STATISTICAL ANALYSIS PLAN

INCB024360 and MK-3475

INCB 24360-202 / NCT02178722

A Phase 1/2 Study Exploring the Safety, Tolerability, and Efficacy of MK-3475 in Combination With INCB024360 in Subjects With Selected Solid Cancers

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This study is being conducted in compliance with Good Clinical Practice, including the archiving of essential documents.

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LIST OF ABBREVIATIONS

The following abbreviations and special terms are used in this Statistical Analysis Plan.

Term	Explanation
ACTH	adrenocorticotropic hormone
AE	adverse event
AEOSI	adverse event of special interest
AFP	alfa fetoprotein
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC_{0-12h}	area under the concentration-time curve from hour 0 to 12
AUC_{0-t}	area under the concentration-time curve from time zero (predose) to time of last observed quantifiable concentration within a subject across all treatments
BID	twice daily
BUN	blood urea nitrogen
CA 125	cancer antigen 125
CEA	carcinoembryonic antigen
CI	confidence interval
CL/F	apparent oral dose clearance
C_{max}	maximum observed concentration
CR	complete response
CRC	colorectal cancer
CRP	C-reactive protein
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	diffuse large B-cell lymphoma
DLCO	diffuse lung capacity for carbon monoxide
DLT	dose-limiting toxicity
DoR	duration of response
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end of treatment
EU	European Union
FDA	Food and Drug Administration

Term	Explanation
$FEF_{25\%-75\%}$	forced expiratory flow 25% to 75%
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GU	genitourinary
HBc	hepatitis B core antibody
HBe	hepatitis Be
HBeAg	hepatitis Be antigen
HBs	hepatitis B surface antigen
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDV	hepatitis D virus
HPV	human papillomavirus
IDO1	indoleamine 2,3 dioxygenase-1
IgG	immunoglobulin G
INR	international normalized ratio
irRECIST	modified Response Evaluation Criteria In Solid Tumors
IV	intravenous
LDL	low-density lipoprotein
LFT	liver chemistry test
LH	luteinizing hormone
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MEL	melanoma
MSI	microsatellite-instability
MTD	maximum tolerated dose
NE	not evaluable
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PAD	pharmacologically active dose
PD	progressive disease
PD-1	programmed death receptor 1
PD-L1	programmed death ligand 1

Term	Explanation
PEF	peak expiratory flow
PFS	progression-free survival
PR	partial response
PK	pharmacokinetic
PT	prothrombin time
Q3W	every 3 weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	recommended Phase 2 dose
SAP	Statistical Analysis Plan
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SJS	Stevens-Johnson syndrome
SMQ	Standardised MedDRA Queries
$t_{½}$	terminal phase half-life
T_{max}	time of occurrence of maximum concentration
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
TNBC	triple negative breast cancer
TPS	tumor proportion score
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
VA	alveolar volume
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

Note: Due to a strategic decision to close the study to future enrollment reflected in Protocol Amendment 10, the primary purpose of SAP Amendment 4 is to document reductions from Protocol-defined analyses for an abbreviated CSR.

INCB 24360-202 is a Phase 1/2 study of INCB024360 (epacadostat) administered in combination with MK-3475 (Keytruda®, pembrolizumab). Phase 1 will be open-label and will include subjects with non–small cell lung cancer (NSCLC), melanoma (checkpoint-naive, primary refractory, and relapsed), transitional carcinoma of the genitourinary (GU) tract, renal cell carcinoma (RCC), triple negative breast cancer (TNBC), adenocarcinoma of the endometrium, or squamous cell carcinoma of the head and neck (SCCHN), and Phase 2 will include open-label expansion cohorts including subjects with NSCLC, melanoma, TNBC, SCCHN, ovarian cancer, transitional cell carcinoma of the GU tract, RCC, diffuse large B-cell lymphoma (DLBCL), MSI (microsatellite-instability)-high colorectal cancer (CRC), gastric cancer, and hepatocellular carcinoma (HCC). Epacadostat represents a novel, potent, and selective inhibitor of the enzyme indoleamine 2,3 dioxygenase-1 (IDO1) in both human tumor cells and human dendritic cells. Pembrolizumab is a potent and highly selective humanized monoclonal antibody of the immunoglobulin (Ig)G4/kappa isotype directed against programmed death receptor 1 (PD-1).

A detailed description of the investigational product, target patient population, rationale for doses to be examined, and potential risks and benefits of treatment with epacadostat and pembrolizumab is provided in the Protocol, Section 1. The purpose of this Statistical Analysis Plan (SAP) is to define the methodology for analyzing and summarizing the data collected during the conduct of Study INCB 24360-202.

2. STUDY INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on INCB 24360-202 Protocol Amendment 10 dated 02 JUL 2018 and case report forms (CRFs) approved on 05 APR 2019 unless superseded by an amendment, this SAP will be effective for all subsequent Protocol amendments and eCRF (electronic case report form) versions.

2.2. Study Objectives

2.2.1. Primary Objectives

The primary objectives of the study are:

- Phase 1: To evaluate the safety, tolerability, and dose-limiting toxicities (DLTs) of a pharmacologically active dose (PAD) of INCB024360 administered in combination with MK-3475 in advanced or metastatic solid tumors, and to select doses for further evaluation.
- Phase 2 expansion cohorts: To assess objective response rate (ORR) in subjects with select cancers as measured by modified RECIST (irRECIST) v1.1 for selected solid tumors and the Lugano Classification (Cheson et al 2014) for DLBCL.

2.2.2. Secondary Objectives (Phase 2)

The secondary objectives of the study are:

- To evaluate the preliminary antitumor activity of the combination of INCB024360 and MK-3475 in subjects with selected advanced solid tumors and DLBCL, including duration of response (DoR), progression-free survival (PFS), and duration of disease control as measured by irRECIST v1.1 for solid tumors or the Lugano Classification (Cheson et al 2014) for DLBCL.
- To evaluate the efficacy with respect to ordinal categorical response score, calculated as the following:
  - 1 = Complete response (CR) per irRECIST v1.1
  - 2 = Very good response, defined as > 60% tumor reduction
  - 3 = Minor response, defined as > 30% to ≤ 60% tumor reduction
  - 4 = Stable disease (SD) per irRECIST v1.1
  - 5 = Progressive disease (PD) per irRECIST v1.1
- To evaluate the efficacy with respect to overall survival (OS).
- To evaluate the safety and tolerability of INCB024360 in combination with MK-3475.

2.3. Study Endpoints

2.3.1. Primary Endpoints

- Phase 1: Safety and tolerability will be assessed by monitoring frequency, duration, and severity of adverse events (AEs), through physical examinations, by evaluating changes in vital signs and electrocardiograms (ECGs), and through clinical laboratory blood and urine sample evaluations.
- Phase 2 expansion cohorts: ORR will be assessed based on irRECIST v1.1 for select solid tumors and the Lugano Classification (Cheson et al 2014) for DLBCL.

2.3.2. Secondary Endpoints (Phase 2)

- Ordinal categorical response score, determined by radiographic disease assessments per irRECIST v1.1. The 5-category ordinal response endpoint is determined at a given timepoint by classifying response into one of the following groups: CR; very good response, defined as partial response (PR) with percent reduction from baseline in tumor line length > 60%; minor response, defined as PR with percent reduction from baseline in tumor line length > 30% to ≤ 60%; SD; and PD.
- Duration of response determined by radiographic disease assessment defined as the time from earliest date of disease response until earliest date of disease progression.
- Progression-free survival determined from treatment start date until first date for confirmed disease progression or death.
- Duration of disease control (including CR, PR, and SD) measuring from treatment start date until the earliest date of disease progression for subjects whose best response is SD or better.
- Overall survival determined from the date of first dose until death due to any cause.
- Safety and tolerability of the treatment regimens through assessment of AEs and changes in safety assessments, including laboratory parameters.

