  - Note: A subject may be granted an exception to continue on treatment with confilmed radiographic progression if clinically stable or clinically improved. See Section 7.6.1.

A subject may be discontinued from study treatment as follows:

- If, during the course of the study, a subject is found not to have met eligibility criteria, the medical monitor, in collaboration with the investigator, will dete1mine whether the subject should be withdrawn from the study.
- If a subject is noncompliant with study procedures or study dmg administration in the investigator's opinion, the sponsor should be consulted for instruction on handling the subject.

5.5.2. Withdrawal Procedures

In the event that the decision is made to pe1manently discontinue the study dmg, the end-of-n·eatment (EOT) visit should be conducted. Reasonable effmts should be made to have the subject retum for a follow-up visit. These visits are desclibed in Section 6. The last date of the last dose of study dmg and the reason for subject withdrawal will be recorded in the eCRF.

If a subject is withdrawn from study treatment:

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

- The date of the EOT visit should be recorded in the eCRF and IRT.
- Subjects must be followed for safety until the time of the follow-up visit or until study dmg-related toxicities resolve, retum to baseline, or are deemed ineversible, whichever is longest.

If the subject discontinues study treatment and actively withdraws consent for collection of follow-up data (safety follow-up or disease assessment), then no additional data collection should occur; however, subjects will have the option of withdrawing consent for study treatment but continuing in the follow-up period of the study for safety/efficacy assessments. Upon implementation of Amendment 4, disease assessment follow-up is no longer required.

5.6. Concomitant Medications

All concomitant medications and treatments must be recorded in the eCRF. Any prior medication received up to 30 days before the first dose of study dmg and 60 days after the last dose of study dmg will be recorded in the eCRF. Any addition, deletion, or change in the dose of these medications will also be recorded. Concomitant medications administered after 60 days after the last dose of study dmg should be recorded for SAEs as defined in Section 8. Concomitant treatments/procedures that are required to manage a subject's medical condition during the study will also be recorded in the eCRF.

5.6.1. Permitted Medications

All treatments that the investigator considers necessa1y for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the eCRF, including all prescription, over-the-counter, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of dmg dosage, frequency, route, and date may also be included on the eCRF.

Use of prophylactic growth factors should be based on American Society of Clinical Oncology guidelines for the use of white blood cell (WBC) growth factors (Smith et al 2006) and the investigator's clinical judgment. Bisphosphonates are allowed while subjects are receiving study treatment.

5.6.2. Restricted Medications

- Systemic steroids may be used at doses:::; 10 mg/day prednisone or equivalents with medical monitor approval.
- Treatment Groups A and Conly: Use of coumarin-based anticoagulants (eg, Coumadin®) is discouraged. Low-dose Coumadin (1 mg) is acceptable; however, other higher doses are discouraged. If an altemative to coumarin-based anticoagulants cannot be used, dose adjustment of the Coumadin dose may be needed. (Note: Coumarin-based anticoagulants are prohibited in Treatment Group B.) Based on the observed magnitude of epacadostat/warfa1in PK interaction and PK/phaimacodynamic modeling results, for an epacadostat dose of 300 mg BID, the dose of warfarin should be reduced by approximately one-third after initiation of epacadostat administration based on approximately 30% to 40% reduction inS- and

R-warfa1in oral clearance values. Close INR monitming is recommended for subjects on a stable dose of warfarin who are sta1lting treatment with epacadostat. Based on PK/phalmacodynamic modeling, recommendations for warfalin dose modifications for subjects receiving other epacadostat doses are summalized in Table 28 based on the INR before sta1ting epacadostat.

- Use of the anticonvulsant carbamazepine (a UGTIA9 inducer) is discouraged. Because there is a potential interaction that could result in lower epacadostat exposures, an altemative to carbamazepine should be used, if possible.

Table 28: Warfarin Dose Modifications

	Epacadostat Dose		
Stable Baseline INR	100 mg BID	200 mg BID	300 mgBID
INR2.5	Close INR monitodng	Close INR monitodng	Reduce warfruin by 33% and monitor INR
INR > 2.5	Close INR monitodng	Reduce wru·fruin by 20%-25% and monitor INR	Reduce wru·fruin by 33% and monitor INR

5.6.3. Prohibited Medications

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

- Any investigational medication other than the study dmgs.
- Any anticancer medications, including chemotherapy or biologic therapy other than the study medications.
- Any immunological-based treatment for any reason. (NOTE: Completed adjuvant therapy [eg, vaccines] is pelmitted with medical monitor approval). Inhaled or topical steroids are allowed, and systemic steroids at doses≤10 mg/day prednisone or equivalents are allowed with medical monitor approval, as described in Section 5.6.2, and immune suppressants are allowed for treatment for immune toxicities.)
- Radiation therapy.

  NOTE: Radiation therapy to a symptomatic solitaly lesion or to the brain may be allowed after consultation with the sponsor's medical monitor.
- Live vaccines within 30 days before the first dose of study treatment and while patticipating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, mbella, chicken pox, yellow fever, rabies, Bacillus Calmette-Guerin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed vims vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist) are live attenuated vaccines and are not allowed.

- Any MAOI or dmg associated with significant MAO inhibitmy activity agents is prohibited from 21 days before Day 1 through 2 weeks after the fmal dose of epacadostat has been taken (see Appendix C).
- Any UGT1A9 inhibitor, including acitretin, amitriptyline, androsterone, cyclospmine, dasatinib, diclofenac, diflunisal, efavirenz, erlotinib, estradiol (17-beta), flutamide, gefitinib, gemfibrozil, glycynhetinic acid glycynhizin, imatinib, imipramine, ketoconazole, linoleic acid, mefenamic acid, mycophenolic acid, niflumic acid, nilotinib, phenobarbital, phenylbutazone, phenytoin, probenecid, quinidine, ritonavir, Sorafenib, sulfinpyrazone, valproic acid, and verapamil.
- Treatment Group B only: Use of couma1in-based anticoagulants (eg, Coumadin) is prohibited. Investigators are encouraged to switch subjects to altemate anticoagulation therapies such as Eliquis®, Pradaxa®, Savaysa®, or Xarelto®. Coagulation panel should be monitored more closely while a subject is on any anticoagulant.

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

6_ STUDY ASSESSMENTS

All study assessments will be perfmmed as indicated in the schedule of assessments (Table 29, Table 31, Table 33, Table 35, Table 37, Table 39, Table 41, Table 43, Table 45, and Table 47), and alllaboratmy assessments will be pe1fmmed as indicated in Table 30, Table 32, Table 34, Table 36, Table 38, Table 40, Table 42, Table 44, Table 46, and Table 48.

Table 49 presents a summay of clinicallaboratmy analytes to be assessed. The order of assessments is suggested by the order of mention within the schedule. See Section 7 for instructions on each assessment. Fmther details of study procedures and assessments can be found in the study reference manual.

Table 29: Schedule of Assessments (Treatment Group A: Part 1 and Part 2 Expansion Cohorts A-1 and A-2)

Visit Day	Screening	Treatment							EOT	Safety Follow-Up	Notes
		CI DI	CI DS-7	CI DIS	C2 DI	C2 DS-7	C2 DIS	C3+ DI			
Evaluation Window	Day -28 to Day-1	DI	DS-7	± 3d	± 3d	DS-7	±3 d	±3 d	+S d	EOT + 42-49 d	
ADMINISTRATIVE PROCEDURES											
Infonned consent	X										
ContactiRT	X	X			X			X	X		
Inclusion/exclusion criteria	X	X									
Medical and cancer hist01y	X										
Prior/concomitant medications	X	X	X*	X	X	X*	X**	X	X	X	* Visit to occm on the fifth day of azacitidine dose administration. ** Cycle 2 Day 15 visits are not required for subjects in Patt 2.
Disttibute reminder cards	X	X	X*	X	X	X*	X**	X	X		* Visit to occm·on the fifth day of azacitidine dose administration. ** Cycle 2 Day 15 visits ru-e not required for subjects in Patt 2.
Study drug dispensing		X			X			X			
Assess study dmg compliance					X			X	X		
CLIl\ICAL PROCEDURES AND ASSESSMENTS											
Physical examination/body weight and height*	X	X	X**	X	X	X**	X***	X	X	X	* Comprehensive exatnination at screening, targeted physical exatnination thereafter. Height at screening only. ** Visit to occm on the fifth day of azacitidine dose adtninistration. *** Cycle 2 Day 15 visits ru·e not required for subjects in Patt 2.
Vital signs	X	X	X*	X	X	X*	X**	X	X	X	* Visit to occm on the fifth day of azacitidine dose adtninistration. ** Cycle 2 Day 15 visits ru-e not required for subjects in Patt 2.
ECOG petfonnance status	X	X	X*	X	X	X*	X**	X	X	X	* Visit to occm on the fifth day of azacitidine dose adtninistration. ** Cycle 2 Day 15 visits ru-e not required for subjects in Patt 2.

Table 29: Schedule of Assessments (Treatment Group A: Part 1 and Part 2 Expansion Cohorts A-1 and A-2) (Continued)

Visit Day	Screening	Treatment							EOT	Safety Follow-Up	Notes
		CI DI	CI DS-7	CI DIS	C2 DI	C2 DS-7	C2 DIS	C3+ DI			
Evaluation Window	Day -28 to Day-I	DI	DS-7	± 3d	± 3d	DS-7	±3 d	±3 d	+S d	EOT + 42-49 d	
12-lead ECG	X*	X**			X**			X***."	X"	X"	* Ttiplicate ECG at baseline. ** Timed t:Iiplicate ECGs (separated by 5 min ± 2 min) at predose and at 2 and 4 hours (± 15 min) postdose. *** ECG will be petfonned on DI of every other cycle after C2 (eg, C4, C6, and C8). " ECGs only need to be performed in t:Iiplicate if there has been a QT prolongation on study or the ECG shows a clinically significant abnonnality not present at baseline.
AE assessment	X	X	X*	X	X	X*	X**	X	X	X	* Visit to occm on the fifth day of azacitidine dose administration. **Cycle 2 Day 15 visits are not required for subjects in Prut 2.
Laboratory assessments	X	X	X*	X	X	X*	X**	X	X	X	* Visit to occm on the fifth day of azacitidine dose administration. **Cycle 2 Day 15 visits rure not required for subjects in Prut 2.
TUMOR BIOPSY COLLECTION											
Tumor biopsy/ tissue collection*	X							X*			* An additional mandat01y on-treat:Inent biopsy will be collected during Week 5 or Week 6. The on-treat:Inent biopsy is optional for Stage 2 of Patt2. An additional optional biopsy may be collected once the subject meets the requirements for SD, response, or progression by radiographic disease assessment. Detailed instmctions for tissue collection, processing, and storage can be found in the study procedmes manual. Fine needle aspirates rure not acceptable.

Table 29: Schedule of Assessments (Treatment Group A: Part 1 and Part 2 Expansion Cohorts A-1 and A-2) (Continued)

Visit Day		Treamt C1 DI	C1 DS-7	C1 DIS	C2 DI	C2 DS-7	C2 DIS	C3+ DI	EOT	Safety Follow-Up	Notes
Evaluation Window	Day -28 to Day -1	DI	DS-7	± 3d	±3 d	DS-7	±3 d	±3 d	+ S d	EOT + 42-49 d	
STUDY DRUG ADMINISTRATION											
azacitidine in clinic•		X	X		X	X		X			• Five doses of azacitidine will be administered in the clinic on D1-D7 of Cycles 1 through 3.
epacadostat in clinic•		X			X						r «>ll«tion on CIDI •nd C2DI.
pembrolizumab in clinic		X			X			X			
EFFICACY											
Radiologic twnor assessments•	X							X	X		• Evety 9 weeks (63 ± 7 days) until disease progression. After 12 months of study treatment, imaging frequency may be reduced to evel y 12 weeks. Imaging should not be delayed for delays in cycle starts or extension of combination treatment cycle intervals.

Table 30: Laboratory Assessments (Treatment Group A: Part 1 and Part 2 Expansion Cohorts A-1 and A-2)

Laboratory Assessment Window	Screening Day -28 to Day-1	Treatment C1 D1	C1 D5-7	C1 D15 ±3 d	C2 D1 ±3 d	C2 D5-7	C2 D15 ±3 d	C3+ D1 ±3 d	EOT +5 d	Safety Follow-Up EOT+ 42-49 d	Notes
LOCAL LABORATORY TESTS											
Comprehensive senun chemistry	X	X	X*	X	X	X*	X**	X	X	X	* Visit to occur on the fifth day of azacitidine dose administration. ** Cycle 2 Day 15 visits are not required for subjects in Part2.
Hematology with differential	X	X	X*	X	X	X*	X**	X	X	X	* Visit to occur on the fifth day of azacitidine dose administration. ** Cycle 2 Day 15 visits are not required for subjects in Part2.
HgbA1c	X										
Coagulation panel	X				X			X*	X		*Only at Cycles 4, 7, 10, etc.
Endocrine panel	X				X			X*	X		* Only at Cycles 4, 7, 10, etc.
U!inalysis	X				X			X*			* Only at Cycles 4, 7, 10, etc.
Senun pregnancy test	X*									X	* A senun pregnancy test will be required for all women of childbearing potential during screening and must be perfonned within 72 hours before the first dose of study dmg.
Serology											
CEA/CA19-9*		X			X			X**	X		* CEA to be petfonned in subjects with CRC only. CA 19-9 to be performed in subjects with pancreatic cancer only. ** CEA and CA 19-9 will be collected every other cycle aftet C2.
[redacted]											

Table 30: Laboratory Assessments (Treatment Group A: Part 1 and Part 2 Expansion Cohorts A-1 and A-2) (Continued)

Laboratory Assessment **Window**	Screening Day -28 to **Day -1**	Treatment C1 D1 **D1**	C1 D5-7 **D5-7**	C1 D15 **± 3 d**	C2 D1 **± 3 d**	C2 D5-7 **D5-7**	C2 D15 **± 3 d**	C3+ D1 **± 3 d**	EOT **+ 5 d**	**Safety Follow-Up EOT + 42-49 d**	**Notes**
[redacted]											

Table 31: Schedule of Assessments (Treatment Group A: Part 2 Expansion Cohort A-3, Azacitidine Monotherapy Lead-In)

Visit Day	Screening	Treatment					EOT	Safety Follow-Up	Notes
		Week-1	C1 **D1**	C2 D1	C2 DS-7	C3+ **D1**			
Evaluation Window	Day -28 to Day -1	C1D1-7 days	**D1**	± 3 d	DS-7	±3 d	+Sd	EOT + 42-49 d	
ADMINISTRATIVE PROCEDURES									
Infonned consent	X								
ContactiRT	X	X	X	X		X	X		
Inclusion/exclusion ctitetia	X	X							
Medical and cancer history	X								
Prior/concomitant medications	X	X*	X	X	X*	X	X	X	* To be assessed at baseline before first azacitidine dose and on the fifth day of azacitidine dose administration.
Disttibute reminder cards	X	X	X	X	X	X	X		
Study drug dispensing			X	X		X			
Assess study dmg compliance				X		X	X		
CLINICAL PROCEDURES AND ASSESSMENTS									
Physical examination/body weight and height*	X	X**	X	X	X**	X	X	X	* Comprehensive examination at screening, targeted physical exatnination thereafter. Height at screening only. ** To be assessed at baseline before first azacitidine dose and on the fifth day of azacitidine dose administration.
Vital signs	X	X*	X	X	X**	X	X	X	* To be assessed at baseline before first azacitidine dose and on the fifth day of azacitidine dose administration. **Visit to occur on the fifth day of azacitidine dose administration.

Table 31: Schedule of Assessments (Treatment Group A: Part 2 Expansion Cohort A-3, Azacitidine Monotherapy Lead-In) (Continued)

Visit Day	Screening	Treatment					EOT	Safety Follow-Up	Notes
		Week-1	C1 **D1**	C2 D1	C2 DS-7	C3+ **D1**			
Evaluation Window	Day -28 to Day -1	C1D1-7 days	D1	± 3d	DS-7	±3 d	+S d	EOT + 42-49 d	
ECOG petfonnance status	X	X*	X	X	X**	X	X	X	* To be assessed at baseline before first azacitidine dose and on the fifth day of azacitidine dose administration. **Visit to occur on the fifth day of azacitidine dose administration.
12-lead ECG	X*		X**	X**		X***."	X"	X"	* Ttiplicate ECG at baseline. ** Timed triplicate ECGs (separated by 5 min ± 2 min) at predose and at 2 and 4 hours(± 15 min) postdose. *** ECG will be petfonned on DI of evety other cycle after C2 (eg, C4, C6, and C8). " ECGs only need to be perf01med in ttiplicate if there has been a QT prolongation on study or the ECG shows a clinically significant abnonnality not present at baseline.
AE assessment	X	X*	X	X	X*	X	X	X	* To be assessed at baseline before first azacitidine dose and on the fifth day of azacitidine dose administration.
Laboratory assessments	X	X*	X	X	X*	X	X	X	* Visit to occm on the fifth day of azacitidine dose administration.
TUMOR BIOPSY COLLECTION									
Tumor biopsy/ tissue collection	X		X*			X**			* A second mandatory on-tt-eattnent biopsy will be collected ptior to CIDI (window Day -5 to predose on C1D1). **A third tnandatory on-treattnent biopsy will be collected dming Week 5 or 6. Additional biopsies may be collected once the subject meets the requirements for SD, response, or progression by radiographic disease assessment. Detailed instmctions for tissue collection, processing, and storage can be found in the study procedures manual. Fine needle aspirates are not acceptable.

Table 31: Schedule of Assessments (Treatment Group A: Part 2 Expansion Cohort A-3, Azacitidine Monotherapy Lead-In) (Continued)

Visit Day	Scl'eening	Tl'eatment					EOT	Safety Follow-Up	Notes
		Week -1	C1 **D1**	C2 **D1**	C2 D5-7	C3+ **D1**			
Evaluation Window	Day -28 to Day **-1**	C1D1-7 days	**D1**	± 3d	D5-7	±3 d	+ 5 d	EOT + 42-49 d	
STUDY DRUG ADMINISTRATION									
Administer azacitidine in clinic		X*		X**	X**	X**			* Five doses of azacitidine will be administered in the clinic over a 5- to 7-day period in Week -1 (before C1D1 of pembroliztunab/epacadostat). ** Azacitidine administration should continue with 5 doses administered in the clinic on Dl-D7 of Cycles 2 and 3. Subjects who remain on treatment beyond the Week *9* scan should continue to receive azacitidine until the second on-study scan (up to the Week 18 scan, for a maximum of 3 additional cycles).
Administer epacadostat in clinic*			X**	X					* Subjects should withhold their AM dose of epacadostat on days. It should be adtninistered in the clinic fo owing the trough collection on C1D1 and C2Dl. ** C1Dl treatment should be initiated within a + 5 day window from the date of the fifth azacitidine dose.
Administer pembroliztunab in clinic			X*	X		X			* C1Dl treatment should be initiated within a + 5 day window from the date of the fifth azacitidine dose.
EFFICACY ASSESSMENTS									
Radiologic twnor assessments*	X					X	X		* Evely *9* weeks (63 ± 7 days) until disease progression. After 12 months of study treatment, imaging frequency may be reduced to evey 12 weeks. Imaging should not be delayed for delays in cycle struts or extension of combination treatment cycle inte vals.