[redacted]

3. STUDY DESIGN

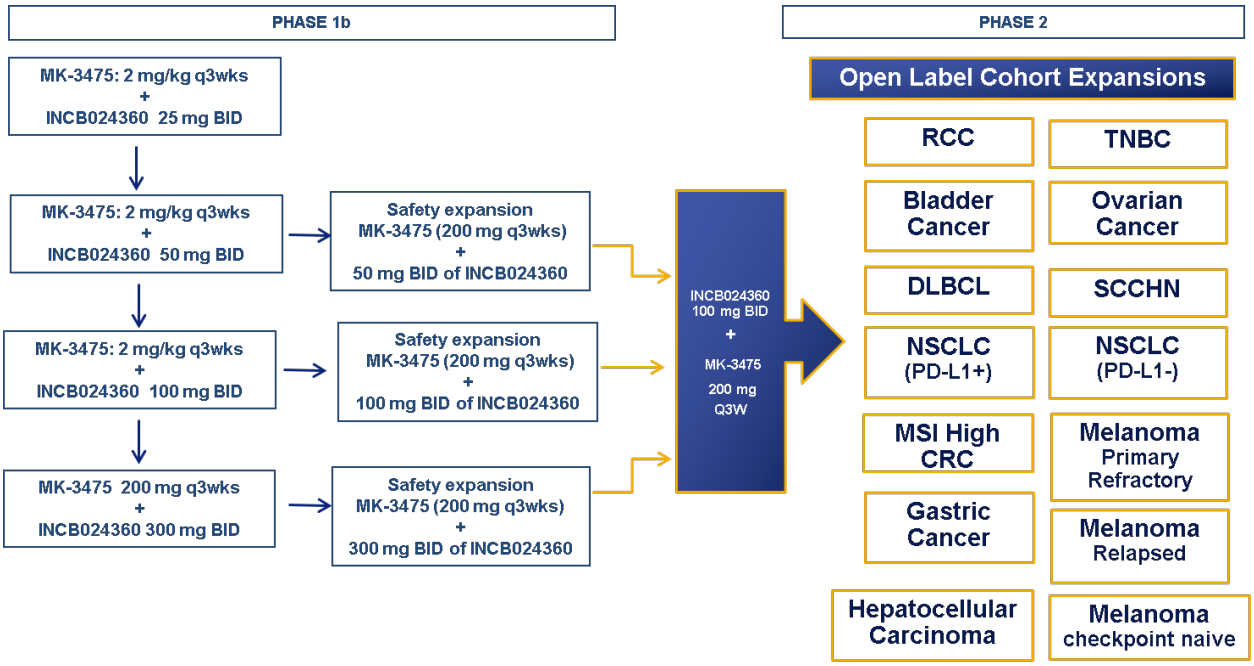
Note: Due to a strategic decision to close the study to future enrollment reflected in Protocol Amendment 10, the primary purpose of SAP Amendment 4 is to document reductions from Protocol-defined analyses for an abbreviated CSR.

This is a Phase 1/2 study, with Phase 1 being a dose escalation of epacadostat in combination with pembrolizumab in subjects with selected advanced or metastatic solid tumors and Phase 2 being an open-label expansion in subjects with select solid tumors as well as DLBCL.

The dose-escalation phase (Phase 1) will be open-label and utilize a 3 + 3 + 3 design that will identify the maximum tolerated dose (MTD) or PAD of epacadostat in combination with pembrolizumab in subjects with the following selected solid tumors: Stage IIIB, Stage IV, or recurrent NSCLC, melanoma, transitional cell carcinoma of the GU tract, RCC, TNBC, adenocarcinoma of the endometrium, or SCCHN who have disease progression on at least 1 line of therapy for advanced or metastatic cancer (except melanoma). Phase 1 will include up to 3 safety expansion cohorts of up to 9 subjects each. The first safety expansion will enroll melanoma subjects only at 50 mg twice daily (BID) once the preliminary safety of the 50 mg BID cohort is established, a second safety expansion will open at 100 mg BID, and, if tolerated, a third safety expansion may occur at 300 mg BID. The recommended Phase 2 dose (RP2D) will be selected from the evaluated safety expansions. At the sponsor's discretion, the second and third safety expansion cohorts may be limited to subjects with specific cancer types among those included in Phase 1 (the tumor-specific determination for this safety expansion will be determined at the time of expansion by the study sponsor). The safety expansion cohorts at the doses lower than the current dose level being tested may begin enrolling during the DLT waiting period of the remaining cohort escalations. Enrollment priority goes to the current dose level being evaluated.

The Phase 2 cohort expansions will further explore the safety and efficacy of the RP2D (determined in Phase 1 to be 100 mg BID) of INCB024360 in combination with MK-3475. Phase 2 will enroll subjects with the following select tumors: melanoma, NSCLC, transitional cell carcinoma of the GU tract, TNBC, SCCHN, ovarian cancer, clear cell RCC, MSI high CRC, DLBCL, gastric cancer, and HCC. There will be 2 NSCLC cohorts in the Phase 2 expansion. For the NSCLC cohorts, 1 cohort will include subjects with PD-L1 high expression (defined as tumor proportion score (TPS) ≥ 50%) and a second cohort will include subjects with low/negative or indeterminate PD-L1 expression (low/negative defined as TPS 0%-49%). There will also be 3 melanoma cohorts; 1 cohort will include subjects who are prior checkpoint-naive (anti–PD-1 or anti–PD-L1 directed therapy), a second cohort will include subjects with primary refractory disease, and a third cohort will include subjects with relapsed disease. Approximately 18 to 42 subjects per cohort will be enrolled (for a total of approximately 446 subjects) to further characterize the efficacy in these select tumor types. See Figure 1 for the overall study design.

Figure 1: Study Design



3.1. Phase 1 Dose-Escalation Design

Phase 1 is the dose-escalation phase, which will include cohorts of subjects treated with epacadostat BID at initial doses of 25 mg BID, 50 mg BID, and 100 mg BID in combination with pembrolizumab 2 mg/kg every 3 weeks (Q3W), and epacadostat 300 mg BID in combination with pembrolizumab 200 mg Q3W. Interim dose levels of 75 mg daily (50 mg in the morning/ 25 mg in the evening), 75 mg BID, or 200 mg BID may be evaluated if DLTs occur at 50 mg BID, 100 mg BID, or 300 mg BID following the review of available safety data at the Dose Escalation/Cohort Review meetings. One treatment cycle will consist of 21 days. A minimum of 3 subjects will be enrolled and treated in each cohort, and all 3 subjects will be observed for a minimum of 42 days (6 weeks) before the subsequent cohort begins enrollment. Subjects must have received the cohort-specific dose of epacadostat for at least 80% of the doses during the 42-day DLT observation period, and must have received 2 doses of pembrolizumab during that

42-day period, or must have experienced a DLT to be included in the cohort review for DLTs. Additional subjects will be enrolled in a cohort to achieve the minimum of 3 evaluable subjects if dropouts or dose interruptions or reductions occur that result in a subject being nonevaluable for DLTs. When the preliminary safety of 50 mg BID and 100 mg BID has been established, additional subjects with melanoma will be enrolled at 50 mg BID for a total of 9 subjects. An additional safety cohort will also be opened at 100 mg BID in parallel to 300 mg BID being tested. This may also be limited to subjects with melanoma, NSCLC, or specific cancer types from among those included in Phase 1 at the sponsor's discretion. If 300 mg BID is also determined to be well tolerated, an additional safety cohort may also be enrolled that, at the sponsor's discretion, may be limited to specific cancer types from among those included in Phase 1. The RP2D will be selected from the evaluated safety expansions. All subjects in these safety expansions will be treated with pembrolizumab 200 mg Q3W.

3 + 3 + 3 Design: The dose of epacadostat will be escalated if 0 of the first 3 evaluable subjects enrolled experience a DLT. If > 1 of the first 3 evaluable subjects enrolled experience a DLT, the prior dose level will be considered the MTD. If 1 of the first 3 evaluable subjects enrolled experience a DLT, the cohort will be expanded to include 3 additional evaluable subjects. If 1 of the 6 evaluable subjects enrolled in the expanded cohort experience a DLT, dose escalation to the next dose level may occur. If 2 of 6 subjects experience a DLT that cohort will be expanded to 9 subjects. If ≥ 2 of 3, 3 of 6, or 3 of 9 subjects experience DLTs within a cohort, then that dose level will be determined to have exceeded the MTD and the prior dose level will be considered the MTD or an intermittent dose may be tested.

For the safety expansion cohorts, if < 4 of the first 9 evaluable subjects experience a DLT at the given dose level, the dose will be deemed tolerable. If ≥ 4 of the first 9 evaluable subjects experience a DLT in the safety expansions, then the next lower dose level of epacadostat will be deemed the RP2D. The RP2D will be selected from one of the doses deemed tolerable (as defined above).

If at least 25 mg BID cannot be combined safely with pembrolizumab 2 mg/kg, other alternative dose schedules (ie, intermittent dosing) of epacadostat may be tested, if needed, following the review of available safety data at the Dose Escalation/Cohort Review meetings. If an alternate schedule is tested and determined to be safe, re-escalation of epacadostat according to Table 1 will proceed with pembrolizumab 2 mg/kg Q3W.

The cohorts and dose levels are shown in Table 1 for the 2 mg/kg Q3W schedule of pembrolizumab and in Table 2 for the 200 mg Q3W safety expansion.

Table 1: Phase 1 Dose-Escalation Schema for Daily Epacadostat in Combination With Pembrolizumab Q3W

Daily Dose[a] of Epacadostat	Dose of Pembrolizumab (Q3W)
25 mg BID orally	**2 mg/kg IV**
50 mg BID orally	2 mg/kg IV
100 mg BID orally	2 mg/kg IV
300 mg BID orally[b]	200 mg IV

[a] Interim dose levels of 75 mg daily (50 mg in the morning/25 mg in the evening), 75 mg BID, or 200 mg BID may be evaluated if DLTs occur at 50 mg BID, 100 mg BID, or 300 mg BID following the review of available safety data at the Dose Escalation/ Cohort Review meetings.

[b] Based on Study INCB 24360-101, in which the average kynurenine inhibition after doses of 100 mg BID and 300 mg BID was 89% and 94%, respectively, a final escalation of epacadostat 300 mg BID may be evaluated but will be tested with the flat dose of pembrolizumab 200 mg.

Table 2: Phase 1 Safety Expansion for Daily Epacadostat in Combination With Pembrolizumab Q3W

Daily Dose of Epacadostat	Dose of Pembrolizumab (Q3W)
50 mg BID	200 mg IV
100 mg BID	200 mg IV
300 mg BID[a]	200 mg IV

[a] The RP2D will be selected from 1 of the safety expansions enrolled (50 mg BID, 100 mg BID, or 300 mg BID).

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

3.1.1. Definition of Dose-Limiting Toxicities

A DLT will be defined as the occurrence of any treatment-emergent adverse event (TEAE) in Table 3 occurring up to and including Study Day 42 (6-week observation period). Dose-limiting toxicities include all TEAEs of the specified grades, regardless of investigator attribution or relatedness. Only toxicities with a clear alternative explanation (eg, due to disease progression) or transient (≤ 72 hours), abnormal laboratory values without associated clinically significant signs or symptoms based on investigator determination can be deemed a non-DLT.

Table 3: Criteria for Defining Dose-Limiting Toxicities

Toxicity
Hematologic Toxicities: • Any Grade 4 thrombocytopenia or neutropenia lasting > 7 days
Nonhematologic Toxicities: • Any Grade 4 toxicity • Any Grade 3 or 4 AST, ALT, or total bilirubin elevation • Any other Grade 3 toxicity EXCLUDING: – Nausea/vomiting controlled by medical intervention within 72 hours – Grade 3 rash in the absence of desquamation, no mucosal involvement, does not require systemic steroids, and resolves to Grade 1 by the next scheduled dose of pembrolizumab or 14 days, whichever is longer. • Episcleritis, uveitis, or iritis of Grade 2 or higher
General: • If subjects are unable to receive 75% of epacadostat or 2 doses of pembrolizumab during the DLT observation period because of toxicity, even if the toxicity does not meet DLT criteria defined above. • Greater than 2 week delay in starting Cycle 3 because of a treatment-related toxicity, even if the toxicity does not meet DLT criteria defined above.

3.2. Phase 2 Cohort Expansion

The purpose of the cohort expansions is to gather additional safety, tolerability, preliminary efficacy, [redacted] information regarding the combination of INCB024360 and MK-3475 200 mg. Once the safety profile of all doses tested has been characterized and the RP2D of combined administration of INCB024360 and MK-3475 has been defined, the cohort expansions will be initiated at the RP2D (determined in Phase 1 to be 100 mg BID). Fourteen expansion cohorts will be restricted to NSCLC (2 cohorts: PD-L1 positive and PD-L1 low/negative or indeterminate), melanoma (3 cohorts: checkpoint-naive, primary refractory, and relapsed), transitional cell carcinoma of the GU tract, TNBC, SCCHN, ovarian cancer, DLBCL, MSI high CRC, clear cell RCC, gastric cancer, and HCC. Continuous evaluation of toxicity events in the cohort expansions will be performed throughout enrollment in the expansion cohorts. If the rate of DLTs exceeds 40%, the findings will be reviewed and further enrollment may be interrupted until the sponsor(s), investigators, and regulatory authorities, if applicable, have determined the appropriate course of action. If an expansion cohort is discontinued due to toxicity, a new cohort may be initiated at a previously tested lower dose level.

In each of the cohorts, approximately 18 to 42 subjects will be enrolled to allow for a more precise estimate of ORR in subjects with these tumors and determine whether a target response rate (20%-62%) is likely.

3.3. Level of Significance

The level of significance for the primary endpoint in Phase 2 is 1-sided 5%, which is deemed acceptable for a proof-of-concept study.

3.4. Sample Size Considerations

3.4.1. Sample Size for the Phase 1 Portion of the Study

The primary objective of the open-label Phase 1 portion of the study is to determine the MTD and DLT of epacadostat in combination with pembrolizumab. The total number of subjects will depend on the number of dose levels tested before the MTD is established. Approximately 54 subjects (3-9 subjects per dose level for 4 dose levels plus an additional 9 subjects treated at 50 mg BID, 100 mg BID and potentially at 300 mg BID) will be included based on the dose escalation. Dose escalation will follow a 3 + 3 + 3 design algorithm, as defined in Section 3.1. Based on this algorithm, 3 evaluable subjects are enrolled in each cohort with a maximum of 9 subjects at any dose level (except for MTD or PAD, where a total of 9 subjects will be treated to further evaluate safety and confirm it as the RP2D).

3.4.2. Sample Size for the Phase 2 Expansion Portion of the Study

The sample size of 18 to 42 subjects is expected to be enrolled in each of the 14 response expansion cohorts (ie, NSCLC PD-L1 high, NSCLC PD-L1 low/negative or indeterminate, melanoma, transitional cell carcinoma of the GU tract, TNBC, ovarian cancer, SCCHN, DLBCL, RCC, MSI-high CRC, gastric cancer, HCC). The sample size for each independent cohort yields a power of 80% to detect an increase in ORR by about 20% (Ha) from historical response rate (H0). This assumes a 1-sided alpha of 5% and 10% lost to follow-up. See details in Table 4.

A Simon 2-stage design will be used for the primary refractory and relapsed melanoma cohorts. In the first stage for the primary refractory cohort, 8 subjects will be enrolled. If at least 1 response is observed in those 8 subjects, an additional 19 subjects will be enrolled, for a total sample size of 27 subjects. The power for this design is 80% and the Type I error is 3.2%.

In the first stage for the relapsed melanoma cohort, 11 subjects will be enrolled. If at least 2 responses are observed in those 11 subjects, an additional 7 subjects will be enrolled, for a total sample size of 18 subjects. The power for this design is 80% and the Type I error is 2.7%.