Table 32: Laboratory Assessments (Treatment Group A: Part 2 Expansion Cohort A-3, Azacitidine Monotherapy Lead-In)

			Treatment						
	Screening	Week -1	C1 DI	C2 DI	C2 DS-7	C3+ DI	EOT	Safety	
Laboratory Assessment Window	**Day -28 to Day -1**	**C1D1 - 7 davs**	**DI**	**±3 d**	**DS-7**	**±3 d**	**+Sd**	**EOT+ 42-49 d**	Notes
LOCAL LABORATORY TESTS									
Comprehensive serum chemistry	X	X	X	X	X	X	X	X	
Hematology with differential	X	X	X	X	X	X	X	X	
HgbA1c	X								
Coagulation panel	X			X		X*	X		* Only at Cycles 4, 7, 10, etc
Endocrine panel	X			X		X*	X		* Only at Cycles 4, 7, 10, etc
Urinalysis	X			X		X*			* Only at Cycles 4, 7, 10, etc
Serum pregnancy test	X*							X	* A senun pregnancy test will be required for all women of childbearing potential during screening and must be pe1fonned within 72 hours before the first dose of study drug.
Serology	X								
[redacted]									

Table 33: Schedule of Assessments (Treatment Group A: Part 2 Expansion Cohort A-4, Pembrolizumab/Epacadostat Lead-In)

Visit Day	Screening	Treatment				EOT	Safety Follow-Up	Notes
		C1 D1	C2 D1	C2 DS-7	C3+ D1			
Evaluation Window	Day -28 to Day-1	D1	± 3 d	DS-7	±3 d	+Sd	EOT + 42-49 d	
ADMINISTRATIVE PROCEDURES								
Infonned consent	X							
Contact iRT	X	X	X		X	X		
Inclusion/exclusion ctitetia	X	X						
Medical and cancer history	X							
Prior/concomitant medications	X	X	X	X•	X	X	X	• Visit to occur on the fifth day of azacitidine dose administration.
Disttibute reminder cards	X	X	X	X•	X	X		• Visit to occur on the fifth day of azacitidine dose administration.
Study drug dispensing		X	X		X			
Assess study dmg compliance			X		X	X		
CLII\ICAL PROCEDURES AND ASSESSMENTS								
Physical examination/body weight and height*	X	X	X	X••	X	X	X	• Comprehensive examination at screening, targeted physical examination thereafter. Height at screening only. •• Visit to occm on the fifth day of azacitidine dose administration.
Vital signs	X	X	X	X•	X	X	X	• Visit to occur on the fifth day of azacitidine dose administration.
ECOG petfonnance status	X	X	X	X•	X	X	X	• Visit to occur on the fifth day of azacitidine dose administration.

Table 33: Schedule of Assessments (Treatment Group A: Part 2 Expansion Cohort A-4, Pembrolizumab/Epacadostat Lead-In) (Continued)

Visit Day	Screening	Treatment				EOT	Safety Follow-Up	Notes
		C1 D1	C2 D1	C2 DS-7	C3+ D1			
Evaluation Window	Day -28 to Day -1	D1	± 3 d	DS-7	±3 d	+ S d	EOT + 42-49 d	
12-lead ECG	X*	X**	X**		X***''	X''	X''	* Triplicate ECG at baseline. ** Timed triplicate ECGs (separated by 5 min± 2 min) at predose and at 2 and 4 hom-s (± 15 min) postdose. *** ECG will be performed on D1 of every other cycle after C2 (eg, C4, C6, and C8). '' ECGs only need to be petfonned in triplicate if there has been a QT prolongation on study or the ECG shows a clinically significant abnormality not present at baseline.
AE assessment	X	X	X	X*	X	X	X	* Visit to occur on the fifth day of azacitidine dose administration.
Laboratory assessments	X	X	X	X*	X	X	X	* Visit to occur on the fifth day of azacitidine dose administration.
TUMOR BIOPSY COLLECTION								
Tmnor biopsy/ tissue collection	X		X*		X**			* A second mandatory on-treatment biopsy will be collected on C2D1 (window C1D15 to C2D1, biopsy before azacitidine administration). **A third mandatory on treatment biopsy will be collected during Week 8 or 9. Additional biopsies may be collected once the subject meets the requirements for SD, response, or progression by radiographic disease assessment. Detailed instmctions for tissue collection, processing, and storage can be found in the study procedures manual. Fine needle aspirates are not acceptable.

Table 33: Schedule of Assessments (Treatment Group A: Part 2 Expansion Cohort A-4, Pembrolizumab/Epacadostat Lead-In) (Continued)

Visit Day	Screening	Treatment				EOT	Safety Follow-Up	Notes
		C1 D1	C2 D1	C2 DS-7	C3+ D1			
Evaluation Window	Day -28 to Day -1	D1	± 3 d	DS-7	±3 d	+ S d	EOT + 42-49 d	
STUDY DRUG ADMINISTRATION								
Administer azacitidine in clinic*			X	X	X			* Five doses of azacitidine will be administered in the clinic on Dl-D7 of Cycles 2 and 3. Subjects who remain on treatment beyond the Week 9 scan should continue to receive azacitidine tmtil the second on-study scan (up to the Week 18 scan, for a maximum of 3 additional cycles).
Administer epacadostat in clinic*		X	X					* Subjects should withhold their AM dose of epacadostat on days. It should be administered in the clinic followmg the trough collection on CIDI and C2DI.
Administer pembrolizumab in clinic		X	X		X			
EFFICACY ASSESSMENTS								
Radiologic twnor assessments*	X				X	X		*Every 9 weeks (63 ± 7 days) tmtil disease progression. After 12 months of study treatment, imaging frequency may be reduced to evety 12 weeks. Imaging should not be delayed for delays in cycle starts or extension of combination treatment cycle intervals.

Table 34: Laboratory Assessments (Treatment Group A: Part 2 Expansion Cohort A-4, Pembrolizumab/Epacadostat Lead-In)

Laboratory Assessment Window	Screening Day -28 to Day -1	C1 D1 D1	C2 D1 ±3 d	C2 DS-7 DS-7	C3+ D1 ±3 d	EOT +5 d	Safety Follow-Up EOT+ 42-49 d	Notes
LOCAL LABORATORY TESTS								
~~Comprehensive~~ serum chemistry	X	X	X	X*	X	X	X	* Visit to occur on the fifth day of azacitidine dose administration.
Hematology with differential	X	X	X	X*	X	X	X	* Visit to occur on the fifth day of azacitidine dose administration.
HgbA1c	X							
Coagulation panel	X		X		X*	X		* Only at Cycles 4, 7, 10, etc.
Endocrine panel	X		X		X*	X		* Only at Cycles 4, 7, 10, etc.
Urinalysis	X		X		X*			* Only at Cycles 4, 7, 10, etc.
Serum pregnancy test	X*						X	* A serum pregnancy test will be required for all women of childbearing potential during screening and must be performed within 72 hours before the first dose of study drug.
Serology	X							
[redacted]								

Table 35: Schedule of Assessments (Treatment Group A: Part 2 Expansion Cohort A-5, Pembrolizumab Monotherapy Lead-In)

Visit Day	Screening	Treatment				EOT	Safety Follow-Up	Notes
		C1 D1	C2 D1	C2 DS-7	C3+ D1			
Evaluation Window	Day -28 to Day -1	D1	±3 d	D5-7	± 3 d	+S d	EOT + 42-49 d	
ADMINISTRATIVE PROCEDURES								
Infonned consent	X							
Contact iRT	X	X	X		X	X		
Inclusion/exclusion ctitetia	X	X						
Medical and cancer history	X							
Prior/concomitant medications	X	X	X	X*	X	X	X	* Visit to occur on the fifth day of azacitidine dose administration.
Disttibute reminder cards	X	X	X	X*	X	X		* Visit to occur on the fifth day of azacitidine dose administration.
Study drug dispensing			X		X			
Assess study dmg compliance					X	X		
CLINICAL PROCEDURES AND ASSESSMENTS								
Physical examination/body weight and height*	X	X	X	X**	X	X	X	* Comprehensive examination at screening, targeted physical examination thereafter. Height at screening only. ** Visit to occur on the fifth day of azacitidine dose administration.
Vital signs	X	X	X	X*	X	X	X	* Visit to occm on the fifth day of azacitidine dose administration.
ECOG petfonnance status	X	X	X	X*	X	X	X	* Visit to occm on the fifth day of azacitidine dose administration.

Table 35: Schedule of Assessments (Treatment Group A: Part 2 Expansion Cohort A-5, Pembrolizumab Monotherapy Lead-In) (Continued)

Visit Day	Screening	Treatment C1 D1	Treatment C2 D1	Treatment C2 DS-7	Treatment C3+ D1	EOT	Safety Follow-Up	Notes
Evaluation Window	Day -28 to Day -1	D1	±3 d	D5-7	± 3 d	+S d	EOT + 42-49 d	
12-lead ECG	X•	X••	X••		X•••"	X"	X"	• Triplicate ECG at baseline. •• Timed triplicate ECGs (separated by 5 min± 2 min) at predose and at 2 and 4 hom-s (± 15 min) postdose. ••• ECG will be performed on D1 of every other cycle after C2 (eg, C4, C6, and C8). " ECGs only need to be petfonned in triplicate if there has been a QT prolongation on study or the ECG shows a clinically significant abnormality not present at baseline.
AE assessment	X	X	X	X•	X	X	X	• Visit to occur on the fifth day of azacitidine dose administration.
Laboratory assessments	X	X	X	X•	X	X	X	• Visit to occur on the fifth day of azacitidine dose administration.
TUMOR BIOPSY COLLECTION								
Tmnor biopsy/ tissue collection	X		X•		X••			• A second mandatory on-treatment biopsy will be collected on C2D1 (window C1D15 to C2D1, biopsy before azacitidine administration). """A third mandatory on treatment biopsy will be collected dming Week 8 or 9. Additional biopsies may be collected once the subject meets the requirements for SD, response, or progression by radiographic disease assessment. Detailed instmctions for tissue collection, processing, and storage can be found in the study procedures manual. Fine-needle aspirates are not acceptable.

Table 35: Schedule of Assessments (Treatment Group A: Part 2 Expansion Cohort A-5, Pembrolizumab Monotherapy Lead-In) (Continued)

Visit Day	Screening	Treatment				EOT	Safety Follow-Up	Notes
		C1 D1	C2 D1	C2 DS-7	C3+ D1			
Evaluation Window	Day -28 to Day -1	D1	±3 d	D5-7	± 3 d	+S d	EOT + 42-49 d	
STUDY DRUG ADMINISTRATION								
Administer azacitidine in clinic*			X	X	X			* Five doses of azacitidine will be administered in the clinic on D1-D7 of Cycles 2 and 3. Subjects who remain on treatment beyond the Week 9 scan should continue to receive azacitidine until the second on-study scan (up to the Week 18 scan, for a maximum of 3 additional cycles).
Administer epacadostat in clinic*			X		X			* Subjects should withhold their AM dose of epacadostat on days. It should be administered in the clinic followmg the trough collection on C2D1 and C3D1.
Administer pembrolizumab in clinic		X	X		X			
EFFICACY ASSESSMENTS								
Radiologic twnor assessments*	X				X	X		* Every 9 weeks (63 ± 7 days) until disease progression. After 12 months of study treatment, imaging frequency may be reduced to every 12 weeks. Imaging should not be delayed for delays in cycle starts or extension of combination treatment cycle intetvals.

Table 36: Schedule of Assessments (Treatment Group B: Part 1 Dose-Escalation and Expansion Cohorts B-1 to B-6 and Part 2E Expansion Cohorts B-7, B-8, and B-9) (Continued)

Laboratory Assessment Window	Screening Day -28 to Day -1	C1 D1 D1	C2 D1 ±3d	C2 DS-7 DS-7	C3+ D1 ±3d	EOT +Sd	Safety Follow-Up EOT+ 42-49 d	Notes
LOCAL LABORATORY TESTS								
~~Comprehensive~~ serum chemistry	X	X	X	X*	X	X	X	* Visit to occur on the fifth day of azacitidine dose administration.
Hematology with differential	X	X	X	X*	X	X	X	* Visit to occur on the fifth day of azacitidine dose administration.
HgbA1c	X							
Coagulation panel	X		X		X*	X		* Only at Cycles 4, 7, 10, etc.
Endocrine panel	X		X		X*	X		* Only at Cycles 4, 7, 10, etc.
Urinalysis	X		X		X*			* Only at Cycles 4, 7, 10, etc.
Serum pregnancy test	X*						X	* A serum pregnancy test will be required for all women of childbearing potential during screening and must be performed within 72 hours before the first dose of study drug.
Serology	X							
[redacted]								

Table 37: Schedule of Assessments (Treatment Group B: Part 1 Dose-Escalation and Expansion Cohorts B-1 to B-6 and Part 2 Expansion Cohorts B-7, B-8, and B-9) (Continued)

NOTE: Upon implementation of Amendment 4, this table is no longer applicable.

		Treatment								EOT	Follow-Up			Notes
Visit Day	Screening	C1 D1	C1 DS	C1 DIS	C2 D1	C2 DS	C2 DIS	C3 D1	C4+ D1		Safety	Disease Status	Survival	
Evaluation Window	Day -28 to Day-1	D1	±3 d	± 3 d	±3 d	±3 d	± 3d	±3 d	± 3 d	+ S d	EOT + 42-49 d	Q9W(± 7 d) AfterEOT	Q12W (+ 7 d)	
ADMINISTRATIVE PROCEDURES														
Infonned consent	X													
Contact iRT	X	X			X			X	X	X				
Inclusion! exclusion criteria	X	X												
Medical and cancer history	X													
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X			
Disttibute reminder cards	X	X	X	X	X	X	X	X	X	X				
Study drug dispensing		X			X			X	X					
Assess study dmg compliance					X			X	X	X				
Post-treatment anticancer therapy status												X	X	
Data collection for survival													X	

Table 37: Schedule of Assessments (Treatment Group B: Part 1 Dose-Escalation and Expansion Cohorts B-1 to B-6 and Part 2 Expansion Cohorts B-7, B-8, and B-9) (Continued)

Visit Day	Screening	Treatment								EOT	Follow-Up			Notes
		C1 D1	C1 DS	C1 DIS	C2 D1	C2 DS	C2 DIS	C3 D1	C4+ D1		Safety	Disease Status	Survival	
Evaluation Window	Day -28 to Day -1	D1	±3 d	± 3 d	±3 d	±3 d	± 3 d	±3 d	± 3 d	+S d	EOT + 42-49 d	Q9W(± 7 d) After EOT	Q12W (+7 d)	
CLINICAL PROCEDURES AND ASSESSMENTS														
Physical examination/body weight and height*	X	X	X	X	X	X	X	X	X	X	X			* Comprehensive examination at screening, targeted physical examination thereafter. Height at screening only.
Vital signs	X	X	X	X	X	X	X	X	X	X	X			
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X			
12-lead ECG	X*	X**			X**			X***/\	X***/\	XA	XA			* Triplicate ECG at baseline. ** Timed triplicate ECGs (separated by 5 min ± 2 min) at predose and at 2 and 4 hours (± 15 min) postdose. *** ECG will be performed on D1 of evety other cycle after C3 (eg, C5, C7, and C9). /\ ECGs only need to be perfonned in ttiplicate if there has been a QT prolongation on study or the ECG shows a clinically significant abnonnality not present at baseline.
AE assessment	X	X	X	X	X	X	X	X	X	X	X			
Laboratory assessments	X	X	X	X	X	X	X	X	X	X	X			

Table 37: Schedule of Assessments (Treatment Group B: Part 1 Dose-Escalation and Expansion Cohorts B-1 to B-6 and Part 2 Expansion Cohorts B-7, B-8, and B-9) (Continued)

		Treatment									Follow-Up			
Visit Day	Screening	C1 D1	C1 DS	C1 DIS	C2 D1	C2 DS	C2 DIS	C3 D1	C4+ D1	EOT	Safety	Disease Status	Survival	Notes
Evaluation Window	Day -28 to Day-1	D1	±3 d	± 3 d	±3 d	±3 d	± 3d	±3 d	± 3 d	+S d	EOT + 42-49 d	Q9W(± 7 d) After EOT	Q12W (+7 d)	
TUMOR BIOPSY COLLECTION														
Tumor biopsy/ tissue collection	X				X•			X••						• Only Expansion Cohort B-9 will have an additional mandatory on-treatment biopsy will be collected at C2D1 (window C1D15 to C2D1). •• An additional mandatory on-treatment biopsy will be collected during Week 8 or Week 9. The on-treatment biopsy is optional for Stage 2 of Part 2. An additional optional biopsy may be collected once the subject meets the requirements for SD, response, or progression by radiographic disease assessment. Detailed instructions for tissue collection, processing, and storage can be found in the study procedures manual. Fine needle aspirates are not acceptable.

Table 37: Schedule of Assessments (Treatment Group B: Part 1 Dose-Escalation and Expansion Cohorts B-1 to B-6 and Part 2 Expansion Cohorts B-7, B-8, and B-9) (Continued)

		Treatment								EOT	Follow-Up			Notes
Visit Day	Screening	C1 D1	C1 DS	C1 DIS	C2 D1	C2 DS	C2 DIS	C3 D1	C4+ D1		Safety	Disease Status	Survival	
Evaluation Window	Day -28 to Day-1	D1	±3 d	± 3 d	±3 d	±3 d	± 3 d	±3 d	± 3 d	+S d	EOT + 42-49 d	Q9W(± 7 d) AfterEOT	Q12W (+7 d)	
STUDY DRUG ADMINISTRATION														
Administer INCB057643 in clinic*		X	X		X	X	–							*INCB057643 and epacadostat should be administered at the same time plior to the pembrolizmnab infusion. Subjects should withhold their AM dose of iNCB057643 on days. It should be administer in the clinic following the trough collection on CIDI , CID8, C2DI, and C2D8.
Administer epacadostat in clinic*					X	X	–							*INCB057643 and epacadostat should be administered at the same time plior to the pembrolizmnab infusion. Subjects should withhold their AM dose of epacadostat on days. It should be administered in the clinic following the trough collection on C2DI and C2D8.
Administer pembrolizumab in clinic					X			X	X					

Table 37: Schedule of Assessments (Treatment Group B: Part 1 Dose-Escalation and Expansion Cohorts B-1 to B-6 and Part 2 Expansion Cohorts B-7, B-8, and B-9) (Continued)

		Treatment									Follow-Up			
Visit Day	Screening	C1 D1	C1 DS	C1 DIS	C2 D1	C2 DS	C2 DIS	C3 D1	C4+ D1	EOT	Safety	Disease Status	Survival	Notes
Evaluation Window	Day -28 to Day -1	D1	± 3d	±3d	± 3d	± 3 d	±3d	± 3d	±3d	+ Sd	EOT + 42-49 d	Q9W(± 7 d) AfterEOT	Q12W (+7 d)	
EFFICACY ASSESSMENTS														
Radiologic twnor assessments*	X							X	X	X		X		* Every 9 weeks (63 ± 7 days) tmtil disease progression. After 12 months of study treatment, imaging frequency may be reduced to every 12 weeks. Imaging should not be delayed for delays in cycle starts or extension of combination treatment cycle intetvals.

Table 38: Laboratory Assessments (Treatment Group B: Part 1 Dose-Escalation and Expansion Cohorts B-1 to B-6 and Part 2 Expansion Cohorts B-7, B-8, and B-9)

NOTE: Upon implementation of Amendment 4, this table is no longer applicable.