Table 4: Sample Size Calculation for Each Cohort: Comparing With a Known Proportion

Tumor Type	ORR		Sample Size
	H0	Ha	
NSCLC high positive (PD-L1 TPS ≥ 50%)	36%	56%	42
NSCLC low/negative or indeterminate (PD-L1 TPS < 50% or indeterminate)	12%	32%	25
Melanoma (immune checkpoint–naive)	32%	52%	40
Transitional cell carcinoma of the GU tract	24%	44%	36
TNBC	19%	39%	32
Ovarian cancer	20%	40%	33
SCCHN	19%	39%	32
DLBCL	36%	57%	37
RCC	25%	45%	36
MSI-high CRC	57%	80%	29
Gastric cancer	14%	34%	27
HCC	19%	39%	32
Melanoma (primary refractory)	3%	20%	27[a]
Melanoma (relapsed)	10%	35%	18[a]
Total			**446**

[a] Maximum possible sample size for Simon 2-stage design. Actual sample size may be less.

3.5. Schedule of Assessments

All study assessments will be performed as indicated in the schedules of assessments for the Q3W schedule (refer to Tables 12 and 13 in Protocol Amendment 10). The order of assessments is suggested by the order of mention within the schedules.

4. DATA HANDLING DEFINITIONS AND CONVENTIONS

4.1. Scheduled Study Evaluations and Study Periods

4.1.1. Day 1

Day 1 is the date of first dose of epacadostat or pembrolizumab.

4.1.2. Study Day

The study day at a visit or reporting date will be calculated by the visit or reporting date minus the Day 1 date plus 1 (visit date – Day 1 date + 1). This study day will be subtracted by 1 if it is ≤ 0, so that a study day of 0 will never occur. A study day of -1 indicates 1 day before Day 1.

4.1.3. Scheduled Visits

Study evaluations in weeks or days from Day 1 are presented in the Schedule of Assessments.

4.1.4. Baseline Assessments

Baseline is defined as the last nonmissing measurement obtained before the first dose of epacadostat or pembrolizumab is administered.

4.1.5. Last Available Value

The last available value is the last nonmissing measurement obtained after starting epacadostat or pembrolizumab and within 90 days after the last dose of epacadostat or pembrolizumab.

4.1.6. Cycle Length and Duration

Cycle 1 Day 1 is defined as the day of the first dose of epacadostat or pembrolizumab. One treatment cycle consists of 21 days. The first cycle of therapy is defined as the period beginning with the first dose of epacadostat or pembrolizumab and ending the earlier of: (1) 21 calendar days (inclusive) later or (2) permanent discontinuation of epacadostat. Subsequent cycles have Day 1 as the corresponding visit date associated with the corresponding cycle.

4.2. Variable Definitions

4.2.1. Prior and Concomitant Medication

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

Concomitant medication is defined as any nonstudy drug that is:

- Started before the date of first administration of epacadostat or pembrolizumab and is ongoing throughout the study or ends on/after the date of first study drug administration.
- Started on/after the date of first administration of epacadostat or pembrolizumab and is ongoing or ends during the course of study drug administration.

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

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

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

5. STATISTICAL METHODOLOGY

5.1. General Methodology

Unless otherwise noted, SAS® software (SAS Institute Inc, Cary, NC; version 9.1 or later) will be used for the generation of all tables, graphs, and statistical analyses. Descriptive summaries for continuous variables will include, but not be limited to, the number of observations, mean, standard deviation, median, minimum, and maximum. Descriptive summaries for categorical variables will include the number and percentage of subjects in each category.

For the dose-escalation portion of the study, the safety evaluable population will be used for all safety analyses. For the cohort portion of the study, the safety evaluable population will be used for all safety analyses, and the efficacy evaluable population will be used for all efficacy analyses. [redacted]

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

5.2. Treatment Groups

Subjects will be summarized overall and based on the dose regimen initially assigned:

- Pembrolizumab 2 mg/kg Q3W intravenously (IV) + epacadostat 25 mg BID
- Pembrolizumab 2 mg/kg Q3W IV + epacadostat 50 mg BID
- Pembrolizumab 2 mg/kg Q3W IV + epacadostat 100 mg BID
- Pembrolizumab 200 mg Q3W IV + epacadostat 300 mg BID
- Pembrolizumab 200 mg Q3W IV + epacadostat 50 mg BID (safety expansion)
- Pembrolizumab 200 mg Q3W IV + epacadostat 100 mg BID (safety expansion)
- Pembrolizumab 200 mg Q3W IV + epacadostat 300 mg BID (safety expansion)
- Pembrolizumab 200 mg Q3W IV + RP2D epacadostat (NSCLC PD-L1 high positive)
- Pembrolizumab 200 mg Q3W IV + RP2D epacadostat (NSCLC PD-L1 low/negative or indeterminate)
- Pembrolizumab 200 mg Q3W IV + RP2D epacadostat (Melanoma immune checkpoint-naive)
- Pembrolizumab 200 mg Q3W IV + RP2D epacadostat (Melanoma primary refractory)
- Pembrolizumab 200 mg Q3W IV + RP2D epacadostat (Melanoma relapsed)
- Pembrolizumab 200 mg Q3W IV + RP2D epacadostat (GU)
- Pembrolizumab 200 mg Q3W IV + RP2D epacadostat (TNBC)
- Pembrolizumab 200 mg Q3W IV + RP2D epacadostat (Ovarian cancer)
- Pembrolizumab 200 mg Q3W IV + RP2D epacadostat (SCCHN)
- Pembrolizumab 200 mg Q3W IV + RP2D epacadostat (DLBCL)
- Pembrolizumab 200 mg Q3W IV + RP2D epacadostat (RCC)
- Pembrolizumab 200 mg Q3W IV + RP2D epacadostat (MSI-high CRC)
- Pembrolizumab 200 mg Q3W IV + RP2D epacadostat (Gastric cancer)
- Pembrolizumab 200 mg Q3W IV + RP2D epacadostat (HCC)

Table summaries, unless otherwise indicated, will be provided by treatment group or tumor type.

5.3. Analysis Populations

5.3.1. Efficacy Evaluable Population

The efficacy evaluable population will include all subjects enrolled in the study who take at least 1 dose of study drug. This population will be used for analyses of all efficacy data.

5.3.2. Safety Evaluable Population

The safety evaluable population will include all subjects enrolled in the study who received at least 1 dose of study drug. Treatment groups for this population will be determined according to the actual treatment the subject receives on Day 1. All safety analyses will be conducted using the safety population.

[redacted]

6. BASELINE, EXPOSURE, AND DISPOSITION VARIABLES AND ANALYSES

Sample data displays are provided in Appendix E.

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

The following demographic and baseline characteristics will be summarized for the safety evaluable population: age, sex, race, ethnicity, weight, height, ECOG performance status, staging, prior radiation (yes/no), prior surgery (yes/no), prior systemic therapy other than radiation (yes/no), and tumor-specific baseline disease characteristics (eg, BRAF mutation status [for melanoma] and human papillomavirus (HPV) status [SCCHN only]; refer to sample table shells for tumor specific details for each indication).

6.2. Disposition of Subjects

The number and percentage of subjects who were enrolled and who were withdrawn from treatment and from the study (with a primary reason for withdrawal) will be summarized for the safety evaluable population.

6.3. Protocol Deviations

Protocol deviations captured on the Protocol Deviation Log will be categorized, summarized, and presented in the subject data listings.

6.4. Exposure

For subjects in the safety evaluable population, descriptive statistics will be provided by cohort; duration of treatment; average daily dose (mg) of epacadostat; and number of cycles of pembrolizumab.

- **Duration of treatment:** The number of study days between Day 1 and the last nonzero dose administration record of epacadostat or pembrolizumab taken by the subject.
- **Number of cycles of pembrolizumab:** The number of cycles of pembrolizumab for a subject will be the number of administered, scheduled infusions of pembrolizumab recorded on the MK-3475 Dosing eCRF.