Laboratory Assessment **Window**	**Day -1**	C1 D1	C1 D8	C1 DIS	C2 D1	C2 D8	C2 DIS	C3 D1	C4+ D1	EOT	Safety **Follow-Up** EOT + 42-49 d	Notes
LOCAL LABORATORY TESTS												
~~Comprehen~~sive serum chemistry	X	X	X	X	X	X	X	X	X	X	X	
Hematology with differential	X	X	X	X	X	X	X	X	X	X	X	
HgbA1c	X											
Coagulation panel	X											
Endocrine panel	X											
Urinalysis	X											
Serum pregnancy test	X*										X	• A senun pregnancy test will be required for all women of childbearing potential dming screening and must be perfonned within 72 hours before the first dose of study drug
Serology	X											
CEA/CA19-9*		X			X				X••	X		• CEA to be performed in subjects with CRC only. CA 19-9 to be petfonned in subjects with pancreatic cancer only. • •CEA and CA 19-9 will be collected every othet· cycle after C2.
[redacted]												

Table 38: Laboratory Assessments (Treatment Group B: Part 1 Dose-Escalation and Expansion Cohorts B-1 to B-6 and Part 2 Expansion Cohorts B-7, B-8, and B-9) (Continued)

Laboratory Assessment	Screening	C1 D1	C1 D8	C1 D15	C2 D1	C2 D8	C2 D15	C3 D1	C4+ D1	EOT	Safety Follow-Up	Notes
Window	**Day -28 to Day -1**	**D1**	**± 3 d**	**± 3 d**	**± 3 d**	**± 3 d**	**± 3 d**	**± 3 d**	**± 3 d**	**+ 5 d**	**EOT + 42-49 d**	
[redacted]												

Table 39: Schedule of Assessments (Treatment Group B: Part 2 Expansion Cohort B-10)

NOTE: Upon implementation of Amendment 4, this table is no longer applicable.

		Treatment									Follow-Up			
Visit Day	Screening	CI DI	CI D8	CI DIS	C2 DI	C2 D8	C2 DIS	C3 DI	C4+ DI	EOT	Safety	Disease Status	Sm'Vival	Notes
Evaluation Window	Day -28 to Day -I	DI	± 3 d	±3 d	± 3d	±3 d	± 3 d	±3 d	± 3d	+ S d	EOT+ 42-49 d	Q9W (± 7 d) After EOT	QI2W (+ 7 d)	
ADMINISTRATIVE PROCEDURES														
Infonned consent	X													
Contact iRT	X	X			X			X	X	X				
Inclusion! exclusion criteria	X	X												
Medical and cancer history	X													
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X			
Disttibute reminder cards	X	X	X	X	X	X	X	X	X	X				
Study drug dispensing		X			X			X	X					
Assess study dmg compliance					X			X	X	X				
Post-treatment anticancer therapy status												X	X	
Data collection for survival													X	

Table 39: Schedule of Assessments (Treatment Group B: Part 2 Expansion Cohort B-10) (Continued)

Visit Day	Screening	Treatment								EOT	Follow-Up			Notes
		C1 D1	C1 D8	C1 D15	C2 D1	C2 D8	C2 D15	C3 D1	C4+ D1		Safety	Disease Status	Survival	
Evaluation Window	Day -28 to Day -1	D1	±3 d	± 3d	±3 d	± 3 d	±3 d	± 3d	±3 d	+5 d	EOT+ 42-49 d	Q9W(± 7 d) After EOT	Q12W (+ 7 d)	
CLINICAL PROCEDURES AND ASSESSMENTS														
Physical examination/body weight and height*	X	X	X	X	X	X	X	X	X	X	X			• Comprehensive examination at screening, targeted physical examination thereafter. Height at screening only.
Vital signs	X	X	X	X	X	X	X	X	X	X	X			
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X			
12-lead ECG	X•	X••			X••			X••• [1]	X••• [1]	X"	X"			• Triplicate ECG at baseline. •• Timed triplicate ECGs (separated by 5 min± 2 min) at predose and at 2 and 4 hours (± 15 min) postdose. """"" ECG will be performed on D1 of every other cycle after C3 (eg, C5, C7, and C9). " ECGs only need to be performed in triplicate if there has been a QT prolongation on study or the ECG shows a clinically significant abnormality not present at baseline.
AE assessment	X	X	X	X	X	X	X	X	X	X	X			
Laboratory assessments	X	X	X	X	X	X	X	X	X	X	X			

Table 39: Schedule of Assessments (Treatment Group B: Part 2 Expansion Cohort B-10) (Continued)

Visit Day	Screening	Treatment								EOT	Follow-Up			Notes
		C1 D1	C1 D8	C1 D15	C2 D1	C2 D8	C2 D15	C3 D1	C4+ D1		Safety	Disease Status	Surv'Val	
Evaluation Window	Day -28 to Day -1	D1	±3 d	± 3d	±3 d	± 3 d	±3 d	± 3d	±3 d	+ 5 d	EOT+ 42-49 d	Q9W(± 7 d) After EOT	Q12W (+ 7 d)	
TUMOR BIOPSY COLLECTION														
Tumor biopsy/ tissue collection*	X				X*			X*						* Two additional mandatory on-treatment biopsies will be collected at C2D1 (window C1D15 to C2D1) and during Week 8 or Week 9. An additional optional biopsy may be collected once the subject meets the requirements for SD, response, or progression by radiographic disease assessment. Detailed instructions for tissue collection, processing, and storage can be found in the study procedures manual. Fine needle aspirates are not acceptable.

Table 39: Schedule of Assessments (Treatment Group B: Part 2 Expansion Cohort B-10) (Continued)

Visit Day	Screening	Treatment								EOT	Follow-Up			Notes
		C1 D1	C1 D8	C1 D15	C2 D1	C2 D8	C2 D15	C3 D1	C4+ D1		Safety	Disease Status	Survival	
Evaluation Window	Day -28 to Day -1	D1	±3 d	± 3d	±3 d	± 3 d	±3 d	± 3d	±3 d	+S d	EOT+ 42-49 d	Q9W(± 7 d) After EOT	Q12W (+ 7 d)	
STUDY DRUG ADMINISTRATION														
Administer INCB057643 in clinic•		X	X		X	X								• INCB057643 and epacadostat should be administered at the same time prior to the pembrolizumab infusion. Subjects should withhold their AM dose of INCB057643 on days. It should be administered in the clirlic following the trough collection on C1D1, C1D8, C2D1, andC2D8.
Administer epacadostat in clinic•		X	X		X	X								• INCB057643 and epacadostat should be administered at the same time prior to the pembrolizum.ab infusion. Subjects should withhold their AM dose of epacadostat on days. It should be admirlistere m the clirlic following the trough collection on C1D1, C1D8, C2D1, and C2D8.
Administer pembroliztunab in clinic					X			X	X					
EFFICACY ASSESSMENTS														
Radiologic tumor assessments•	X							X	X	X		X		• Evety 9 weeks (63 ± 7 days) until disease progression. After 12 months of study treatment, imaging frequency may be reduced to evety 12 weeks. Imaging should not be delayed for delays in cycle starts or extension of combination treatment cycle intetvals.

Table 40: Laboratory Assessments (Treatment Group B: Part 2 Expansion Cohort B-10)

NOTE: Upon implementation of Amendment 4, this table is no longer applicable.

Laboratory Assessment	Screening	C1 D1	C1 D8	C1 D15	C2 D1	C2 D8	C2 D15	C3 D1	C4+ D1	EOT	Safety Follow-Up	Notes
Window	Day -28 to Day -1	D1	±3d	±3d	±3d	±3d	±3d	±3d	±3d	+5d	EOT+ 42-49d	
LOCAL LABORATORY TESTS												
Comprehensive serum chemistry	X	X	X	X	X	X	X	X	X	X	X	
Hematology with differential	X	X	X	X	X	X	X	X	X	X	X	
HgbA1c	X											
Coagulation panel	X				X			X	X*	X		* Only at Cycles 5, 8, 11, etc.
Endocrine panel	X				X				X*	X		* Only at Cycles 5, 8, 11, etc.
Urinalysis	X				X				X*	X		* Only at Cycles 5, 8, 11, etc.
Serum pregnancy test	X*										X	* A serum pregnancy test will be required for all women of childbearing potential during screening and must be performed within 72 hours before the first dose of study drug.
Serology	X											
[redacted]												

Table 40: Laboratory Assessments (Treatment Group B: Part 2 Expansion Cohort B-10) (Continued)

Laboratory Assessment Window	Screening Day -28 to Day -1	C1 D1 D1	C1 D8 ± 3 d	C1 D15 ± 3 d	C2 D1 ± 3 d	C2 D8 ± 3 d	C2 D15 ± 3 d	C3 D1 ± 3 d	C4+ D1 ± 3 d	EOT + 5 d	Safety Follow-Up EOT + 42-49 d	Notes
[redacted]												

Table 41: Schedule of Assessments (Treatment Group B: Part 2 Expansion Cohort B-11)

NOTE: Upon implementation of Amendment 4, this table is no longer applicable.

		Treatment									Follow-Up			
Visit Day	Screening	C1 D1	C1 DS	C1 DIS	C2 D1	C2 DS	C2 DIS	C3 D1	C4+ D1	EOT	Safety	Disease Status	Sm'Vival	
Evaluation Window	Day -28 to Day -I	D1	± 3 d	±3 d	± 3 d	± 3d	± 3 d	± 3 d	±3 d	+ Sd	EOT + 42-49 d	Q9W(± 7 d) After EOT	Q12W (+ 7 d)	Notes
ADMINISTRATIVE PROCEDURES														
Infonned consent	X													
Contact iRT	X	X			X			X	X	X				
Inclusion/exclusion ctitetia	X	X												
Medical and cancer history	X													
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X			
Disttibute reminder cards	X	X	X	X	X	X	X	X	X	X				
Study drug dispensing		X			X			X	X					
Assess study dmg compliance					X			X	X	X				
Post-treatment anticancer therapy status												X	X	
Data collection for survival													X	

Table 41: Schedule of Assessments (Treatment Group B: Part 2 Expansion Cohort B-11) (Continued)

Visit Day	Screening	Treatment								EOT	Follow-Up			Notes
		C1 **DI**	C1 DS	C1 DIS	C2 **DI**	C2 DS	C2 DIS	C3 D1	C4+ **DI**		Safety	Disease Status	Sm'Vival	
Evaluation Window	Day -28 to Day -I	**DI**	± 3 d	±3 d	±3 d	± 3d	±3 d	± 3 d	±3 d	+ S d	EOT + 42-49 d	Q9W(± 7 d) After EOT	Q12W (+ 7 d)	
CLII\'ICAL PROCEDURES AND ASSESSMENTS														
Physical examination/body weight and height*	×	×	×	×	×	×	×	×	×	×	×			• Comprehensive examination at screening, targeted physical examination thereafter. Height at screening only.
Vital signs	×	×	×	×	×	×	×	×	×	×	×			
ECOG petfonnance status	×	×	×	×	×	×	×	×	×	×	×			
12-lead ECG	X•	X••			X••			X••• /\	X••• /\	XA	XA			• Ttiplicate ECG at baseline. •• Timed ttiplicate ECGs (separated by 5 min± 2min) at predose and at 2 and 4 hours (± 15 min) postdose. """"" ECG will be petfonned on D1 of evety other cycle after C3 (eg, C5, C7, and C9). /\ ECGs only need to be performed in ttiplicate if there has been a QT prolongation on study or the ECG shows a clinically significant abnonnality not present at baseline.
AE assessment	×	×	×	×	×	×	×	×	×	×	×			
Laboratory assessments	×	×	×	×	×	×	×	×	×	×	×			

Table 41: Schedule of Assessments (Treatment Group B: Part 2 Expansion Cohort B-11) (Continued)

Visit Day	Screening	Treatment								EOT	Follow-Up			Notes
		C1 **D1**	C1 DS	C1 DIS	C2 **D1**	C2 DS	C2 DIS	C3 D1	C4+ **D1**		Safety	Disease Status	Sm'Vival	
Evaluation Window	Day -28 to Day -I	**D1**	± 3 d	±3 d	±3 d	± 3d	±3 d	± 3 d	±3 d	+ S d	EOT + 42-49 d	Q9W(± 7 d) After EOT	Q12W (+ 7 d)	
TUMOR BIOPSY COLLECTION														
Tumor biopsy/ tissue collection*	X				X*									• An additional nllllldatOiy on-treatment biopsy will be collected dming Week 5 or Week 6. An additional optional biopsy may be collected once the subject meets the requirements for SD, response, or progression by radiographic disease assessment. Detailed instmctions for tissue collection, processing, and storage can be found in the study procedures manual. Fine needle aspirates are not acceptable.

Table 41: Schedule of Assessments (Treatment Group B: Part 2 Expansion Cohort B-11) (Continued)

Visit Day	Screening	Treatment								EOT	Follow-Up			Notes
		C1 D1	C1 DS	C1 DIS	C2 D1	C2 DS	C2 DIS	C3 D1	C4+ D1		Safety	Disease Status	Sm'Vival	
Evaluation Window	Day -28 to Day -I	D1	± 3 d	±3 d	±3 d	± 3d	±3 d	± 3 d	±3 d	+ S d	EOT + 42-49 d	Q9W(± 7 d) After EOT	Q12W (+ 7 d)	
STUDY DRUG ADMINISTRATION														
Administer INCB057643 in clinic•		X	X		X	X								• INCB057643 and epacadostat should be administered at the same time prior to the pembrolizumab infusion. Subjects should withhold their AM dose of INCB057643 on days. It should be administered in the clirlic following the trough collection on CIDI , CID8, C2D1, andC2D8.
Adrnirlister epacadostat in clinic•		X	X		X	X								• INCB057643 and epacadostat should be administered at the same time prior to the pembrolizum.ab infusion. Subjects should withhold their AM dose of epacadostat ondays. It should be admirlistere m the clirlic following the trough collection on C1D1, C1D8, C2D1, and C2D8.
Administer pembroliztunab in clinic		X			X			X	X					
EFFICACY ASSESSMENTS														
Radiologic tumor assessments•	X							X	X	X		X		• Evety 9 weeks (63 ± 7 days) until disease progression. After 12 months of study treatment, imaging frequency may be reduced to evety 12 weeks. Imaging should not be delayed for delays in cycle starts or extension of combination treatment cycle intetvals.

Table 42: Laboratory Assessments (Treatment Group B: Part 2 Expansion Cohort B-11)

NOTE: Upon implementation of Amendment 4, this table is no longer applicable.

Laboratory Assessment	Screening	C1 D1	C1 D8	C1 D15	C2 D1	C2 D8	C2 D15	C3 D1	C4+ D1	EOT	Safety Follow-Up	Notes
Window	Day -28 to Day -1		±3d	±3d	±3d	±3d	±3d	±3d	±3d	+5d	EOT + 42-49d	
LOCAL LABORATORY TESTS												
Comprehensive serum chemistry	X	X	X	X	X	X	X	X	X	X	X	
Hematology with differential	X	X	X	X	X	X	X	X	X	X	X	
HgbA1c	X											
Coagulation panel	X				X			X	X*	X		* Only at Cycles 5, 8, 11, etc.
Endocrine panel	X				X				X*	X		* Only at Cycles 5, 8, 11, etc.
Urinalysis	X				X				X*	X		* Only at Cycles 5, 8, 11, etc.
Serum pregnancy test	X*										X	* A serum pregnancy test will be required for all women of childbearing potential during screening and must be performed within 72 hours before the first dose of study drug.
Serology	X											
[redacted]												

Table 42: Laboratory Assessments (Treatment Group B: Part 2 Expansion Cohort B-11) (Continued)

		Treatment										
Laboratory Assessment **Window**	**Screening** **Day -28 to Day -1**	C1 D1 **D1**	C1 D8 **± 3 d**	C1 D15 **± 3 d**	**C2 D1** **± 3 d**	**C2 D8** **± 3 d**	C2 D15 **± 3 d**	C3 D1 **± 3 d**	C4+ D1 **± 3 d**	EOT **+ 5 d**	**Safety Follow-Up** **EOT + 42-49 d**	**Notes**
[redacted]												

Table 43: Schedule of Assessments (Treatment Group C: Part 1 Dose-Escalation and Expansion Cohorts C-1 to C-8 and Part 2 Expansion Cohorts C-9, C-10, and C-11)

NOTE: Upon implementation of Amendment 4, this table is no longer applicable.

		Treatment										Follow-Up			Notes
Visit Day	Screening	C1 D1	C1 D8	C1 DIS	C2 D1	C2 D2/4*	C2 D8	C2 DIS	C3 D1	C4+ D1	EOT	Safety	Disease Status	Survival	* For subjects receiving INCB059872 QoD, an additional visit is required during C2 on D2 or D4 so that the samples and ECGs are collected on the day when INCB059872 is administered.
Evaluation Window	Day -28 to Day-1	D1	± 3 d	± 3 d	± 3 d	D2or D4	± 3 d	± 3 d	± 3 d	± 3 d	+S d	EOT + 42-49 d	Q9W (± 7 d) After EOT	Q12W (+ 7 d)	
ADMINISTRATIVE PROCEDURES															
Infonned consent	X														
Contact iRT	X	X			X				X	X	X				
Inclusion! exclusion criteria	X	X													
Medical and cancer hist01y	X														
Prior/concomitant medications	X	X	X	X	X		X	X	X	X	X	X			
Disttibute reminder cards	X	X	X	X	X		X	X	X	X	X				
Study drug dispensing		X			X				X	X					
Assess study dmg compliance					X				X	X	X				
Post-treatment anticancer therapy status													X	X	
Data collection for smvival														X	

Table 43: Schedule of Assessments (Treatment Group C: Part 1 Dose-Escalation and Expansion Cohorts C-1 to C-8 and Part 2 Expansion Cohorts C-9, C-10, and C-11) (Continued)

Visit Day		Ti<:aiUJ<UI									EOT	Follow-Up			Notes
	…..!>	C1 D1	C1 D8	C1 DIS	C2 D1	C2 D2/4*	C2 D8	C2 DIS	C3 D1	C4+ D1		Safety	Disease Status	Survival	* For subjects receiving INCB059872 QoD, an additional visit is required during C2 on D2 or D4 so that the samples and ECGs are collected on the day when INCB059872 is administered.
Evaluation Window	Day -28 to Day-1	D1	± 3 d	± 3 d	± 3 d	D2or D4	± 3 d	± 3 d	± 3 d	± 3 d	+S d	EOT + 42-49 d	Q9W (± 7 d) After EOT	Q12W (+ 7 d)	
CCI.TNTCCAT PROrF.nTJRF.S AND ASSF.SSMF.NTS															
Physical examination/body weight and height*	X	X	X	X	X		X	X	X	X	X	X			* Comprehensive examination at screening, targeted physical examination thereafter. Height at only.
Vital signs	X	X	X	X	X		X	X	X	X	X	X			
ECOG performance status	X	X	X	X	X		X	X	X	X	X	X			
12-lead ECG	X*	X**		–	x•d	x•d			X*** 1\	X*** 1\	X''	X''			* Triplicate ECG at baseline. **Timed triplicate ECGs (separated by 5 min ± 2 min) at predose and at 2 and 4 hours(± 15 min) postdose. *** ECG will be perfonned on D1 of every other cycle after C3 (eg, C5, C7, and C9). '' ECGs only need to be perfonned in ttiplicate if there has been a QT prolongation on study or the ECG shows a clinically significant abnonnality not present at baseline. # For subjects receiving INCB059872 QoD, an additional visit is required during C2 on D2 or D4 so that the ECGs are collected on the day when INCB059872 is administered. The ECGs only need e performed on the day of the collection (C2D2 or C2D4).