Subjects who stop pembrolizumab with SD or better may continue on monotherapy INCB024360 for up to 12 months or stop both therapies; if these subjects later experience disease progression, they may be eligible for up to 1 year of additional combination therapy followed by the option to continue monotherapy INCB024360 for up to 12 months as long as they are receiving benefit from treatment or they may stop both therapies.

NOTE: Protocol Amendment 10 removed the option for monotherapy epacadostat and re-treatment combination treatment for any subject who has not already started initiated such treatment.

6.5. Study Drug Compliance

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

$$\text{overall compliance (\%)} = 100 \times (\text{total dose taken}) / (\text{intended dose}).$$

The intended dose will be determined up to the earliest study day of permanent discontinuation of epacadostat (ie, AE discontinuation is the first AE with action taken being "drug withdrawn"), last study drug record in the database, or subject death. Intended dose is defined as the sum of the doses prescribed by the investigator accounting both for planned dose reductions as well as those reductions or increases mandated by the investigator.

6.6. Medical History

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

6.7. Prior and Concomitant Medication

For subjects in the safety evaluable population, prior medications and concomitant medications will be coded using the WHO Drug Dictionary and summarized by WHO drug class and WHO drug term. In the data listing, each medication will be recorded as prior, concomitant, or both prior and concomitant. Results will be summarized as number and percentage of subjects with prior and concomitant medications by WHO drug term and WHO drug class.

Prior medication information will also be used to identify anticancer medication received by subjects before enrollment into the study. Prior anticancer medication data will be summarized and presented by treatment group as well as listed.

7. EFFICACY

The list of table and listing displays are provided in Appendix E.

7.1. General Considerations

Not applicable.

7.2. Efficacy Hypotheses

Objective Response Rate (Primary Endpoint): Administration of epacadostat in combination with pembrolizumab increases ORR by irRECIST in Phase 2 subjects with various tumor types compared with historical rate.

7.3. Analysis of the Primary Efficacy Parameter

7.3.1. Primary Efficacy Analysis

The primary variable for the Phase 2 expansion portion of the study is ORR, which is defined as the proportion of subjects with best overall response (CR or PR) by irRECIST v1.1 for select solid tumors and modified Lugano Classification (Cheson et al 2014) for DLBCL. Subjects' overall response will be evaluated as CR, PR, SD, PD, or not evaluable (NE) at each postbaseline radiological assessment based on changes in target lesions, nontarget lesions, and appearance of new lesions. The best overall response will be determined from response assessments before and including the date of starting new anticancer therapy. If any alternative cancer therapy is taken while on study, any subsequent assessments will be excluded from the best overall response determination.

For subjects with measurable disease at baseline, the irRECIST version 1.1 assessment criteria presented in Table 5 can be used to determine the overall response at a given timepoint based on the target lesion, nontarget lesion, and new lesion assessment.

Table 5: irRECIST for Overall Response: Measurable Disease at Baseline

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

A subject is considered an objective responder as assessed by irRECIST if they have an overall response of CR or PR at any postbaseline visit. The proportion of responders within each treatment group will be estimated with 90% confidence intervals (CIs) by treatment group. Confidence intervals will be calculated based on the Clopper-Pearson method for binomial distributions. Within each treatment group, 1 sample binomial test will be used to test the null hypothesis.

Using irRECIST criteria, a PD needs to be confirmed as follows.

For each PD, if there is a second PD on the first response assessment that was ≥ 4 weeks after the PD, then the PD is defined as confirmed, and the date of progression is the date of the first PD. Otherwise the PD is defined as unconfirmed.

If a subject had an unconfirmed PD, and there are no valid response assessments after that PD (not NE or missing), then the PD will be counted as follows:

- If the subject discontinued both epacadostat and pembrolizumab or had end-of-study disposition date before a subsequent valid response assessment, then the PD will be counted as confirmed and the date of progression is the date of the PD; or
- If a subject is in the treatment period (≤ 18 months from treatment start date), they should be getting scans every 9 weeks. After the unconfirmed PD mentioned above, if the subject had not discontinued both epacadostat and pembrolizumab or had not had end-of-study disposition date before a subsequent valid response assessment, and if the clinical data cutoff date is ≤ 18 months from treatment start date and > 9 weeks after the subject's last scan, then the PD will be counted as confirmed, and the date of progression is the date of the PD. If the clinical data cutoff date is ≤ 18 months from treatment start date and ≤ 9 weeks after the subject's last scan, then the PD will NOT be counted as confirmed, and confirmation will be determined at their next 9-week scan.
- If a subject is in the follow-up period (> 18 months from treatment start date), then they should be getting scans every 12 weeks. After the unconfirmed PD mentioned above, if the subject had not discontinued both epacadostat and pembrolizumab or had not had end-of-study disposition date before a subsequent valid response assessment, and if the clinical data cutoff date is > 18 months from treatment start date and > 12 weeks after the subject's last scan, the PD will be counted as confirmed, and the date of progression is the date of the PD. If the clinical data cutoff date is > 18 months from treatment start date and ≤ 12 weeks after the subject's last scan, the PD will NOT be counted as confirmed, and confirmation will be determined at their next 12 week scan.

If a subject had a confirmed PD, then the PD will be counted as an event.

7.4. Analysis of Secondary Efficacy Parameters (Phase 2)

7.4.1. Ordinal Categorical Response Score

The ordinal response scores are defined as the following:

- 1 = CR per irRECIST v1.1
- 2 = Very good response, defined as > 60% tumor reduction
- 3 = Minor response, defined as >30% to ≤ 60% tumor reduction
- 4 = SD per irRECIST v1.1
- 5 = PD per irRECIST v1.1

The frequency of subjects in each category will be summarized by treatment group.

7.4.2. Duration of Response

For objective responders, the DoR is the time from the first overall response contributing to an objective response (CR or PR) to the earlier of the subject's death or first overall response of PD (by irRECIST v1.1 for selected solid tumors and the modified Lugano Classification for DLBCL) occurring after the first overall response contributing to the objective response. Median DoR and CIs will be estimated using the Kaplan-Meier method. Subjects who are still responding at the time of database freeze or discontinuation will be right-censored at the last valid response assessment date before starting any new anticancer therapy. The DoR evaluation will be performed separately for each treatment group and no statistical comparison will be made.

7.4.3. Progression-Free Survival

Progression-free survival is defined as the number of days from the date of first dose (which is not necessarily Day 1) to the earlier of death or disease progression by irRECIST v1.1 for selected solid tumors and the modified Lugano Classification for DLBCL. Date of death will be determined using the Death Report, the Survival Follow-Up, and the Subject Status eCRFs. Disease progression is defined as progression confirmed by a second, consecutive assessment at least 4 weeks apart with the option for continuing treatment while awaiting radiologic confirmation of progression. Censoring for PFS will follow the algorithm outlined in Table 6, which is based on FDA guidance (FDA 2007). Note that the Protocol mandates radiological evaluation of subjects every 9 weeks for the first 18 months and then may be done every 12 weeks thereafter. The analyses will be based on the efficacy evaluable population, according to treatment assignment. Time-to-event data will be analyzed by the Kaplan-Meier method.

Table 6: Evaluation and Censoring of Progression-Free Survival

Situation	Outcome	Date of Progression or Censoring
No baseline tumor assessments	Censored	Treatment start date
Progression documented between scheduled visits	Progressed	Earliest of: • Date of radiological assessment showing new lesion (if progression is based on new lesion); or • Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions)
No progression	Censored	Date of last valid radiologic assessment (not NE and not missing)
Treatment discontinuation for undocumented progression	Censored	Date of last valid radiologic assessment (not NE and not missing)
Treatment discontinuation for toxicity or other reason	Censored	Date of last valid radiologic assessment (not NE and not missing)
New anticancer treatment started	Censored	Date of last valid radiologic assessment (not NE and not missing)
Death before first PD assessment	Progressed	Date of death
Death between adequate assessment visits	Progressed	Date of death
Death or progression after more than 1 missed assessment	Censored	Date of last valid radiologic assessment (not NE and not missing)

7.4.4. Duration of Disease Control

The duration of disease control is the time from the first dose date to the first objective response of PD (by irRECIST v1.1 or modified Lugano Classification [Cheson et al 2014]), death, or last tumor assessment date (if PD/death not present), for subjects with best overall response of SD or better. In the case of SD, measurements must meet the SD criteria at least once after study entry at a minimum interval of 56 days. Median duration of disease control and CIs will be estimated using the Kaplan-Meier method. Subjects who have SD or better at the clinical data cutoff or discontinuation will be right-censored at last valid response assessment date before starting any new anticancer therapy. The duration of disease control evaluation will be performed separately for each treatment group and no statistical comparison will be made.