Table 43: Schedule of Assessments (Treatment Group C: Part 1 Dose-Escalation and Expansion Cohorts C-1 to C-8 and Part 2 Expansion Cohorts C-9, C-10, and C-11) (Continued)

		Treatment										Follow-Up			Notes
Visit Day	Screening	C1 D1	C1 D8	C1 DIS	C2 D1	C2 D2/4*	C2 D8	C2 DIS	C3 D1	C4+ D1	EOT	Safety	Disease Status	Survival	* For subjects receiving INCB059872 QoD, an additional visit is required during C2 on D2 or D4 so that the samples and ECGs are collected on the day when INCB059872 is administered.
Evaluation Window	Day -28 to Day-1	D1	± 3 d	± 3 d	± 3 d	D2or D4	± 3 d	± 3 d	± 3 d	± 3 d	+S d	EOT + 42-49 d	Q9W (± 7 d) After EOT	Q12W (+ 7 d)	
AE assessment	X	X	X	X	X		X	X	X	X	X	X			
Laboratory assessments	X	X	X	X	X	X*	X	X	X	X	X	X			* For subjects receiving INCB059872 QoD, an additional visit is required during C2 on D2 or D4 so that the samples are collected on the day when INCB059872 is administered.
TUMOR BIOPSY COLLECTION															
Tumor biopsy/ tissue collection*	X				X*				X**						* Only Expansion Cohort C-11 will have an additional mandatory on-treatment biopsy will be collected at C2D1 (window C1D15 to C2D1). ** An additional mandatory on-treatment biopsy will be collected during Week 8 or Week 9. T11e on-treatment biopsy is optional for Stage 2 of Part 2. An additional optional biopsy may be collected once the subject meets the requirements for SD, response, or progression by radiographic disease assessment. Detailed instructions for tissue collection, processing, and storage can be found in the study procedures manual. Fine needle aspirates are not acceptable.

Table 43: Schedule of Assessments (Treatment Group C: Part 1 Dose-Escalation and Expansion Cohorts C-1 to C-8 and Part 2 Expansion Cohorts C-9, C-10, and C-11) (Continued)

		Treatment										Follow-Up			Notes
Visit Day	Screening	C1 D1	C1 D8	C1 DIS	C2 D1	C2 D2/4*	C2 D8	C2 DIS	C3 D1	C4+ D1	EOT	Safety	Disease Status	Survival	* For subjects receiving INCB059872 QoD, an additional visit is required during C2 on D2 or D4 so that the samples and ECGs are collected on the day when INCB059872 is administered.
Evaluation Window	Day -28 to Day-1	D1	± 3 d	± 3 d	± 3 d	D2 or D4	± 3 d	± 3 d	± 3 d	± 3 d	+S d	EOT + 42-49 d	Q9W (± 7 d) After EOT	Q12W (+ 7 d)	
STUDY DRUG ADMINISTRATION															
Administer INCB059872 in clinic*		X	X		X	X	X								* INCB059872 and epacadostat should be administered at the same time prior to the pembrolizmnab infusion. Subjects should withhold their AM dose ofiNCB057643 on ▬ days. It should be administered m the clinic following the trough collection on C1D1, C1D8, C2D1 or
Administer epacadostat in clinic*					X	X	X								* INCB059872 and epacadostat should be administered at the same time prior to the pembrolizmuab infusion. Subjects should withhold their AM dose of epacadostat on days. It should be administered m the clinic following the trough collection on C2D1 or C2D2/C2D4 andC2D8.
Administer pembrolizumab in clinic					X				X	X					
EFFICACY ASSESSMENTS															
Radiologic ttunor assessments*	X								X	X	X		X		* Evety 9 weeks (63 ± 7 days) until disease progression. After 12 months of study treatment, imaging frequency tuay be reduced to every 12 weeks. Imaging should not be delayed for delays in cycle struts or extension of combination treatment cycle intetvals.

Table 44: Laboratory Assessments (Treatment Group C: Part 1 Dose-Escalation and Expansion Cohorts C-1 to C-8 and Part 2 Expansion Cohorts C-9, C-10, and C-11)

NOTE: Upon implementation of Amendment 4, this table is no longer applicable.

Laboratory Assessment **Window**	Screening **Day -1**	C1 D1 D1	C1 D8 ± 3 d	C1 D15 ±3 d	C2 D1 ±3 d	C2 D2/4* D2 or D4	C2 D8 ± 3 d	C2 D15 ±3 d	C3 D1 ±3 d	C4+ D1 ±3 d	EOT +S d	Safety EOT + 42-49 d	* For subjects receiving INCB059872 QoD, an additional visit is required during C2 on D2 or D4 so that the samples are collected on the day when INCB059872 is administered.
LOCAL LABORATORY TESTS													
~~Comprehensive~~ serum chemistry	X	X	X	X	X		X	X	X	X	X	X	
Hematology with differential	X	X	X	X	X		X	X	X	X	X	X	
HgbA1c	X												
Coagulation panel	X				X				X	X*	X		* Only at Cycles 5, 8, 11, etc.
Endocrine panel	X				X					X*	X		* Only at Cycles 5, 8, 11, etc.
Urinalysis	X				X					X*	X		* Only at Cycles 5, 8, 11, etc.
Serum pregnancy test	X*											X	* A serum pregnancy test will be required for all women of childbearing potential during screening and must be performed within 72 hours before the first dose of study drug.
Serology	X												
CEA/CA19-9*		X			X					X**	X		* CEA to be petfonned in subjects with CRC only. CA 19-9 to be petfonned in subjects with pancreatic cancer only. ** CEA and CA 19-9 will be collected every other cycle after C2.
[redacted]													

Table 44: Laboratory Assessments (Treatment Group C: Part 1 Dose-Escalation and Expansion Cohorts C-1 to C-8 and Part 2 Expansion Cohorts C-9, C-10, and C-11) (Continued)

Laboratory Assessment Window	Screening Day -28 to Day -1	Treatment C1 D1 D1	C1 D8 ± 3 d	C1 D15 ± 3 d	C2 ± 3 d	C2 D2 or D4	C2 D8 ± 3 d	C2 D15 ± 3 d	C3 D1 ± 3 d	C4+ D1 ± 3 d	EOT + 5 d	Safety Follow-Up EOT + 42-49 d	* For subjects receiving INCB059872 QoD, an additional visit is required during C2 on D2 or D4 so that the samples are collected on the day when INCB059872 is administered.
[redacted]													

Table 45: Schedule of Assessments (Treatment Group C: Part 2 Expansion Cohort C-12)

NOTE: Upon implementation of Amendment 4, this table is no longer applicable.

		Treatment										Follow-Up			Notes
Visit Day	Screening	C1 D1	C1 D8	C1 DIS	C2 D1	C2 D2/4*	C2 D8	C2 DIS	C3 D1	C4+ D1	EOT	Safety	Disease Status	Survival	• For subjects receiving INCB059872 QoD, an additional visit is required during C2 on D2 or D4 so that the samples and ECGs are collected on the day when INCB059872 is administered.
Evaluation Window	Day -28 to Day -1	D1	±3 d	±3 d	± 3 d	D2 or D4	± 3 d	± 3 d	±3 d	±3 d	+ S d	EOT + 42-49 d	Q9W (± 7 d) After EOT	Q12W (+ 7 d)	
ADMINISTRATIVE PROCEDURES															
Infonned consent	X														
Contact iRT	X	X			X				X	X	X				
Inclusion! exclusion criteria	X	X													
Medical and cancer history	X														
Prior/concomitant medications	X	X	X	X	X		X	X	X	X	X	X			
Disttibute reminder cards	X	X	X	X	X		X	X	X	X	X				
Study drug dispensing		X			X				X	X					
Assess study dmg compliance					X				X	X	X				
Post-treatment anticancer therapy status													X	X	
Data collection for survival														X	

Table 45: Schedule of Assessments (Treatment Group C: Part 2 Expansion Cohort C-12) (Continued)

		Treatment										Follow-VI			Notes
Visit Day	Unscheduled	C1 D1	C1 D8	C1 D15	C2 D1	C2 D2/4*	C2 D8	C2 D15	C3 D1	C4+ D1	EOT	Safety	Disease Status	Survival	• For subjects receiving INCB059872 QoD, an additional visit is required during C2 on D2 or D4 so that the samples and ECGs are collected on the day when INCB059872 is administered.
Evaluation Window	Day -28 to Day -1	D1	±3 d	±3 d	±3 d	D2 or D4	± 3 d	±3 d	±3 d	±3 d	+S d	EOT + 42-49 d	Q9W (± 7 d) AfterEOT	Q12W (+ 7 d)	
CLINICAL PROCEDURES AND ASSESSMENTS															
Physical examination/body weight and height*	X	X	X	X	X		X	X	X	X	X	X			• Comprehensive examination at screening, targeted physical examination thereafter. Height at screening; only.
Vital signs	X	X	X	X	X		X	X	X	X	X	X			
ECOG performance status	X	X	X	X	X		X	X	X	X	X	X			
12-lead ECG	X•	X••			X•• #	X•• #			X••• ††\	X***' ††\	X''	X''			• Triplicate ECG at baseline. '''*Timed triplicate ECGs (separated by 5 min ± 2 min) at predose and at 2 and 4 hours(± 15 min) postdose. **''' ECG will be petfonned on D1 of every other cycle after C3 (eg, C5, C7, and C9). '' ECGs only need to be petfonned in ttiplicate if there has been a QT prolongation on study or the ECG shows a clinically significant abnonnality not present at baseline. # For subjects receiving INCB059872 QoD, an additional visit is required during C2 on D2 or D4 so that the ECGs are collected on the day when INCB059872 is administered. TI1e ECGs only need to be petformed on the day of the collection (C2D2 or C2D4).

Table 45: Schedule of Assessments (Treatment Group C: Part 2 Expansion Cohort C-12) (Continued)

Visit Day	Screening	Treatment									EOT	Follow-Up			Notes
		C1 D1	C1 D8	C1 DIS	C2 D1	C2 D2/4*	C2 D8	C2 DIS	C3 D1	C4+ D1		Safety	Disease Status	Survival	• For subjects receiving INCB059872 QoD, an additional visit is required during C2 on D2 or D4 so that the samples and ECGs are collected on the day when INCB059872 is administered.
Evaluation Window	Day -28 to Day -1	D1	±3 d	±3 d	± 3d	D2 or D4	± 3 d	± 3 d	± 3d	±3 d	+S d	EOT + 42-49 d	Q9W (± 7 d) AfterEOT	Q12W (+ 7 d)	
AE assessment	X	X	X	X	X		X	X	X	X	X	X			
Laboratory assessments	X	X	X	X	X	X•	X	X	X	X	X	X			• For subjects receiving INCB059872 on a QoD schedule, an additional visit is required dtuing Cycle 2 on Day 2 or Day 4 so that thesamples are collected on the day w1en INCB059872 is administered.
TUMOR BIOPSY COLLECTION															
Tumor biopsy/ tissue collection*	X				X•				X•						• Two additional mandatory on-treatment biopsies will be collected at C2D1 (window ClD15 to C2D1) and dming Week 8 or Week 9. An additional optional biopsy may be collected once the subject meets the requirements for SD, response, or progression by radiographic disease assessment. Detailed instructions for tissue collection, processing, and storage can be found in the study procedlU'es manual. Fine needle aspirates are not acceptable.

Table 45: Schedule of Assessments (Treatment Group C: Part 2 Expansion Cohort C-12) (Continued)

		Treatment										Follow-Up			Notes
Visit Day	Screening	C1 D1	C1 D8	C1 DIS	C2 D1	C2 D2/4*	C2 D8	C2 DIS	C3 D1	C4+ D1	EOT	Safety	Disease Status	Survival	• For subjects receiving INCB059872 QoD, an additional visit is required during C2 on D2 or D4 so that the samples and ECGs are collected on the day when INCB059872 is administered.
Evaluation Window	Day -28 to Day -1	D1	±3 d	±3 d	± 3d	D2 or D4	± 3 d	± 3 d	± 3d	±3 d	+S d	EOT + 42-49 d	Q9W (± 7 d) AfterEOT	Q12W (+ 7 d)	
STUDY DRUG ADMINISTRATION															
Administer INCB059872 in clinic•		X			X	X	X								• INCB059872 and epacadostat should be administered at the same time prior to the pembrolizmuab infusion. Subjects should withhold their AM dose ofiNCB057643 on ▬ days. It should be administered in the clinic following the trough ▬ collection on C2D1 or
Administer epacadostat in clinic•		X			X	X	X								• INCB059872 and epacadostat should be administered at the same time prior to the pembrolizmuab infusion. Subjects should withhold their AM dose of epacadostat on days. It should be administered in the clinic following the trough collection on C2D1 or C2D2/C2D4, andC2D8.
Administer pembroliztuuab in clinic					X				X	X					
EFFICACY ASSESSMENTS															
Radiologic ttunor assessments•	X								X	X	X		X		• Evety 9 weeks (63 ± 7 days) until disease progression. After 12 months of study treatment, imaging frequency may be reduced to every 12 weeks. Imaging should not be delayed for delays in cycle struts or extension of combination treatment cycle inte1vals.

Table 46: Laboratory Assessments (Treatment Group C: Part 2 Expansion Cohort C-12)

NOTE: Upon implementation of Amendment 4, this table is no longer applicable.

Laboratory Assessment **Window**	Screening **Day -1**	C1 **D1**	C1 D8 ± 3 d	C1 D15 ± 3 d	C2 **D1** ± 3 d	C2 D2/4* D2 or **D4**	C2 D8 ±3 d	C2 D15 ± 3d	C3 **D1** ± 3d	C4+ **D1** ± 3 d	EOT + 5 d	Safety	* For subjects receiving INCB059872 QoD, an additional visit is required during C2 on D2 or D4 so that the samples are collected on the day when INCB059872 is administered.
LOCAL LABORATORY TESTS													
Comprehensive serum chemistry	X	X	X	X	X		X	X	X	X	X	X	
Hematology with differential	X	X	X	X	X		X	X	X	X	X	X	
HgbA1c	X												
Coagulation panel	X				X				X	X*	X		
Endocrine panel	X				X					X*	X		
Urinalysis	X				X					X*	X		
Serum pregnancy test	X*											X	* A serum pregnancy test will be required for all women of childbearing potential during screening and must be performed within 72 hours before the first dose of study drug.
Serology	X												
[redacted]													

Table 46: Laboratory Assessments (Treatment Group C: Part 2 Expansion Cohort C-12) (Continued)

			Treatment										
			C1	C1	C2			C2	C3	C4+			* For subjects receiving INCB059872 QoD, an additional visit is required during C2 on D2 or D4 so that the samples are collected on the day when INCB059872 is administered.
Laboratory Assessment Window	Day -28 to Day -1	D1	D8 ± 3 d	D15 ± 3 d	D21 ± 3 d	D2 or D4	D4 ± 3 d	D1 ± 3 d	D8 ± 3 d	D15 ± 3 d	D22 + 5 d	EOT + 42-49 d	
[redacted]													

Table 47: Schedule of Assessments (Treatment Group C: Part 2 Expansion Cohort C-13)

NOTE: Upon implementation of Amendment 4, this table is no longer applicable.

		Treatment										Follow-Up			Notes
Visit Day	Screening	C1 D1	C1 DS	C1 D15	C2 D1	C2 D2/4*	C2 DS	C2 D15	C3 D1	C4+ D1	EOT	Safety	Disease Status	Survival	* For subjects receiving INCB059872 QoD, an additional visit is required during C2 on D2 or D4 so that the samples and ECGs are collected on the day when INCB059872 is administered.
Evaluation Window	Day -28 to Day-1	D1	± 3 d	± 3 d	± 3 d	D2 or D4	± 3 d	± 3 d	±3 d	± 3 d	+ 5 d	EOT+ 42-49 d	Q9W (± 7 d) After EOT	Q12W (+ 7 d)	
ADMINISTRATIVE PROCEDURES															
Infonned consent	X														
Contact iRT	X	X			X				X	X	X				
Inclusion! exclusion criteria	X	X													
Medical and cancer history	X														
Prior/concomitant medications	X	X	X	X	X		X	X	X	X	X	X			
Disttibute reminder cards	X	X	X	X	X		X	X	X	X	X				
Study drug dispensing		X			X				X	X					
Assess study dmg compliance					X				X	X	X				
Post-treatment anticancer therapy status													X	X	
Data collection for survival														X	

Table 47: Schedule of Assessments (Treatment Group C: Part 2 Expansion Cohort C-13) (Continued)

Visit Day		Treatment									EOT	Follow-Up			Notes
		C1 D1	C1 DS	C1 D15	C2 D1	C2 D2/4*	C2 DS	C2 D15	C3 D1	C4+ D1		Safety	Disease Status	Survival	* For subjects receiving INCB059872 QoD, an additional visit is required during C2 on D2 or D4 so that the samples and ECGs are collected on the day when INCB059872 is administered.
Evaluation Window	Day -28 to Day -1	D1	± 3 d	± 3 d	± 3 d	D2 or D4	± 3 d	± 3 d	±3 d	± 3 d	+ 5 d	EOT + 42-49 d	Q9W (± 7 d) After EOT	Q12W (+ 7 d)	
CLINICAL PROCEDURES AND ASSESSMENTS															
Physical exatnination/body weight and height*	X	X	X	X	X		X	X	X	X	X	X			* Comprehensive exatnination at screening, targeted physical examination thereafter. Height at ...,,.,nin0; only.
Vital signs	X	X	X	X	X		X	X	X	X	X	X			
ECOG J:I¥1LV!LII<III'-¥ status	X	X	X	X	X		X	X	X	X	X	X			
12-lead ECG	X*	X**			*X****	*X****			X*** 1\	X*** 1\	X''	X''			* Triplicate ECG at baseline. ** Timed triplicate ECGs (separated by 5 tnin ± 2 tnin) at predose and at 2 and 4 hours (± 15 Inin) postdose. *** ECG will be performed on D1 of every other cycle after C3 (eg, C5, C7, and C9). '' ECGs only need to be petfonned in ttiplicate if there has been a QT prolongation on study or the ECG shows a clinically significant abnonnality not present at baseline. #For subjects receiving INCB059872 QoD, an additional visit is required during C2 on D2 or D4 so that the ECGs are collected on the day when INCB059872 is administered. The ECGs only need to be petfonned on the day of the collection (C2D2 or C2D4).

Table 47: Schedule of Assessments (Treatment Group C: Part 2 Expansion Cohort C-13) (Continued)

		Treatment										Follow-Up			Notes
Visit Day	Screening	C1 D1	C1 DS	C1 D15	C2 D1	C2 D2/4*	C2 DS	C2 D15	C3 D1	C4+ D1	EOT	Safety	Disease Status	Survival	* For subjects receiving INCB059872 QoD, an additional visit is required during C2 on D2 or D4 so that the samples and ECGs are collected on the day when INCB059872 is administered.
Evaluation Window	Day -28 to Day -1	D1	± 3 d	± 3 d	± 3 d	D2 or D4	± 3 d	± 3 d	±3 d	± 3 d	+ 5 d	EOT + 42-49 d	Q9W (± 7 d) After EOT	Q12W (+ 7 d)	
AE assessment	X	X	X	X	X		X	X	X	X	X	X			
Laboratory assessments	X	X	X	X	X	X*	X	X	X	X	X	X			* For subjects receiving INCB059872 QoD, an additional visit is required during C2 on D2 or D4 so that the samples are collected on the day when INCB059872 is administered.
TUMOR BIOPSY COLLECTION															
Tumor biopsy/ tissue collection*	X				X*										* An additional mandatory on-treatment biopsy will be collected during Week 5 or Week 6. An additional optional biopsy may be collected once the subject meets the requirements for SD, response, or progression by radiographic disease assessment. Detailed instmctions for tissue collection, processing, and storage can be fotmd in the study procedmes manual. Fine needle aspirates are not acceptable.

Table 47: Schedule of Assessments (Treatment Group C: Part 2 Expansion Cohort C-13) (Continued)

Visit Day	Screening	Treatment									EOT	Follow-Up			Notes
		C1 D1	C1 DS	C1 D15	C2 D1	C2 D2/4*	C2 DS	C2 D15	C3 D1	C4+ D1		Safety	Disease Status	Survival	* For subjects receiving INCB059872 QoD, an additional visit is required during C2 on D2 or D4 so that the samples and ECGs are collected on the day when INCB059872 is administered.
Evaluation Window	Day -28 to Day-1	D1	± 3 d	± 3 d	± 3 d	D2 or D4	± 3 d	± 3 d	±3 d	± 3 d	+5 d	EOT+ 42-49 d	Q9W (± 7 d) After EOT	Q12W (+ 7 d)	
STUDY DRUG ADMINISTRATION															
Administer INCB059872 in clinic*		X	X		X	X	X								* INCB059872 and epacadostat should be administered at the same time prior to the pembroliztunab infusion. Subjects should withhold their AM dose ofiNCB057643 on ▬ days. It should be administered ill the clinic following the trough ▬ collection on CIDS, C2D1 or
Administer epacadostat in clinic*		X	X		X	X	X								* INCB059872 and epacadostat should be administered at the same time prior to the pembroliztunab infusion. Subjects should withhold their AM dose of epacadostat on days. It should be adtninistered ill the clinic following the trough collection on C1DS, C2DI or C2D2/C2D4, and C2D8.
Adtninister pembroliztunab in clinic		X			X				X	X					
EFFICACY ASSESSMENTS															
Radiologic twnor assessments*	X								X	X	X		X		*Every 9 weeks (63 ± 7 days) tilltil disease progression. After 12 months of study treatment, imaging frequency may be reduced to every 12 weeks. Imaging should not be delayed for delays in cycle starts or extension of combination treatment cycle intetvals.

Table 48: Laboratory Assessments (Treatment Group C: Part 2 Expansion Cohort C-13)

NOTE: Upon implementation of Amendment 4, this table is no longer applicable.

Laboratory Assessment **Window**	Screening **Day -1**	C1 **D1**	C1 D8 ± 3 d	C1 D15 ± 3 d	C2 D1 ± 3 d	C2 D2/4* D2 or D4	C2 D8 ±3 d	C2 D15 ± 3d	C3 D1 ± 3d	C4+ D1 ± 3 d	EOT +S d	Safety	* For subjects receiving INCB059872 QoD, an additional visit is required dming C2 on D2 or D4 so that the samples are collected on the when INCB059872 is administered.
LOCAL LABORATORY TESTS													
Comprehensive serum chemistry	X	X	X	X	X		X	X	X	X	X	X	
Hematology with differential	X	X	X	X	X		X	X	X	X	X	X	
HgbA1c	X												
Coagulation panel	X				X				X	X*	X		
Endocrine panel	X				X					X*	X		
Urinalysis	X				X					X*	X		
Serum pregnancy test	X*											X	* A sermn pregnancy test will be required for all women of childbearing potential during screening and must be performed within 72 hours before the first dose of study dmg.
Serology	X												
[redacted]													

Table 48: Laboratory Assessments (Treatment Group C: Part 2 Expansion Cohort C-13) (Continued)

			Treatment										
			C1	C1	C2			C2	C3	C4+			* For subjects receiving INCB059872 QoD, an additional visit is required during C2 on D2 or D4 so that the samples are collected on the day when INCB059872 is administered.
Laboratory Assessment Window	Day -28 to Day -1	D1	D8 ± 3 d	D15 ± 3 d	D21 ± 3 d	D2 or D4	D4 ± 3 d	D1 ± 3 d	D8 ± 3 d	D15 ± 3 d	D22 + 5 d	EOT + 42-49 d	
[redacted]													

Table 49: Local Laboratory Tests: Required Analytes

Serum Chemistries	Hematology	Urinalysis With Microscopic Examination	Hepatitis Screening	Coagulation
Albumin Alkaline phosphatase ALT AST Bicarbonate Blood urea nitrogen Calcium Chloride Creatinine Glucose Lactate dehydrogenase Phosphate Potassium Sodium Total bilirubin Direct bilirubin (if total bilirubin is elevated above ULN) Total protein Uric acid	Complete blood count, including: Hemoglobin Hematocrit Platelet count Red blood cell count White blood cell count Differential count, including: Basophils Eosinophils Lymphocytes Monocytes Neutrophils Absolute values must be provided for: WBC differential laboratory results: Lymphocytes Neutrophils	Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein Urobilinogen	HBV surface antigen HBV-DNA HCV antibody HCV-RNA	PT PTT INR
		Endocrine Monitoring	[redacted]	Pregnancy Testing
		ACTH HgbA1c Serum cortisol Prolactin TSH Free thyroxine (T4) Total triiodothyronine (T3) Serum testosterone	[redacted]	Women of childbearing potential only require a serum test at screening (must be performed within 72 hours before the first dose of study drug) and at safety follow-up. Pregnancy tests (serum or urine) should be repeated if required by local regulations.

ACTH = adrenocorticotropic hormone.
Note: Additional tests may be required, as agreed by investigator and sponsor, based on emerging safety data.

6-L Screening

Screening is the inte1val between signing the ICF and the day the subject is emolled in the study (Cycle **1** Day 1 or Day 1 of Week **-1** for Expansion Cohmt A-3). Screening may not exceed 28 days. Assessments that are required to demonstrate eligibility may be perfmmed over the course of 1 or more days during the screening process.

Procedures conducted as part of the subject's routine clinical management (eg, blood count, imaging study) and obtained before signing of infmmed consent may be used for screening or baseline purposes provided the procedure meets the Protocol-defined crite1ia and has been perfmmed in the timeframe of the study (ie, within 28 days of Cycle **1** Day **1**). All infmmation associated with eligibility requirements must be entered into the appropriate eCRF pages.

Results from the screening visit evaluations will be reviewed to confi1m subject eligibility before emollment or the administration of study dmg. Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the results to be in enor. For screening assessments that are repeated, the most recent available result before treatment assignment will be used to dete1mine subject eligibility. Treatment should stmt as soon as possible, but within 7 days after the date of registration. Additionally, a subject who fails screening may repeat the screening process **1** time if the investigator believes there has been a change in eligibility status (eg, after recovery from an infection).

The screening period will be used to dete1mine the baseline assessments of clinical condition and disease status. Tumor assessments appropriate to the type of malignancy will be perfmmed and recorded in the eCRF.

6-2- Treatment

The treatment pe1iod begins on the day that the subject receives the first dose of study dmg (Cycle **1** Day I) through the point at which the investigator dete1mines that the subject will be pe1manently discontinued from study dmg or until the subject has received 35 administrations of pembrolizumab (approximately 2 years). 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 embrolizumab or the combination must be discussed and approved by the medical monitor.
mandatmy tumor biopsies will not be perfmmed. Re-treatment with azacitidine, INCB057643, or INCB059872 (based on miginal 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 with medical monitor approval. Three additional cycles of azacitidine are pe1mitted (for subjects miginally emolled in Treatment Group A). Cycle **1** Day 1 (or Day 1 of Week -1 for Expansion Cohmt A-3) must be no more than 28 days after the subject has signed the ICF.

Subjects will have regularly scheduled study visits on Day **1** of eve1y cycle± 3 days. Additional visits will be required during Cycles 1 and 2 for study dmg administration and/or safety assessments. During study visits, the subject will have clinical and assessments as outlined in Section 6. At certain study visits, subjects will have [redacted]

[redacted] Toxicities will be monitored continuously and will be graded using the NCI CTCAE v4.03 criteria.

6_3_ End of Treatment

When the subject permanently discontinues study drug, the EOT visit should be conducted (EOT + 5 days). If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the eCRF. The subject should be encouraged to return for the follow-up visit.

6-4- Follow-Up

6.4.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visits, which should occur 42 to 49 days after the EOT visit (or after the last dose of study drug if the EOT visit was not performed). Adverse events and SAEs must be reported up until at least 42 days (90 days for SAEs) after the last dose of study drug, the date of the follow-up visit, or until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer, or if a subject initiates new anticancer therapy, whichever is earlier. Reasonable efforts should be made to have the subject return for the follow-up visit and report any AEs that may occur during this period. If the subject cannot return to the site for the safety follow-up visit (eg, lives far away), the subject should be contacted by telephone for assessment of AEs and SAEs. This contact with the subject should be documented in the source.

If a subject is scheduled to begin a new anticancer therapy before the end of the 42-day safety follow-up period, the safety follow-up visit should be performed before new anticancer therapy is started. Once new anticancer therapy has been initiated, the subject will move into the survival follow-up period. Upon implementation of Amendment 4, the survival follow-up visit will no longer be required.

6.4.2. Disease Status Follow-Up

Subjects who discontinue study treatment for a reason other than disease progression will move into the disease status follow-up period and should be assessed every 9 weeks (63 ± 7 days) by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until:

- The start of new antineoplastic therapy.
- Disease progression.
- Death.
- The end of the study.

Upon implementation of Amendment 4, disease status follow-up will no longer be required.

6.4.3. Survival Follow-Up

Once a subject has confirmed disease progression or starts a new anticancer therapy, the subject moves into the survival follow-up period and should be contacted by telephone, email, or visit at

least every 12 weeks(+ 7 days) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first. Upon implementation of Amendment 4, survival follow-up will no longer be required.

6.5. End of Study

Subjects will be considered as having completed the study if they meet any of the following crite1ia:

- Subject has completed the safety follow-up period.
- Subject dies and a date of death is available.
- Subject is known to have died; however, the date of death cannot be obtained. (NOTE: Eve1y effort must be made to obtain the date of death.)
- Consent is withdrawn for any fu1ther contact related to this study.
  - Subjects may choose to withdraw from the study at any time without penalty of jeopardizing their health care or loss of benefits to which the subject is othe1wise entitled. Eve1y reasonable effmt should be made to determine the reason a subject withdraws prematurely, and this infmmation should be recorded in the eCRF.
- The study is te1minated by the sponsor.
- The study is te1minated by the local health authority or IRB or IEC.

6.6. Unscheduled Visits

Unscheduled visits may occur at any time as medically wa1ranted. Visits where study dmg is held are considered unscheduled visits. Any assessments perfmmed at those visits should be recorded in the eCRF.

7_ CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

7-L Administration of Informed Consent Form

Valid infmmed consent must be obtained from the study subject before conducting any study-specific procedures using an ICF approved by the local IRB/IEC that contains all elements required by ICH E6 and describes the nature, scope, and possible consequences of the study in a fmm understandable to the study subject. Local and institutional guidelines for ICF content and administration must be followed; the original signed ICF must be retained by the investigator, and a copy of the signed ICF must be provided to the study subject. The infmmed consent process for each subject must be documented in writing within the subject source documentation.

7-2- Interactive Response Technology Procedure

The IRT will be contacted to obtain a subject ID number when a subject enters screening. Upon dete1mining that the subject is eligible for study entiy, the IRT will be contacted to obtain the treatment assignment. Additionally, the IRT will be contacted at each regular study visit to update the study dmg supply. Refer to the study procedures manual for specific details regarding IRT.

7_3_ Demography and Medical History

7.3.1. Demographics and General Medical History

Demographic data and general medical histmy will be collected at screening. This will include complete documentation of the histmy of medical or surgical ti·eatment for the malignancy under study.

7.3.2. Disease Characteristics and Treatment History

A disease-targeted medical and medication histmy will be collected at screening.

7.4. Prior and Concomitant Medications and Procedures

Prior and concomitant medications and procedures will be reviewed to dete1mine subject eligibility. All concomitant medications and measures must be recorded in the eCRF, and any medication received or procedure perfmmed within 30 days before Cycle 1 Day 1 and up to the end of study will be recorded in the eCRF. The medication record will be maintained after signing the ICF to document concomitant medications, including any changes to the dose or regimen. Concomitant medications include any prescription, over-the-counter, or natural/herbal preparations taken or administered during the study period. Concomitant tieatments and/or procedures that are required to manage a subject's medical condition dming the study will also be recorded in the eCRF.

7_5_ Safety Assessments

7.5.1. Adverse Events

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

7.5.2. Physical Examinations

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

Clinically notable abnmmalities that are considered clinically significant in the judgement of the investigator are to be repmted as AEs.

7.5.2.1. Comprehensive Physical Examination

The comprehensive physical examination will include height (at screening) and body weight, and assessment(s) of the following organ or body systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); ext:I·emities; and lymph nodes; as well as a brief neurological examination.

7.5.2.2. Targeted Physical Examination

The targeted physical examination will be a symptom-directed evaluation. The targeted physical examination will include body weight and assessment(s) of the body systems or organs, as indicated by subject symptoms, AEs, or other fmdings.

7.5.3. Vital Signs

Vital sign measurements include blood pressure, pulse, respiratmy rate, and body temperature. Blood pressure and pulse will be taken with the subject in the recumbent, semirecumbent, or sitting position after 5 minutes of rest. Clinically notable abnmmalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

7.5.4. Electrocardiograms

All 12-lead ECGs will be perfmmed with the subject in a recumbent or semirecumbent position after 5 minutes of rest. Baseline and Cycle 1 Day 1 and Cycle 2 Day 1 ECGs should be tr·iplicate. Subsequent ECGs only need to be perfmmed in tr·iplicate if there has been a QT prolongation on study or the ECG shows a clinically significant abnmmality not present at baseline.

The 12-lead ECGs will be interpreted by the investigator at the site to be used for immediate subject management. The decision to include or exclude a subject or withdraw a subject from the study based on an ECG flagged as "Abnmmal, Clinically Significant" is the responsibility of the investigator, in consultation with the sponsor's medical monitor, as appropriate. Clinically notable abnmmalities that are considered clinically significant in the judgment of the investigator are to be repmted as AEs. The conection method (Fridericia) used for calculating QTc will need to be provided in the eCRF.

7.5.4.1. Timed Electrocardiograms

Timed triplicate (separated by 5 minutes ± 2 min) ECGs will be perfmmed at baseline, Cycle 1 Day 1, and Cycle 2 Day 1.

For subjects receiving INCB059872 QoD, an additional visit is required during Cycle 2 on Day 2 or Day 4 so that the ECGs are collected on the day when INCB059872 is administered. The ECGs only need to be pe1fmmed on the day of the II collection (Cycle 2 Day 2 or Day 4).

Electrocardiograms will be conducted predose and will be conducted in conjunction with the 2-hour and 4-homll timepoints with a ± 30 minute window. Electrocardiograms should be conducted before but within 30 minutes ofthell blood draw at the COITesponding timepoint. The specified postdose timepoint may be adjusted based on emerging II data.

7.5.5. Laboratory Assessments

A laboratmy local to the study site and subject will pe1f01m all clinicallaboratmy assessments for safety. The investigative site will enter the laboratory results and laboratmy nmmal ranges into the eCRF. Hematology, sennn chemistry, and urinalysis should be perfmmed using standard procedures on the days indicated in Section 6.

7.5.5.1. Serum Chemistry Tests

A panel of semm chemistr·ies will be perfmmed as indicated in Section 6; analytes required for this panel are listed in Table 49.

7.5.5.2. Endocrine Function Testing

Endocrine function testing will be perfmmed as indicated in Section 6; required analytes are listed in Table 49.

7.5.5.3. Pregnancy Testing

A sennn pregnancy test will be required for all women of childbearing potential during screening and must be within 72 hours before the first dose of study u·eatment. A semm pregnancy test should also be repeated at the safety follow-up visit. Pregnancy testing is not required if a subject is going to hospice. Urine pregnancy tests will be conducted as medically indicated, or per countiy-specific requirement. U1ine pregnancy tests will be perfmmed locally. If a mine pregnancy test is positive, the results should be confi1med with a semm pregnancy test.

If the semm pregnancy test is negative after a urine test was positive, the investigator will assess the potential benefit/risk to the subject and dete1mine whether it is in the subject's best interest to resume study dmg and continue pa1ticipation in the study.

7.5.5.4. Hepatitis Screening Tests

Hepatitis screening assessments will be perfmmed at the screening visit (see Section 6) to mle out hepatitis infection; required analytes are shown in Table 49. Additional tests may be perfmmed if clinically indicated.

7.5.5.5. CA 19-9 Testing

CA 19-9 testing will be perfmmed in subjects with pancreatic cancer only as indicated in Section 6.

[redacted]

7.6. Efficacy Assessments

[redacted]

[redacted]

7.6.1.1. Initial Tumor Imaging

Initial tumor imaging must be perfmmed within 28 days before the first dose of study treatment. The site study team must review prestudy images to confirm the subject has measurable disease per RECIST v1.1. Tumor lesions that are located in a previously inadiated area or in an area subjected to other locoregional therapy should not be selected as target lesions. If a subject to be emolled only has lesions that are found in an area previously inadiated or subjected to locoregional therapy, then the subject will be allowed to emoll. Additionally, it is recommended that tumor lesions that will be biopsied should not be selected as target lesions.

Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and perfmmed within 28 days before the first dose of study treatment. The same imaging technique should be used in a subject throughout the study. Baseline scan must be a contrast computed tomography (CT) or magnetic resonance imaging (MRI), except in circumstances where there is a contrast allergy or with medical monitor approval. A PET/CT scan that uses higher energy and thinner slices for the CT component may be acceptable (with medical monitor approval). Images of the chest and abdomen are required for all subjects. In addition, neck imaging is also required for subjects with SCCHN. Imaging of the pelvis is only required for subjects with TCC of the GU tract but is strongly encouraged for all subjects.

7.6.1.2. Tumor Imaging During the Study

Tumor imaging may be perfmmed by CT or MRI, but the same imaging technique should be used in a subject throughout the study. Scans must be a contrast CT or MRI, except in circumstances where there is a contrast allergy or with medical monitor approval. A PET/CT scan that uses higher energy and thinner slices for the CT component may be acceptable (with medical monitor approval) if it was the same technique used for baseline. Imaging should be perfmmed every 9 weeks (63 days ± 7 days) or more frequently if clinically indicated. After 12 months of study treatment, imaging frequency may be reduced to every 12 weeks. Imaging should not be delayed for delays in cycle starts or extension of combination treatment cycle intervals.

[redacted]

Imaging should continue to be perfmmed until documented disease progression, the start of new anticancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first. Disease progression should be confnmed at least 4 weeks and not later than 8 weeks after the fust scan indicating PD in clinically stable subjects. Subjects who have unconfirmed disease progression may continue on treatment until progression is confirmed provided that they have met the conditions detailed in Section 7.6.1.

7.6.2. **Tumor** Biopsy

Tumor biopsy samples are required for subject participation in all patts of the study. Mandatmy tumor biopsies will be collected at baseline (before Day 1 administration) and while the subject is receiving study treatment as specified in the following:

- An additional mandatmy on-treatment biopsy will be collected during Week 5 or Week 6 (Treatment Group A) or Week 8 or Week 9 (Treatment Groups B and C); the on-treatment biopsy is optional for Stage 2 cohmts in Patt 2. On-treatment biopsies should be collected from the same tumor lesion that was biopsied at baseline.
- Cohmts A-3, A-4, A-5, B-9, B-10, C-11, and C-12: A baseline biopsy and 2 on-treatment biopsies are required for subjects emolled in the treatment sequencing biopsy cohmts. The timing for the biopsies is presented in Table 5, Table 7, and Table 9.
- An additional optional biopsy may be collected once the subject meets the requirements for SD, response, or progression by radiographic disease assessment.