7.4.5. Overall Survival

For OS analysis, the Kaplan-Meier method will be used to estimate the survival time distribution and the median survival of each treatment group. Subjects will continue to be followed-up for OS even after a positive PFS analysis and a final analysis of OS will be conducted after OS data are mature (eg, ~70% or more than 52 subjects are dead).

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

For each subject, the percentage change from baseline in sum of the longest diameters of target lesions will be derived for each postbaseline period at which a valid target lesion assessment is provided. The best percentage change for each subject will be derived for waterfall plots and potential exploratory analyses.

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

7.4.7. Other Efficacy Analyses

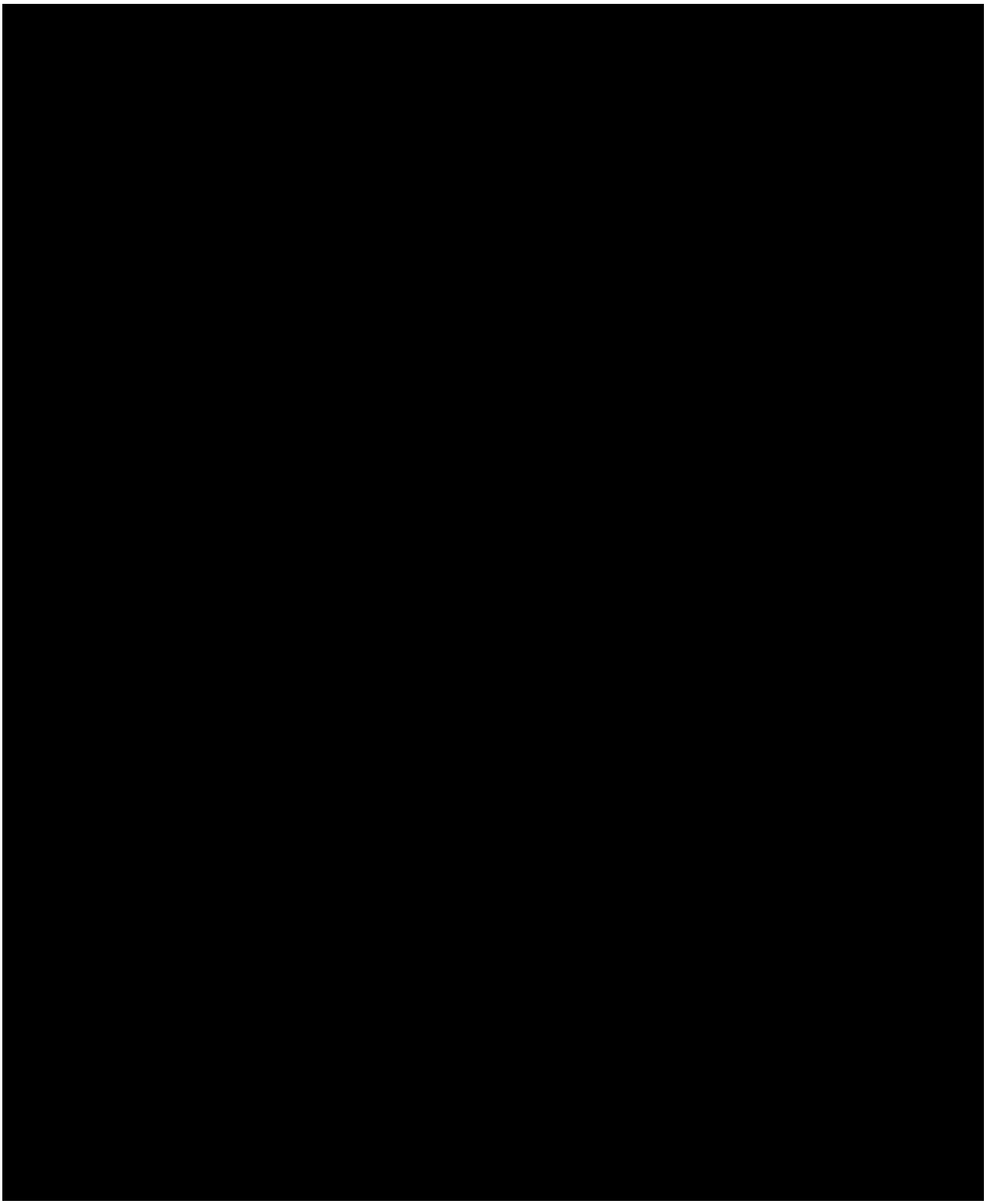
7.4.7.1. Eastern Cooperative Oncology Group Performance Status

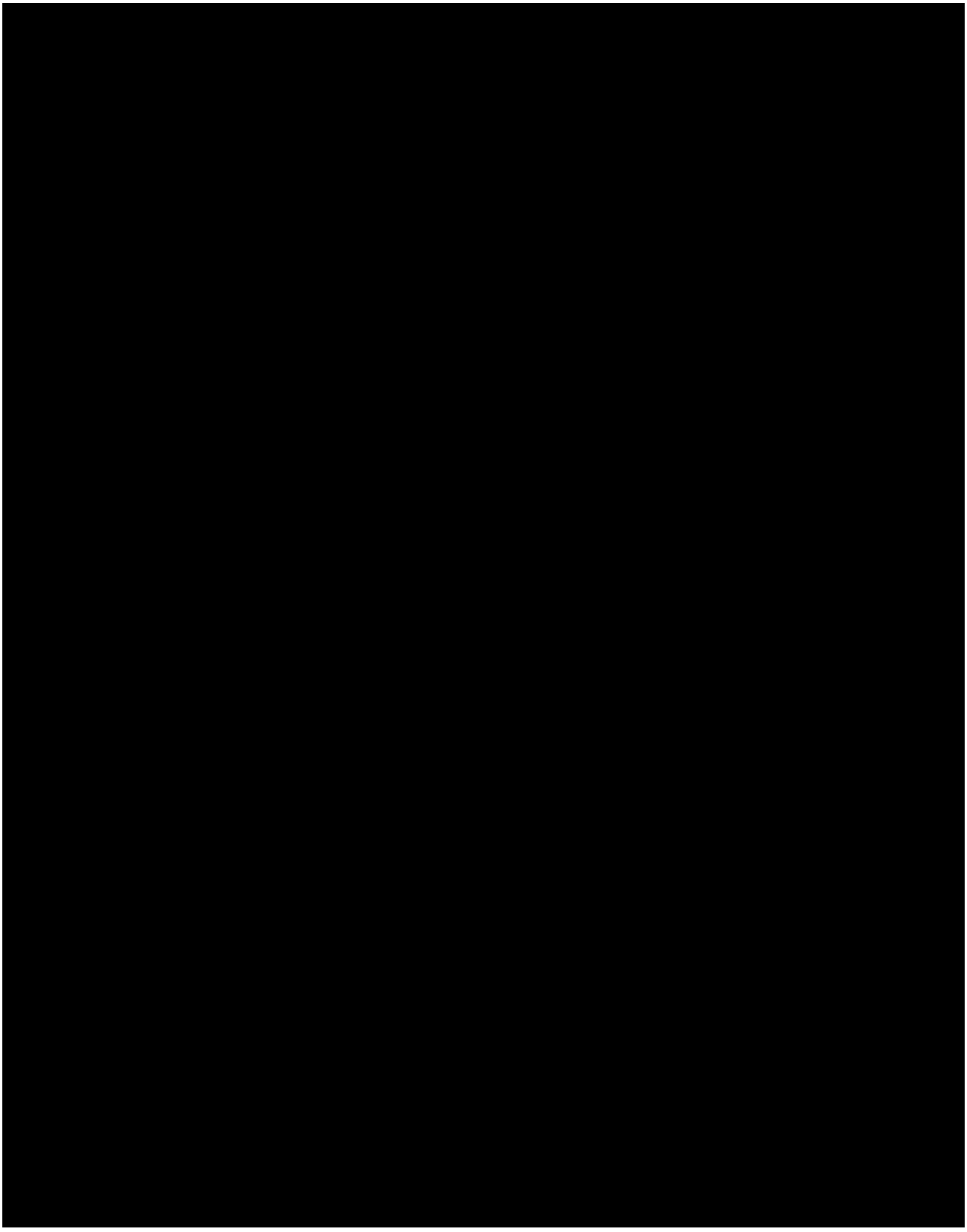
Subjects' ECOG performance status and changes in status at scheduled assessment times will be summarized.