Note: If a subject is scheduled to have a tumor biopsy for the purposes of this study and it is subsequently detetmined that tumor tissue cannot safely be obtained, then the subject may still emoll in the study, and such subjects may be replaced.

Note: Care should be taken to biopsy the same lesion for the baseline and on-treatment samples If a subject has a [redacted], this should not be biopsied. [redacted]

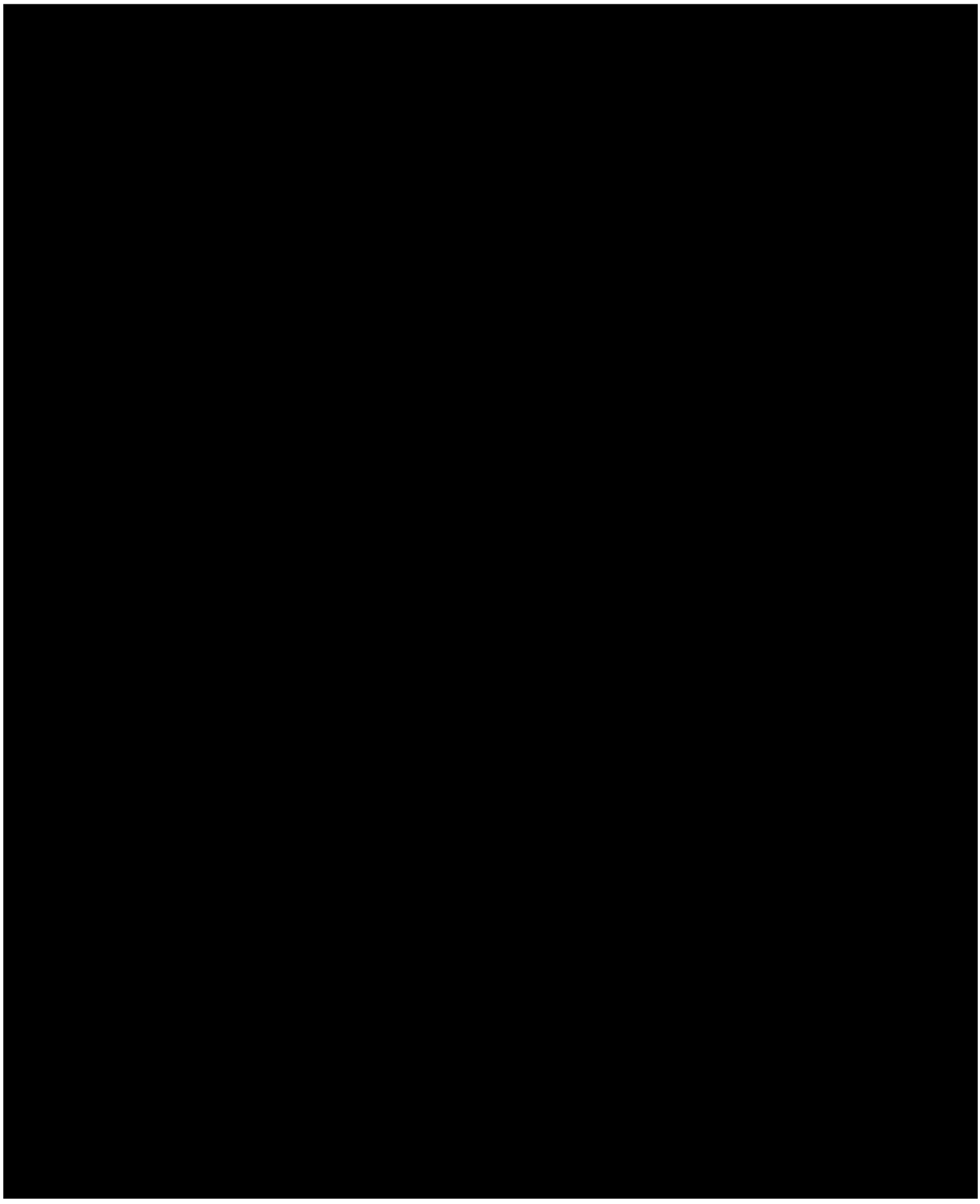
Note: As a quality control step, prior to submitting the tumor tissue to the central laboratmy vendor, all tumor tissue will be fmmalin-fixed and paraffin-embedded locally. An H&E stain will be perfmmed and reviewed by a local pathologist to verify the adequacy of the tumor biopsy. Additionally, a quality control fotm will be signed and dated by the reviewing pathologist. For the screening biopsy, this fmm will ideally be submitted to the sponsor at the same time the registration fmm is submitted for emollment.

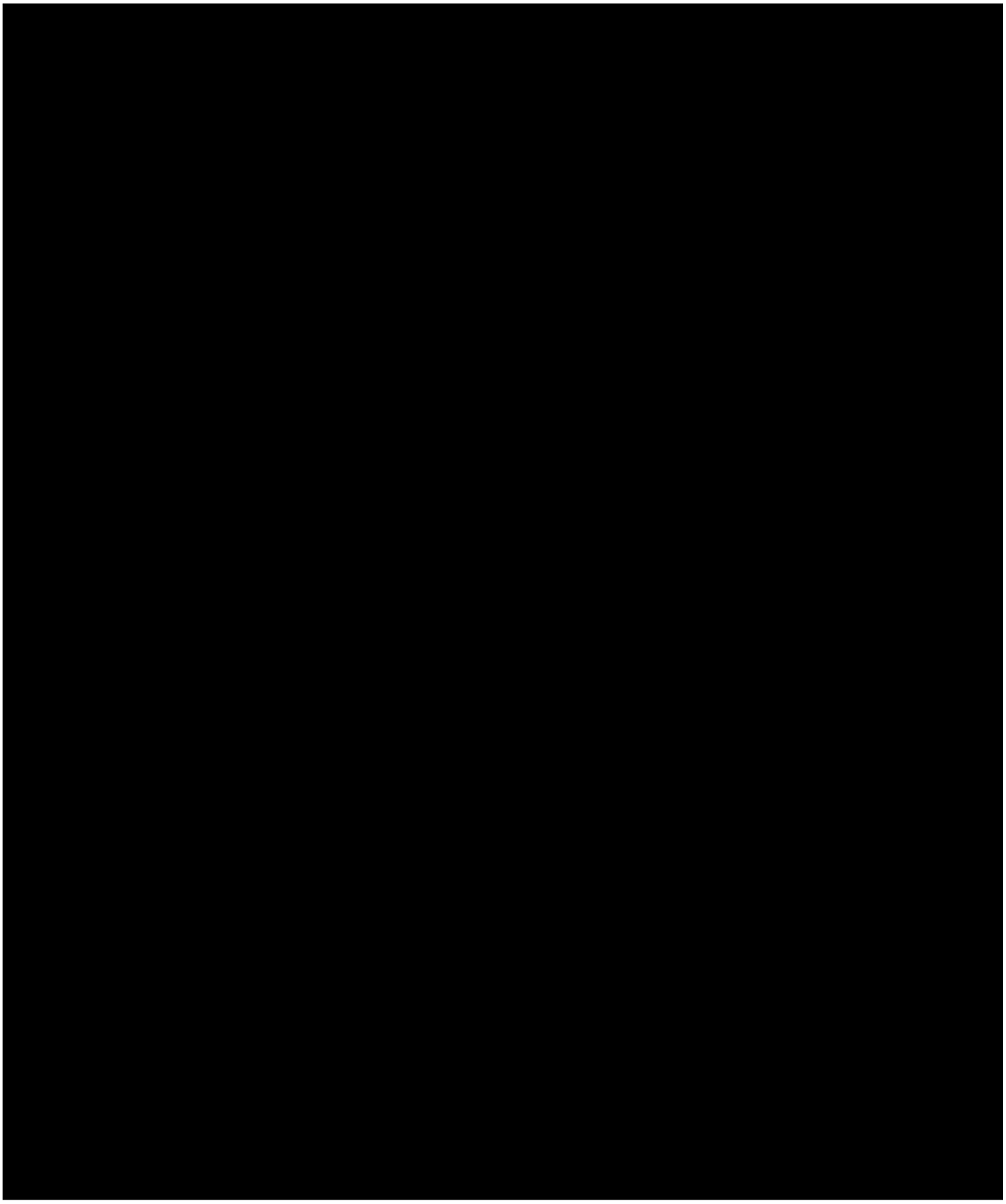
Details and methods for obtaining, processing, and [redacted] the tumor biopsy samples will be provided in the [redacted] Manual for the study. [redacted]

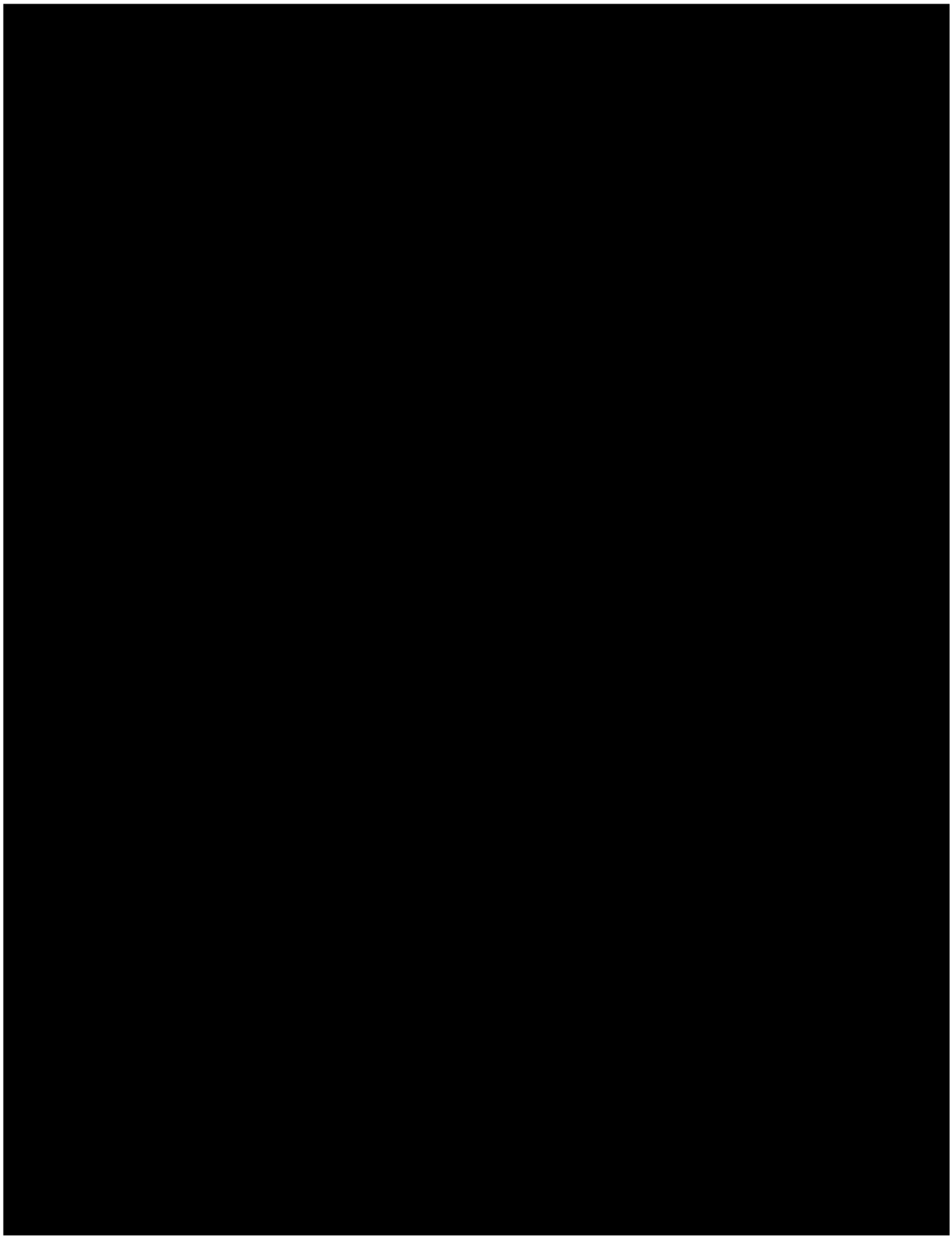
7.7. **Performance and Quality-of-Life** Assessments

ECOG perfmmance status (see Appendix D) must be assessed by a medically qualified individual and recorded in the eCRF at visits indicated in Section 6.

[redacted]







[redacted]

7_10. Other Study Procedures

7.10.1. Distribution of Subject Reminder Cards and Subject Diaries

Subjects will be provided with subject reminder cards at each visit. The subject reminder cards will indicate the date and time of the next visit. Reminder cards will include instructions specific for Day 1 visits, at which time the subject will refrain from taking the study dmg at home in the moming before the clinic visit. All necessary instmctions, such as administr·ation instructions for study dmg, concomitant medications, and reminders of visits to conduct laboratory tests, should be provided to the subject in writing on this reminder card, or on accompanying written materials. Subject diaries will be provided for the purpose of documenting study dmg administr·ation and AEs. The subject dialy will have an area on which the date and time of the last dose taken before each visit will be recorded as well as the time (and content if applicable to the visit) of the last meal

7.10.2. Data Collection for Survival Follow-Up

For subjects having entered the survival follow-up period of the study, the site will use continuing subject records to supply data on subsequent tr·eatment regimens, tumor assessments (if discontinued tr·eatlnent for a reason other than progression), and OS in the eCRF. For subjects who do not intend to retum to the study investigator for their ongoing care, follow-up should be maintained by phone contact, patient records, and public records/databases at intervals of no longer than 12 weeks (see Section 6.4.3). Upon implementation of Amendment 4, survival follow-up is no longer required.

8_ SAFETY MONITORING AND REPORTING

8-L Adverse Events

8.1.1. Definitions

For the purposes of this Protocol, an AE is defined as any untoward medical occunence associated with the use of a dmg in humans, whether or not considered dmg related, that occurs after a subject provides infmmed consent. Abnmmallaboratmy values or test results occmTing after infmmed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically meaningful, require therapy (eg, hematologic abnmmality that requires transfusion), or require changes in the study dmg(s).

8.1.2. Reporting

Adverse events that begin or worsen after infmmed consent should be recorded on the Adverse Events fmm of the eCRF. Conditions that were already present at the time of infmmed consent should be recorded on the Medical Histmy fmm in the eCRF. Monitoring for the occunence of new AEs should be continued for at least 42 days after the last dose of study dmg. Adverse events (including laboratmy abnmmalities that constitute AEs) should be desc1ibed using a diagnosis whenever possible rather than by individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

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

The sevelity of AEs will be assessed using CTCAE v4.03 Grades 1 through 4. The CTCAE v4.03 severity of Grade 5 will not be used; AEs resulting in death will be graded accordingly using Grades 1 through 4 and have the outcome noted as fatal. If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of sevelity.

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

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

- The severity grade (CTCAE Grade 1 to 4).
- Whether there is at least a reasonable possibility that the AE is related to the study treatment: suspected (yes) or not suspected (no).
- The sta1t and end dates, unless unresolved at final follow-up.
- The action taken with regard to study dmg.
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The se1iousness, as per SAE definition provided in Section 8.3.1.

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

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

Once an AE is detected, it should be followed until it has resolved or until it is judged to be pelmanent; assessment should be made at each visit (or more frequently if necessa1y) of any changes in severity, the suspected relationship to the study dmg, the interventions required to treat the event, and the outcome.

When the severity of an AE changes over time for a repmting period (eg, between visits), each change in severity will be repmted as a separate AE until the event resolves. For example, 2 separate AEs will be repmted if a subject has Grade 1 dianhea, meeting the definition of an AE, that lasts for 3 days before worsening to a Grade 3 severity. The Grade 1 event will be repmted as an AE with a sta1t date equal to the day the event met the Grade 1 AE definition and a stop date equal to the day that the event increased in severity from Grade 1 to Grade 3. The Grade 3 event will also be repmted as an AE, with the sta1t date equal to the day the event changed in intensity from Grade 1 to Grade 3 and a stop date equal to the day that the event either changed severity again or resolved.

8-2- Laboratory Test Abnormalities

Laboratmy abnmmalities that constitute an AE in their own light (considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study dmg) should be recorded on the Adverse Event fmm in the eCRF. Whenever possible, a diagnosis rather than a symptom should be provided (eg, "anemia" instead of "low hemoglobin"). Laboratory abnmmalities that meet the critelia for AEs should be followed until they have retumed to nmmal or an adequate explanation of the abnmmality is found. When an abnmmal laboratmy test result conesponds to a sign or symptom of a previously repmted AE, it is not necessa1y to separately record the laboratmy test result as an additional event.

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

8.3. Serious Adverse Events

8.3.1. Definitions

An SAE is defmed as an event that meets at least 1 of the following cliteria:

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

8.3.2. Reporting

Evely SAE, regardless of suspected causality (eg, relationship to study dmg(s) or study procedure or disease progression), occmTing after the subject has signed the ICF through the last study visit (or 90 days after the last dose of study dmg, whichever is later) must be repmted to the sponsor (or designee) within 24 hou rs of leaming of its occmTence, unless othe1wise specified by the Protocol. Any SAEs occmTing more than 90 days after the last dose of study dmg should be reported to the sponsor or its designee only if the investigator suspects a causal relationship to the study dmg.

Infmmation about all SAEs is collected and recorded on the Adverse Event fmm of the eCRF. The investigator must assess and record the causal relationship of each SAE to the study treatment.

The investigator must also complete the Incyte Serious Adverse Event Repo1t Fmm, in English, and send the completed and signed fmm to the sponsor or designee within 24 hours of becoming aware of the SAE. The investigator must provide a causality assessment, that is, assess whether there is at least a reasonable possibility that the SAE is related to the study treatment: suspected (yes) or not suspected (no). Refer to the Incyte Reference Guide for Completing the Serious Adverse Event Repmt Fmm.

The contact infmmation of the sponsor's study-specific representatives is listed in the investigator manual provided to each site. The original copy of the SAE Repmt Fmm and the confi1mation sheet must be kept at the study site.

Investigational site personnel must repmt any new infmmation regarding the SAE within 24 hours of becoming aware of the infmmation in the same manner that the initial SAE Repmt Fmm was sent. Follow-up infmmation is recorded on an amended or new SAE Repmt Fmm, with an indication that it is follow-up to the previously repo1ted SAE and the date of the miginal repmt. The follow-up repmt should include infmmation that was not provided on the previous SAE Repmt Fmm, such as the outcome of the event (eg, resolved or ongoing), treatment provided, action taken with study dmg because of the SAE (eg, dose reduced, intenupted, or discontinued), or subject disposition (eg, continued or withdrew from study pa1ticipation). Each recurrence, complication, or progression of the miginal event should be repmted as follow-up to that event, regardless of when it occurs.

If the SAE is not documented in the IB for the study dmg, or in the US package inse1t or Summa1y of Product Characte1istics for marketed drugs as appmp1iate, (new occunence) and is thought to be related to the sponsor's study dmg, the sponsor or its designee may urgently require fmther infmmation from the investigator for repmting to health authmities. The sponsor or its designee may need to issue an Investigator Notification (IN) to infmm all investigators involved in any study with the same dmg that this SAE has been repmted. Suspected Unexpected Se1ious Adverse Reactions (SUSARs) will be collected and repmted to the competent authmities and relevant ethics committees in accordance with Directive 2001/20/EC, or as per national regulatmy requirements in pa1ticipating countries.

8-4- Adverse Events of Special Interest

Adverse events of special interest include irAEs that are seen with immunotherapy and any other observed autoimmune phenomenon. Guidance for the assessment, diagnosis, and management of irAEs is provided in Section 5.4.1.3. Immune-related AEs will be monitored carefully at each cycle and dming the safety follow-up period.

As noted in Section 1.8.1, there is an uncommon risk that epacadostat could cause an increase in serotonin levels in the brain that might t1igger SS (Boyer and Shannon 2005) when administered in combination with other serotonergic agents. This syndi-ome has been most closely associated with use ofMAOis, mepe1idine, linezolid, or methylene blue; all of these agents are prohibited during the study. Selective serotonin reuptake inhibitors and SNRis are pe1mitted in the study. Procedures listed in Section 5.4.3 will be implemented if subjects exhibit the signs/symptoms of SS, including tremor, hypeneflexia, spontaneous, ocular, or inducible clonus together with agitation, fever, diaphoresis, or muscle 1igidity.

8.5. Emergency Unblinding of Treatment Assignment

Not applicable.

8.6. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study dmg may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confi1med in a subject dming matemal or patemal exposure to study dmg, the following procedures should be followed in order to ensure subject safety:

- The study dmg must be discontinued immediately (female subjects only; see Section 5.4.1.2 for the maximum pe1mitted duration of study dmg intenuption).
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy fmm to the sponsor or its designee within 24 hours of leaming of the pregnancy.

Data on fetal outcome and breastfeeding are collected for regulatmy reporting and dmg safety evaluation. Follow-up should be conducted for each pregnancy to dete1mine outcome, including spontaneous or voluntaly te1mination, details of the birth, and the presence or absence of any birth defects, congenital abnmmalities, or matemal and/or newbom complications, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Trial Pregnancy fmm and repmted by the investigator to the sponsor or its designee. Pregnancy follow-up infmmation should be recorded on the same fmm and should include an assessment of the possible causal relationship to the sponsor's study dmg to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Fmm.

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

8.7. Warnings and Precautions

Special wamings or precautions for the study dmg, derived from safety infmmation collected by the sponsor or its designee, are presented in the epacadostat Investigator's Brochure (IB). Additional safety infmmation collected between IB updates will be communicated in the fmm of INs. Any impmtant new safety infmmation should be discussed with the subject dming the study, as necessa1y. If new significant risks are identified, they will be added to the ICF.

8.8. Data Monitoring Committee

Not applicable.

8.9. Product Complaints

The sponsor collects product complaints on study dmgs and dmg delive1y systems used in clinical studies in order to ensure the safety of study pa1ticipants, monitor quality, and facilitate process and product improvements.

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

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

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

9. STATISTICS

9.1. Study Populations

The safety population includes all subjects emolled in the study who received at least 1 dose of study dmg (azacitidine, INCB057643, INCB059872, pembrolizumab, or epacadostat). All safety analyses will be based on the safety population.

The full analysis set includes all subjects emolled in the study who received at least 1 dose of study dmg (azacitidine, INCB057643, INCB059872, pembrolizumab, or epacadostat) and had at least 1 postbaseline assessment or discontinued treatment. All efficacy analyses will be based on the full analysis set.

[redacted]

9.2. Selection of Sample Size

9.2.1. Sample Size in Part 1

9.2.1.1. Dose Escalation

The prima1y objective ofPa1t 1 of the study is to dete1mine the MTD, maximum tested dose, or PAD of the triplet combination of azacitidine, INCB057643, or INCB059872 with pembrolizumab and epacadostat. The total number of subjects will depend on the number of dose levels tested before the MTD, maximum tested dose, or PAD is established.

A 3 + 3 + 3 dose-escalation design will be used in Pa1t 1. Based on 3 + 3 + 3 design algorithm, 3 to 9 subjects will be emolled at each dose level. The algmithm of3+3+3 is detailed in Section 4.1.1. The probability of dose de-escalation from a given dose level for the various DLT rates are provided in Table 55. For example, if the tme DLT rate is 20% at a given dose level, there is a 78.4% chance that the dose would be escalated.

Table 55: Probability of Dose De-Escalation for Various Dose-Limiting Toxicity Rates

True DLT Rate	Probability of Dose De-Escalation
20%	21.6%
30%	43.9%
40%	65.0%
50%	81.1%
60%	91.2%

9.2.1.2. Dose Expansion

In addition to the dose-escalation cohmts, dose-expansion cohmts 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 [redacted] at each dose level tested that clears the DLT window for signal detection analysis to guide an RP2D.

The expansion will include:

1. Safety/efficacy cohorts in NSCLC
    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
    d. C-1: INCB059872 1 mg QoD followed by the pembrolizumab/epacadostat doublet
    e. C-3: INCB059872 2 mg QoD followed by the pembrolizumab/epacadostat doublet
    f. C-5: INCB059872 1 mg QD followed by the pembrolizumab/epacadostat doublet
    g. C-7: INCB059872 3 mg QoD followed by the pembrolizumab/epacadostat doublet
2. Safety/efficacy cohmts in CRC
    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
    d. C-2: INCB059872 1 mg QoD followed by the pembrolizumab/epacadostat doublet
    e. C-4: INCB059872 2 mg QoD followed by the pembrolizumab/epacadostat doublet
    f. C-6: INCB059872 1 mg QD followed by the pembrolizumab/epacadostat doublet
    g. C-8: INCB059872 3 mg QoD followed by the pembrolizumab/epacadostat doublet

9.2.2. Sample Size in Part 2

9.2.2.1. Safety/Efficacy Expansion Cohorts

The safety/efficacy expansion in Part 2 will include 2 cohmts 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 cohmts. The response rates for the histmical control (po), desired response rates for the combination (p1), number of subjects needed in Stage 1 (n1) and Stage 2 (n2), total number of subjects (n), first stage threshold declaring cohmt undesirable (r1), 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 cohmt in Table 56. The calculation is based on a 1-sided Type I error of 0.05 and power of 80%.

Table 56: Simon 2-Stage Design

Cohort	Tumor Type	Po	Pt	nt	nz	n	Tt	r
Expansion Cohmt 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 Cohmt A-2	MSSCRC	3%	20%	8	19	27	0	2
Expansion Cohmt 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 Cohmt B-8	MSSCRC	3%	20%	8	19	27	0	2
Expansion Cohmt 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 Cohmt C-10	MSSCRC	3%	20%	8	19	27	0	2

9.2.2.2. Sample Size for Treatment Sequencing Tumor Biopsy Cohorts

Three treatment sequencing tumor biopsy cohmts per treatment group will be emolled to evaluate epigenetic and tumor microenvironment changes. Five to 8 evaluable subjects per each tumor type will be emolled in Expansion Cohmts A-3, A-4, B-9 through B-11, and C-11 through C-13. The eligible tumor types are HNSCC, melanoma, urothelial carcinoma, and MSS CRC. Subjects with tumor types other than MSS CRC must have had disease progression on a plior PD-1 pathway–targeted agent. Ten subjects with first-line melanoma will be emolled in Expansion Cohmt 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 tme rate of subjects positive for the biomarker is 70%, the probability of observing 16 or more subjects out of25 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 obselving 6 or more subjects out of 10 subjects with the biomarker is 85% for Expansion Cohmt A-5.

9.3. Level of Significance

For the prima1y efficacy endpoints, the 1-sided Type I enor will be controlled at 0.05 for each individual cohmt expansion. For other endpoints, Cis will be repmted at a 95% confidence level. Note that this level of significance does not account for the multiple expansion cohmts.

9-4_ Statistical Analyses

9.4.1. Primary Analyses

Part 1: The clinical safety data (vital signs, ECGs, routine laboratory tests, and AEs) for subjects with advanced or metastatic solid tumors will be summarized using descriptive statistics (eg, mean, frequency) using the safety population, which is detailed in Section 9.4.4.

Part 2: The proportion of subjects with previously treated Stage IV or recunent NSCLC, Stage IV MSS CRC, and other selected solid tumors who meet the objective response critelia (CR + PR), as per RECIST v1.1, will be estimated with 95% CI.

9.4.2. Secondary Analyses

Part 1: The proportion of subjects with advanced or metastatic solid tumors who meet the objective response criteria (CR + PR), as per RECIST v1.1, will be estimated with 95% CI.

Part 2: The clinical safety data (vital signs, ECGs, routine laboratory tests, and AEs) for subjects with previously treated Stage IV or recunent NSCLC, Stage IV MSS CRC, and other select solid tumors will be summarized using descriptive statistics (eg, mean, frequency) using the safety population, which is detailed in Section 9.4.4.

Parts 1 and 2: The percentage of TIL responders for subjects with advanced or metastatic solid tumors and previously treated Stage IV or recunent NSCLC and Stage IV MSS CRC will be estimated with 95% CI. A subject is considered a TIL responder if the subject has 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.

Paits 1 and 2: PFS and DOR of subjects with advanced or metastatic solid tumors and previously treated Stage IV or recunent NSCLC and Stage IV MSS CRC will be estimated using Kaplan-Meier method as per RECIST v1.1 ifthere are enough obselvations.

[redacted]

9.4.4. Safety Analyses

9.4.4.1. Adverse Events

A TEAE is any AE either repmted for the first time or worsening of a pre-existing event after first dose of study dmg. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing to study dmg administration. Adverse events will be tabulated by the MedDRA prefened te1m and system organ class. Severity of AEs will be based on the NCI CTCAE v4.03 using Grades 1 through 4.

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

9.4.4.2. Clinical Laboratory Tests

Laboratmy test values outside the nmmal range will be assessed for severity based on the nmmal ranges for the clinical reference laboratmy. The incidence of abnmmallaboratory values and shift tables relative to baseline will be tabulated.

Laboratmy data will be classified into Grades 1 through 4 using CTCAE v4.03. The following summa1ies will be produced for the laboratory data:

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

9.4.4.3. Vital Signs

Descriptive statistics and mean change from baseline will be dete1mined for vital signs (blood pressure, pulse, respiratmy rate, and body temperature) at each assessment time. Vital sign results will be reviewed for clinically notable abnmmalities (see Table 57), and subjects exhibiting clinically notable vital sign abnmmalities will be listed. A value will be considered an "ale1t" value if it is outside the established range and shows a > 25% change from baseline.

Table 57: Criteria for Clinically Notable Vital Sign Abnormalities

Parameter	High Threshold	Low Threshold
Systolic blood pressure	> 155 rrunHg	< 85 mmHg
Diastolic blood pressure	> 100 rrunHg	< 40nunHg
Pulse	> 100 bpm	< 45 bpm
Temperature	> 38°C	< 3s.soc
Respirato1y rate	> 24/min	< 8/min

9.4.4.4. Electrocardiograms

Descriptive statistics and mean change from baseline will be dete1mined for each ECG parameter at each assessment time. Electrocardiogram results will be reviewed for clinically notable abnmmalities according to predefined crite1ia (see Table 58). Subjects exhibiting clinically notable ECG abnmmalities will be listed.

Table 58: Criteria for Clinically Notable Electrocardiogram Abnormalities

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

QTcF = Fndencta correction.

9.4.4.5. Adverse Events of Special Interest

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

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

[redacted]

[redacted]

9_5_ Analyses for the Data Monitoring Committee

Not applicable.

9_6_ Interim Analysis

In Pa1t 2, there will be a planned interim analysis for futility in Expansion Cohmts A-1, A-2, B-7, B-8, C-9, and C-10. The Simon 2-stage design will be applied to each safety/efficacy expansion cohmt independently. During Stage **1,** 8 NSCLC subjects who progressed on a PD-1 pathway-targeted agent and 8 MSS CRC subjects will be emolled. If no responses are observed in the NSCLC PD-1 failure and MSS CRC cohmts, the cohmt will be tenninated for futility. If at least 1 response is obsetved in the NSCLC PD-1 failure or MSS CRC cohmt, 19 additional NSCLC PD-1 failure or MSS CRC subjects will be emolled for Stage 2 evaluation.

Based on this early termination mle, the probability of early temlination is 0.7837 for subjects with NSCLC who are PD-1 failures and subjects with MSS CRC under the assumption of historical control response rate; the probability of early tetmination is 0.1678 for subjects with NSCLC who are PD-1 failures and subjects with MSS CRC under the assumption of desired response rate.

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

10. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

10.1. Investigator Responsibilities

This study will be performed in accordance with ethical principles that originate in the Declaration of Helsinki and conducted in adherence to the study Protocol; GCPs as defined in Title 21 of the US CFR Pa1ts 11, 50, 54, 56, and 312; ICH E6 GCP consolidated guidelines; and local regulatory requirements as applicable to the study locations.

The investigator will be responsible for:

- Pe1mitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatmy inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predete1mined plan. The investigator must allow the study monitors to review any study materials and subject records at each monitming visit.
  - Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all subjects.
  - Regulatmy inspection: Regulatmy authmities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents suppmting the eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatmy authority for the purposes of conducting an inspection.
- Obtaining infmmed consent and ensming that the study subjects' questions have been answered and the subjects fully understand study procedures:
  - Infmmed consent must be obtained before any study-related procedures are conducted, unless othe1wise specified by the Protocol.
  - Infmmed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the subject. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatmy authmities have direct access to subject records.

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

10.2. Accountability, Handling, and Disposal of Study Drug

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

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

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

Completed accountability records will be archived by the site. The investigator or designee will be expected to collect and retain all used, unused, and paltially used containers of study dmgs until verified by the study monitor (unless othe1wise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee shipment of any remaining study dmgs back to the sponsor or its designee for destmction according to institutional standard operating procedures. If local procedures mandate on-site destmction of investigational supply, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study dmgs are destroyed before monitor inspection, the monitors rely on documentation of destmction per the site standard operating procedure.

10.3. Data Management

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

The investigator will be provided with access to an EDC system so that an eCRF can be completed for each subject. Enn·ies made in the eCRF must be verifiable against source documents; if updates to the database are not possible, any discrepancies should be explained and documented. The investigator will be responsible for reviewing all data and eCRF enn·ies, and will sign and date the designated fmms in each subject's eCRF, velifying that the infmmation is hue and COlTect. The investigator is responsible for the review and approval of all que ly responses.

Protocol deviations will be identified and recorded in the Protocol Deviation fmm of the eCRF. The study monitor will reference the Monitoring Plan in order to ensure that each issue identified is approp1iately documented, repmted, and resolved in a timely manner in accordance with the plan's requirements.

10.4. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor or its designee must adhere to applicable data privacy laws and regulations. The investigator and the sponsor or its designee are responsible for ensming that sensitive infmmation is handled in accordance with local requirements (eg, HIPAA). Approp1iate consent and authorizations for use and disclosure and/or nansfer (if applicable) of protected infmmation must be obtained.

Subject names will not be supplied to the sponsor or its designee, if applicable. Only the subject number and subject's initials (subject's initials will only be recorded if allowable by local regulations) will be recorded in the eCRF, where pe1mitted; if the subject's name appears on any

other document (eg, laboratmy repo1t), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be infmmed that representatives of the sponsor or its designee, IRB or IEC, or regulatmy authorities may inspect their medical records to verify the infmmation collected, and that all personal infmmation made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

10.5. Financial Disclosure

Before study initiation, all clinical investigators pa1ticipating in clinical studies subject to FDA Regulation Title 21 CFR Palt 54 – Financial Disclosure by Clinical Investigators (ie, "covered studies") are required to submit a completed Clinical Investigator Financial Disclosure fmm that sufficiently details any financial interests and anangements that apply. For the purpose of this regulation, "clinical investigator" is defmed as any investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects, including the spouse and each dependent child of the clinical investigator or subinvestigator. These requirements apply to both US and foreign clinical investigators conducting covered clinical studies.

Any new clinical investigators added to the covered clinical study during its conduct must also submit a completed Investigator Financial Disclosure Fmm. During a covered clinical study, any changes to the financial infmmation previously repmted by a clinical investigator must be repmted to the sponsor or its designee. At the conclusion of the covered clinical study, the clinical investigators will be reminded of their obligations. In the event that the clinical investigator is not reminded, they neve1theless will remain obligated to repmt to the sponsor or its designee any changes to the financial infmmation previously repmted, as well as any changes in their fmancial infmmation for a period of 1 year after completion of the covered clinical study.

10.6. Publication Policy

By signing the study Protocol, the investigator and his or her institution agree that the results of the study may be used by the sponsor, Incyte Corporation (Incyte), for the purposes of national and intemational registration, publication, and infmmation for medical and pha1maceutical professionals. Study results will be published in accordance with applicable local and national regulations. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. The te lms regarding the publication of study results are contained in the agreement signed with the sponsor or its designee. A signed agreement will be retained by the sponsor or its designee.

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APPENDIX A- INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

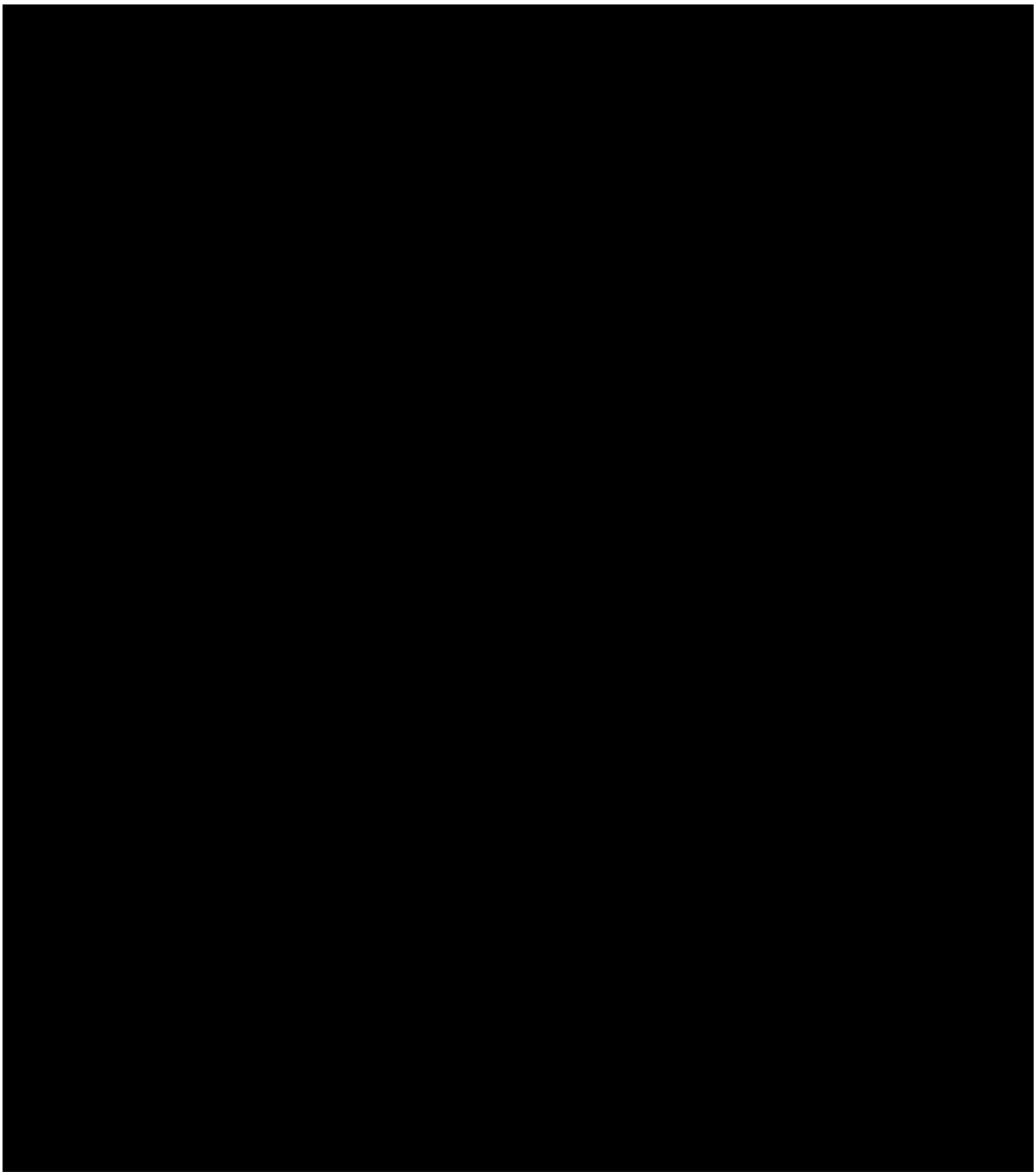
For Subjects Participating in the Study:

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

Such methods include:

- Combined (estrogen and progestogen containing) hmmonal contraception associated with inhibition of ovulation [1]
  - oral
  - intravaginal
  - transdetmal
- Progestogen-only hmmonal contraception associated with inhibition of ovulation [1]
  - oral
  - injectable
  - implantable[2]
- Intrauterine device (nJD)Z
- Intrauterine hmmone-releasing system (nJSf
- Bilateral tubal occlusion[2]
- Vasectomised partnel2,J
- Sexual abstinence[4]

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.
[2] Contraception methods that in the context of this guidance are considered to have low user dependency.
[3] Vasectomised partner is a highly effective method provided of avoiding pregnancy that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
[4] In the context of this guidance, sexual abstinence is considered a highly effective method only if defmed as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.
Source: CTFG 2014.