7.4.8. Subgroup Analyses for Efficacy Endpoints

Subgroups will be formed based on the following subject characteristics and baseline variables for subjects with different tumor types whose data are available.

- For all tumor types:
  - PD-L1 status (positive, negative)





8. SAFETY AND TOLERABILITY

The list of table and listing displays are provided in Appendix E.

8.1. General Considerations

The analyses for this section will be provided using the safety evaluable population. Summary tables may be replaced with listings when appropriate. For instance, an AE frequency table may be replaced with a listing if it only contains a few unique preferred terms reported on relatively few subjects.

8.2. Adverse Events

8.2.1. Adverse Event Definitions

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

Adverse events will be tabulated by the MedDRA preferred term and system organ class. Severity of AEs will be described and graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.03. The CTCAE reporting guidelines and grading details are available on the Cancer Therapy Evaluation Program website (NCI 2010).

A grading (severity) scale is provided for each AE term. If the toxicity is not included in the CTCAE v4.03 criteria, it will be rated on a scale of 1 to 4 as follows: 1 = mild, 2 = moderate, 3 = severe, and 4 = life-threatening. All toxicities will be graded based on the worst level reached, not the level they may have reached if they had not been treated. When the intensity of an AE changes over time for a reporting period (eg, between visits), each change in intensity will be collected as an AE until the event resolves. Only the worst grade will be reported in AE summaries. Also, the Grade 3 or higher AEs will be reported in a summary table to display all higher-intensity AEs.

The subset of AEs considered by the investigator to be related to epacadostat or pembrolizumab will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study drug, then the AE will be considered to be treatment-related. The incidence of AEs and treatment-related AEs will be tabulated. Serious TEAEs will also be tabulated.

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

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

For purposes of analysis, all AEs will be considered TEAEs unless the AE can unequivocally be defined as not treatment emergent. Therefore, an unsolved missing onset date will be considered treatment emergent, with the following exceptions:

- If the stop/resolution date is before the first dose administration date on Day 1, then the AE will be considered as not being treatment emergent.
- If both the month and day are missing, and the last day of the year is before the first dose administration date on Day 1, then the AE will not be considered treatment emergent.
- If only the day is missing, and the last day of the month is before the first dose administration date on Day 1, then the AE will not be considered treatment emergent.
- If only the day is missing, and the first day of the month is after the first dose administration date on Day 1, then the AE will be considered treatment emergent.

8.2.2. Adverse Event Summaries

An overall summary of AEs by treatment group will include the following:

- Subjects who had a TEAE
- Subjects who had a Grade 3 or higher TEAE
- Subjects who had a serious TEAE
- Subjects who had a fatal TEAE
- Subjects who had a TEAE leading to dose interruption of INCB024360
- Subjects who had a TEAE leading to dose interruption of MK-3475
- Subjects who had a TEAE leading to dose interruption of INCB024360 and MK-3475
- Subjects who had a TEAE leading to dose reduction of INCB024360
- Subjects who had a TEAE leading to discontinuation of INCB024360
- Subjects who had a-TEAE leading to discontinuation of MK-3475
- Subjects who had a TEAE leading to discontinuation of INCB024360 and MK-3475
- Subjects who had a treatment-related (INCB024360 or MK-3475) TEAE
- Subjects who had a INCB024360-related TEAE
- Subjects who had a MK-3475-related TEAE
- Subjects who had a Grade 3 or higher treatment-related (INCB024360 or MK-3475) TEAE
- Subjects who had a treatment-related (INCB024360 or MK-3475) serious TEAE
- Subjects who had a fatal treatment-related (INCB024360 or MK-3475) TEAE
- Subjects who had a treatment-related (INCB024360 or MK-3475) TEAE leading to dose interruption of INCB024360

- Subjects who had a treatment-related (INCB024360 or MK-3475) TEAE leading to dose interruption of MK-3475
- Subjects who had a treatment-related (INCB024360 or MK-3475) TEAE leading to dose interruption of INCB024360 and MK-3475
- Subjects who had a treatment-related (INCB024360 or MK-3475) TEAE leading to dose reduction of INCB024360
- Subjects who had a treatment-related (INCB024360 or MK-3475) TEAE leading to discontinuation of INCB024360
- Subjects who had a treatment-related (INCB024360 or MK-3475) TEAE leading to discontinuation of MK-3475
- Subjects who had a treatment-related (INCB024360 or MK-3475) TEAE leading to discontinuation of INCB024360 and MK-347

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

- Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term
- Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency
- Summary of Treatment-Related (Epacadostat or Pembrolizumab) Adverse Events by MedDRA System Organ Class and Preferred Term
- Summary of Treatment-Related (Epacadostat or Pembrolizumab) Adverse Events by Preferred Term in Decreasing Order of Frequency
- Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term
- Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency
- Summary of Treatment-Emergent Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term
- Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term
- Summary of Serious Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency
- Summary of Treatment-Emergent Adverse Events Leading to Any Dose Interruption by MedDRA System Organ Class and Preferred Term
- Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Any Study Drug by MedDRA System Organ Class and Preferred Term

- Summary of Treatment-Emergent Adverse Events Leading to Any Dose Reduction by MedDRA System Organ Class and Preferred Term
- Summary of Treatment-Emergent Adverse Events of Special Interest by Category and Preferred Term (AEOSI)

The sponsor-defined, immune-related adverse events of special interest (AEOSIs) and events of clinical interest (ECIs) are provided in Appendix C and Appendix D, respectively.

8.3. Clinical Laboratory Tests

8.3.1. Laboratory Value Definitions

Laboratory values and change from baseline values will be summarized descriptively by visit. The baseline value will be determined using the last nonmissing values collected before the first dose. For baseline laboratory values with the same date and time, additional rules may be provided after consultation with the medical monitor to delineate which value will be defined as baseline.

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

8.3.2. Laboratory Value Summaries

Clinical laboratory tests, including hematology and serum chemistry (see Appendix A), will be performed for each subject during the study in accordance with Table 13 in Protocol Amendment 10.

If specific safety issues arise, additional unscheduled laboratory tests/analyses may be performed at the discretion of the investigator.

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

Laboratory parameters identified in Table 10 will be summarized. Shift tables based on worst postbaseline value recorded will use all postbaseline values. Other laboratory parameters collected will only be listed in an appendix to the Clinical Study Report in their original units without SI conversions. A detailed listing of the serum chemistry, hematology, and urinalysis tests is provided in Appendix A.