APPENDIX C_ PROHIBITED MONOAMINE OXIDASE INIDBITORS AND DRUGS ASSOCIATED WITH SIGNIFICANT MONOAMINE OXIDASE INHIBITORY ACTIVITY

Monoamine Oxidase Inhibitors	Drugs Associated With Significa nt Monoamine Oxidase Inhibitory Activity
Hydrazines (example phenelzine)	Meperidine
Caroxazone	Linezolid
Echinopsidine	Methylene blue
Furazolidone	
Tranylcypromine	
Brofaromine	
Metralindole	
Minapdne	
Moclobemide	
Pirlindole	
Toloxatone	
Lazbemide	
Pargyline	
Rasagiline	
Selegiline	

APPENDIX D- EASTERN COOPERATIVE ONCOLOGY GROUP PERFO ANCESTATUS

Grade	Performance Status
0	Fully active, able to cany on all predisease perf01mance without restliction.
1	Restt·icted in physically stt·enuous activity but ambulat01y and able to cany out work of a light or sedentmy nature, eg, light house work, office work.
2	Ambulat01y and capable of all selfcare but unable to cm1y out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confmed to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot cm1y on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken et al 1982.

APPENDIX E. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment (Version) 1:	18 JAN2016
Amendment (Version) 2:	08 JUL2016
Amendment (Version) 3:	20 OCT 2017
Amendment (Version) 4:	30AUG2018

Amendment 4 (30 AUG 2018)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to 1) specify that scans to confirm disease progression should be conducted at least 4 weeks and no later than 8 weeks from the initial scans showing PD and 2) remove the disease assessment and survival follow up visits.

1. Synopsis; Section 4.4, Duration of Treatment and Subject Participation; Section 5.5.2, Withdrawal Procedures; Section 6, Study Assessments (schedule of assessment Tables 29, 31, 33, 35); Section 6.4.1, Safety Follow-Up; Section 6.4.2, Disease Status Follow-Up; Section 6.4.3, Survival Follow-Up; Section 6.5, End of Study; Section 7.6.1, Assessment of Disease According to Modified RECIST v1.1; Section 7.10.2, Data Collection for Survival Follow-Up

   Description of change: Follow-up visits and contacts for disease assessment and survival will no longer be required. For Treatment Group A, reference to subject contact after the safety follow-up visit (42-49 days after EOT) have been revised. As of Amendment 4, Treatment Groups B and C are no longer applicable. No subjects have been or will be enrolled in these cohorts.

   Rationale for change: Based on an External Data Monitoring Committee's (eDMC) analysis of the ECH0-301/KEYNOTE-252 Phase 3 melanoma clinical study, Incyte made a strategic decision to stop further enrollment in the INCB 24360-206 study. The eDMC analysis determined that the ECH0-301/KEYNOTE-252 clinical study did not meet the prespecified endpoint of improvement in PFS for the combination of pembrolizumab and epacadostat compared to pembrolizumab and placebo. Of note, based on review of the safety analysis, the eDMC concluded that there were no safety concerns with the ECH0-301/KEYNOTE-252 investigational group compared to pembrolizumab alone. Data collection for disease assessment and survival follow-up is no longer required.

2. Section 5.4.2, Treatment After Initial Evidence of Radiographic Disease Progression (including Table 26); [redacted]

[redacted]

Rationale for change: This modification has been made per FDA request.

3. Synopsis; Section 4.1, Overall Study Design; Section 4.4, Duration of Treatment and Subject Participation; Section 5.2.3.1, Description and Administration

   Description of change: Text has been added to clarify that medical monitor approval is needed for those subjects with SD or better for at least 6 months who expelience disease progression and wish to be re-treated.

   Rationale for change: This is an administrative change made in order to hamonize the Synopsis and Sections 4.1 and 4.4 with Section 6.2.

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

Amendment 3 (20 OCT 2017)

Overall Rationale for the Amendment:

The primaly purpose of this amendment is to add 2 additional treatment groups, which include epigenetic pliming regimens with a bromodomain and extra-telminal protein (BET) inhibitor (INCB057643) and with a lysine-specific demethylase IA (LSDI) inhibitor (INCB059872).

This amendment includes the changes to Protocol INCB 24360-206 Amendment 2 (02 JUN 2017) summarized below. A redline version of the amendment depicting the updated and previous text is also provided.

1. Synopsis; Section 1, Introduction; Section 2, Study Objectives and Endpoints; Section 3, Subject Eligibility; Section 4, Investigational Plan; Section 5, Treatment; Section 6, Study Assessments; Section 7, Conduct of Study Assessments and Procedures; Section 9, Statistics

   Description of change: Two additional treatment groups were added to include new epigenetic pliming regimens with a BET inhibitor (INCB057643) and LSDI inhibitor (INCB059872). All relevant Protocol sections, tables, and figures have been updated accordingly.

   Rationale for change: To evaluate the addition of2 novel epigenetic agents to the combination of pembrolizumab and epacadostat.

2. Synopsis; Section 2, Study Objectives and Endpoints; Section 3.1, Subject Inclusion Criteria; Section 9, Statistics

   Description of change: The inclusion criteria were updated to enroll non-small-cell lung cancer (NSCLC) subjects with metastatic (Stage IV) or recurrent disease and to clarify that subjects with NSCLC, head and neck squamous cell carcinoma (HNSCC), and urothelial carcinoma should have documented disease progression while on a programmed death receptor-I (PD-1) pathway–targeted agent. Progression following cessation of PD-1 pathway–targeted therapy is not sufficient. All relevant Protocol sections were updated accordingly.

   Rationale for change: To clarify that the disease progression on a PD-1 pathway–targeted therapy should have occmTed while receiving PD-1 therapy, not upon relapse.

3. Synopsis; Section 3.2, Exclusion Criteria; Section 6, Study Assessments

   Description of change: A new exclusion critelion was added to exclude subjects with semm albumin < 3 g/dL. Additionally, a new exclusion criterion was added to exclude subjects with uncontrolled type I or type II diabetes mellitus (defined as HgbA1c > 8). All relevant Protocol sections, including tables, were updated accordingly.

   Rationale for change: To include new measures to confnm perfmmance status of subjects.

Synopsis; Section 4.1, Overall Study Design; Section 7.6.2, Tumor Biopsy

Description of change: A note was added to clarify that tumor tissue will be fmmalin-fixed and paraffin-embedded locally and further assessed with hematoxylin and eosin staining. A pathologist will complete a quality control fmm to document tissue quality.

Rationale for change: To specify the cunent tumor biopsy collection procedures.

5. Section 1.7.3.3, Treatment Sequencing Tumor Biopsy Cohort Indications

   Description of change: Rationale for the treatment of HNSCC, melanoma, and urothelial carcinoma was added based on the most recent prescribing information for nivolumab, pembrolizumab, and atezolizumab and prelimina1y clinical data from the ongoing clinical study INCB 24360-202.

   Rationale for change: To provide rationale for the inclusion of the 3 additional tumor types that will be enrolled in the treatment sequencing tumor biopsy cohmts during Pait 2, dose expansion.

6. Section 5.4.1.3.7, Procedures for Immune-Mediated Myocarditis

   Description of change: Dose modification and management guidelines were added for immune-mediated myocarditis.

   Rationale for change: To provide guidance for potential immune-related myocarditis.

7. Section 5.6.3, Prohibited Medications

   Description of change: Melatonin and propofol were removed from the list of prohibited medications, as they are now pel mitted.

   Rationale for change: After a review of the cunent literature, there is no longer a need to exclude melatonin supplements. Propofol was removed as it is not a significant UGTIA9 inhibitor.

8. Section 6.2, Treatment

   Description of change: Clarification that possible re-treatment with pembrolizumab or the combination may be allowed wit it has been discussed and approved by the medical monitor. mandatmy biopsies will not be perfmmed.

   Rationale for change: To provide details for possible re-treatment with pembrolizumab or the combination.

9. Section 9, Statistics (Table 55: Probability of Dose De-Escalation for Various Dose-Limiting Toxicity Rates)

   Description of change: Probabilities of dose de-escalation for various dose-liiniting toxicity (DLT) rates were updated in Table 55.

   Rationale for change: To provide conect probabilities of dose de-escalation for various DLT rates.

10. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment, including the addition of summary of changes for all amendments to Appendix E.

Amendment 2 (02 JUN 2017)

Overall Rationale for the Amendment:

The primaly purpose of this amendment is to extend the length of azacitidine treatment and add new expansion cohmts to evaluate different sequences of treatment for the 3 study dmgs.

This amendment includes the changes to Protocol INCB 24360-206 Amendment 1 (04 NOV 2016) summarized below. A redline version of the amendment depicting the updated and previous text is also provided.

1. Synopsis; Section 2.1.1, Primary Ob[redacted]; Section 2.2.1, Primary Endpoints; [redacted] Section 9.4.1, Primary Analyses; **Section 9.4.2, Secondary Analyses; Section 9.4.3,** Other Analyses

   Description of change: The plimary and secondaly efficacy objectives and endpoints were revised so that [redacted]ective rate is evaluated standard RECIST v1.1. [redacted]

   Rationale for change: Updated to be in alignment with the primary analysis, which will be per RECIST v1.1. [redacted]

[redacted]

3. Synopsis; Section 4.1, Overall Study Design; Section 4.4, Duration of Treatment and Subject Participation; Section 5.2.3.1, Azacitidine Description and Administration; Section 6, Study Assessments (Tables 18, 20, 22, and 24, Schedules of Assessments); Section 6.2, Treatment

   Description of change: The number of cycles of azacitidine was increased from a maximum of 2 to 6. All subjects will receive 5 doses of azacitidine in Cycles 1 through 3. Subjects who remain on treatment beyond the Week 9 scan should continue to receive azacitidine until the second on-study scan (up to the Week 18 scan, for a maximum of 3 additional cycles).

   Rationale for change: Recent research suggests that the response time for epigenetic agents may va1y. The combination of azacitidine with pembrolizumab and epacadostat has been well tolerated to date, and additional cycles of azacitidine have been added to maximize potential efficacy.

4. Synopsis; Section 1, Introduction; Section 3.1, Subject Inclusion Criteria; Section 4.1, Overall Study Design; Section 4.1.2 Part 2: Expansion; Section 4.3.1, Number of Subjects; Section 6, Study Assessments (Tables 18-25, Schedules of Assessments and Laboratory Assessments); Section 7.8.1, Blood Sample Collection

   Description of change: The safety/efficacy expansion cohmt for non-small-cell lung cancer (NSCLC) subjects who are PD-1–naive has been removed. Safety/efficacy expansion cohmts remain for subjects with NSCLC who have had disease progression on a PD-1–targeted therapy (A-1) and microsatellite stable colorectal cancer (MSS CRC; A-2). Additional treatment sequencing tumor biopsy cohmts (A-3 through A-5) will emoll 4 specific tumor types and include 3 tumor biopsies. Inclusion cliteria were added for each specific tumor type, and Protocol sections have been updated throughout.

   Rationale for change: The PD-1-naive NSCLC expansion cohort was removed because of expected emollment difficulty. The additional treatment sequencing tumor biopsy cohmts (A-3 through A-5) have been added to identify epigenetic changes and changes in the tumor microenvironment induced by each of the components of the regimen in each of the additional tumor types.

5. Synopsis; Section 3.1, Subject Inclusion Criteria; Section 4.1, Overall Study Design; Section 6, Study Assessments (Tables 18, 20, 22, and 24, Schedules of Assessments); Section 7.6.2, Tumor Biopsy

   Description of change: The tumor biopsy requirements were updated to require fresh baseline tumor biopsies rather than archival.

   Rationale for change: The tumor biopsy study procedures were amended to require fresh biopsies to more precisely evaluate changes in the tumor microenvironment.

6. Synopsis; Section 3.1, Subject Inclusion Criteria

   Description of change: Added a note in the inclusion criteria for Pa1t 2 to specify that subjects must have failed available therapies that confer clinical benefit as indicated for each of the specific tumor types, unless they are ineligible, intolerant, or refused standard treatment.

   Rationale for change: To specify that all subjects should have failed available approved therapies with the exception of being ineligible, intolerant, or refused standard-of-care therapies.

7. Synopsis; Section 4.1.1, Part 1: Dose Escalation

   Description of change: Text has been added to allow for determination of a dose-limiting toxicity (DLT) by the principal investigators and medical monitor in ce1tain cases where toxicities due to the combination agent may be indistinguishable from toxicities due to immunotherapy.

   Rationale for change: To allow for flexibility with dete1mining a DLT in situations where there are overlapping toxicities and the subject has received < 75% dose intensity.

8. Synopsis; Section 9, Statistics

   Description of change: The statistical sections were updated to reflect the changes of the Part 2 expansion. Detail on the interim analysis was provided, and other minor changes were made.

   Rationale for change: To update the planned analyses based on the changes to the expansion cohmts and provide additional detail for the intelim analysis.

9. Section 1.4, Overview of Azacitidine

   Description of change: Azacitidine background was updated to include fmther details from the European Union Summmy of Product Characteristics (SmPC).

   Rationale for change: To add specific details from the SmPC.

10. Section 1.6.1, Risks from Epacadostat; Section 5.4.3, Procedures for Subjects Exhibiting Serotonin Syndrome; Section 8.4, Adverse Events of Special Interest

    Description of change: The sections were updated to clarify that serotonin syndrome is an uncommon risk, provide data from the cunent clinical studies, and provide an ove1view of the existing preclinical data.

    Rationale for change: Updated in alignment with cunent epacadostat program infmmation.

11. Section 6.4.1, Safety Follow-Up

    Description of change: The repmting requirements for AEs and SAEs were conected to specify that AEs should be repmted up until at least 42 days after the last dose of study dmg and 90 days for SAEs.

    Rationale for change: Conected to be in alignment with Sections 8.1.2 and 8.3.2.

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

Amendment 1 (04 NOV 2016)

Overall Rationale for the Amendment:

The primaly purpose of this amendment is to address FDA's October 20, 2016, clinical infmmation request.

This amendment includes the changes to Protocol INCB 24360-206 (30 SEP 2016) summarized below. A redline version of the amendment depicting the updated and previous text is also provided.

1. Synopsis, Part 1: Dose Escalation, Estimated Number of Subjects, Statistical Methods; Section 4.1.1, Part 1: Dose Escalation; Section 4.3.1, Planned Number of Subjects; Section 9.2.1, Sample Size in Part 1

   Description of change: The study was switched from a 3 + 3 to a 3 + 3 + 3 dose-escalation design. The description of the dose-escalation scheme and estimated number of subjects was updated to reflect this change.

   Rationale for change: To provide a more thorough assessment of the maximum tolerated dose (MTD).

2. Synopsis, Part 1: Dose Escalation; Section 4.1.1, Part 1: Dose Escalation, Table 1 (Dose Levels: Treatment Group A)

   Description of change: Additional clarification was added to specify the critelia for dose escalation from Cohmt 1 to Cohmt 2. The tables showing the planned dose levels were updated to present the 2 options for escalation of the second cohmt.

   Rationale for change: FDA request.

3. Synopsis, Key Inclusion Criteria; Section 3.1, Subject Inclusion Criteria

   Description of change: Revised inclusion criterion #7 to specify that the contraception period for males and female must extend until 120 days after the last dose of study dmg. fuclusion cliterion #10 was conected to state that subjects in Cohmt A1 must be checkpoint inhibitor–naive. Added clarification to inclusion cliterion #12 to specify that microsatellite instability testing should be perfmmed locally.

   Rationale for change: FDA request. The bilth control requirements have been updated to 120 days after the last dose of study dmg to be consistent with the pembrolizumab package inselt.

4. Synopsis, Key Exclusion Criteria; Section 3.2, Subject Exclusion Criteria

   Description of change: fu exclusion critelion #14, a note was added to specify that in Part 2, subjects with treated hepatitis B are eligible as long as they have no evidence of active infection. A new exclusion critelion (#28) was added to specify that subjects with bleeding associated with tumors in proximity to major blood vessels are excluded except with medical monitor approval.

   Rationale for change: FDA request to consider expanding the eligibility crite1ia. The new critelion #28 was added to exclude subjects who are at high risk for early progression and bleeding.

5. **Section 1.5.2, Justification for the Treatment Regimen**

   Description of change: Background infmmation on the epacadostat combination dose from the INCB 24360-202 and INCB 24360-301 studies was added.

   Rationale for change: To provide infmmation regarding the clinical experience with an epacadostat 300 mg BID dose.

6. **Section 5.4.1.1, Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose**

   Description of change: Three new DLTs were added to specify that Grade 4 vomiting and dianhea, Grade 4 electrolyte abnmmalities, and Grade 4 systemic reactions would be considered DLTs. The Grade 4 thrombocytopenia and neutropenia DLT definition was revised to define Grade 4 thrombocytopenia of any duration and Grade 4 neutropenia lasting > 3 days as DLTs.

   Rationale for change: FDA request.

7. **Incorporation of administrative changes.** Other minor administrative changes and inconsistencies in the protocol have been incorporated.

Signature Manifest

Document Number: IC-DEV-PROT-AMEND-0384 **Revision:** 0

Title: INCB 24360-206 Protocol Amendment 4

All dates and times are in Eastern Standard Time.

APPROVAL: 24360-206 Amendment 4

Approval and Release

Name/Signature	Title	Date	Meaning/Reason
[redacted]	[redacted]	30 Aug 2018, 11:48:15 AM	Approved
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