Table 10: Laboratory Parameters To Be Summarized

Panel	Parameter
Serum chemistry	Albumin, alkaline phosphatase[a,b], ALT[a,b], AST[a,b], amylase, bicarbonate, BUN, calcium, chloride, creatinine, glucose, iron, lactate dehydrogenase, phosphorus, potassium, serum or plasma lipase, sodium, total bilirubin[a,b], direct bilirubin, total protein, uric acid
Lipid	Total cholesterol, triglycerides, LDL, HDL, CRP[b]
Hematology	Hemoglobin, hematocrit, platelet count, red blood cell count, reticulocyte count, WBC[b], basophils, eosinophils, lymphocytes[b], monocytes, neutrophils[b]
Endocrine monitoring	ACTH[c], serum cortisol[c], LH, prolactin[c], TSH[c], free T4[c], T3[c], serum testosterone[c]
Urinalysis	Color and appearance, pH and specific gravity, bilirubin, glucose, ketones, leukocytes, nitrite, occult blood, protein, urobilinogen
Pregnancy test	Female subjects of childbearing potential only require a serum test at screening; pregnancy tests (serum or urine) should be repeated if required by local regulations
Coagulation	PT, aPTT, INR
Serology	HBsAG, HBsAG antibody, HBc, HCV antibody, HCV-RNA, HBV-DNA, HCV genotype, HCV viral load (for subjects with HCC only), anti-HDV, anti-HBe, HBV viral load, anti-HBc (total), HBeAg (for subjects with HCC who are HBsAg+ or anti-HBc+, anti-HBs-, HBsAg- viral load < 100 IU/mL only)
Other	CA 125 (ovarian cancer only), CEA (gastric cancer only), AFP (HCC only)

[a] Summaries of LFTs will be performed on a weekly basis instead of by cycle.
[b] Line graph and box-and-whisker plots will be provided.
[c] Only normal-high-low shift tables will be provided.

Numeric laboratory values will be summarized descriptively, and non-numeric test values will be tabulated.

For test results that will be summarized with available normal ranges, the number and percentage of subjects with the laboratory values being low (but never high), normal, high (but never low), and both low and high will be calculated for each test. Laboratory values with greater than or less than signs will require medical monitor review. Laboratory ranges with greater than or less than signs will be handled as follows: if only an upper limit exists, for example, < 200, then the range will be (0,199.99); similarly, if only the lower limit exists, for example, > 0, then the range will be (0.001, 9999).

This shift summary will be produced for each test for the safety population. The denominator for the percentage calculation will use the number of subjects in the baseline category (ie, low, high, normal, missing) as the denominator for the percentage in each of the categories during the treatment period.

For all gradable laboratory parameters identified in Table 10, the values will be classified into grade levels corresponding to CTCAE v4.03 criteria. For specific laboratory values requiring clinical intervention to grade, the classification according to the quantitative component will be provided. See Appendix B for laboratory grading criteria.

The number and percentage of subjects with the laboratory values of Grade 1, 2, 3, or 4 will be calculated for each treatment according to the largest treatment-emergent worsening of

laboratory grade. Separate summaries for abnormally high and abnormally low laboratory values will be provided when the laboratory in question has both high and low grading criteria. For instance, if a subject has a baseline fasting glucose of 210 mg/dL, maximum fasting glucose after starting treatment of 245 mg/dL, and minimum fasting glucose after starting treatment of 52 mg/dL, then the subject will be counted as follows:

- The subject will be counted as a Grade 2 "Glucose decreased" in summaries of hypoglycemia because the subject was not hypoglycemic at study entry but became hypoglycemic after treatment.
- The subject will not count as a "Glucose increased" in summaries of hyperglycemia because the subject met the numeric requirements for Grade 2 hyperglycemia at baseline (fasting glucose value > 160 to 250 mg/dL) and did not increase in grade after starting treatment.

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

8.4. Vital Signs

Vital signs, including systolic blood pressure, diastolic blood pressure, pulse, respiration rate, and body temperature, will be taken with subjects in the seated position during the study in accordance with Table 12 in Protocol Amendment 10. Change and percentage change from baseline will be calculated using the last nonmissing value before first dose of study drug (Day 1) as the baseline value.

Incidences of clinically notable vital sign abnormalities are defined in Table 11. The abnormal values for subjects exhibiting clinically notable vital sign abnormalities will be listed along with their assigned treatment group. Alert vital signs are defined as an absolute value outside the defined range and percentage change from baseline greater than 25%.

Table 11: Criteria for Clinically Notable Vital Sign Abnormalities

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

8.5. Electrocardiograms

Twelve-lead ECGs will be obtained for each subject during the study in accordance with Table 12 in Protocol Amendment 10. The baseline for each parameter is the average of all available values collected at screening, Day -1, and Day 1 predose. A table of clinically significant ECG abnormalities and a listing of 12-lead ECG values will be reported in the abbreviated CSR. Electrocardiogram results will be reviewed for clinically notable

abnormalities according to predefined criteria (see Table 12). Number and percentage of subjects with alert ECG values (outliers), defined as the absolute value outside the defined range (see Table 12) and percentage change from baseline greater than 25% (30% for QRS interval), will be summarized.

Table 12: Criteria for Clinically Notable Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold
QTcF[a]	> 460 msec	< 295 msec
PR	> 220 msec	< 75 msec
QRS	> 120 msec	< 50 msec
QT	> 500 msec	< 300 msec
RR	> 1500 msec	< 600 msec

[a] QTcF (Fridericia correction).

9. INTERIM ANALYSES

9.1. Overview of Interim Analysis

No planned interim analysis for efficacy or futility will be conducted in this study.

9.2. Guidelines for Decision Rules

An interim safety analysis is planned for Phase 2 after 20 subjects have been enrolled and treated for 9 weeks, and then every 3 months thereafter. If the following is reported during these reviews, then enrollment of subjects would be suspended until the sponsor(s), investigators, and regulatory authorities, if applicable, have determined the appropriate course of action:

- > 40% of subjects have had an AE ≥ Grade 3 that was attributable to the investigational agent.

Based on these rules, the probabilities of stopping a treatment group for safety is provided in Table 13.

Table 13: Probability of Early Termination for Various Safety Event Rates

Proportion of Subjects Having an AE ≥ Grade 3 That Was Attributable to the Investigational Agent	Probability of Early Termination Based on an AE ≥ Grade 3 That Was Attributable to the Investigational Agent[ab]
5%	0.0%
10%	0.1%
15%	0.6%
20%	3.3%
25%	10.2%
30%	23.3%
40%	80.7%

[a] Assumes the interim safety analyses occur when enrollment is 20, 80, 160, 240, and 276, etc, subjects. Probability estimated via simulation with 100,000 replications.

[b] The probability of early termination = Prob ((≥ 40% of subjects in the active treatment group have had an AE ≥ Grade 3 at the first interim safety analysis OR at the second interim OR at the third interim OR at the fourth interim).

10. CHANGES AND MODIFICATIONS TO THE ANALYSIS PLAN

All versions of the SAP are listed in Table 14.

Table 14: Statistical Analysis Plan Versions

SAP Version	Date
Original	22 DEC 2014
Amendment 1	27 JUL 2016
Amendment 2	21 AUG 2017
Amendment 3	08 MAR 2018
Amendment 4	17 MAY 2019

10.1. Changes to Protocol-Defined Analyses

Study enrollment was permanently discontinued on 17 MAY 2018 as a strategic decision. This decision was made following the recommendation of the external Data Monitoring Committee of the INCB 24360-301 blinded melanoma clinical study, which determined that the study did not meet the prespecified endpoint of progression-free survival improvement for the combination of pembrolizumab + epacadostat compared with pembrolizumab + placebo; in addition, the overall survival (OS) endpoint was not expected to reach statistical significance. Of note, there were no new safety concerns identified in either arm of the melanoma study.

Due to this strategic decision, Protocol-defined analyses were reduced. Efficacy analyses will only be performed for primary and secondary endpoints [redacted] See Appendix E for a detailed list of outputs that will be included in the abbreviated CSR for both safety and efficacy.

10.2. Changes to the Statistical Analysis Plan

10.2.1. Original to Amendment 1

The purpose of SAP Amendment 1 was to coincide with changes in Protocol Amendment 5: to replace the randomized, placebo-controlled portion of the study conducted in subjects with NSCLC with an open-label expansion in subjects with select cancers including melanoma, transitional cell carcinoma of the GU tract, TNBC, ovarian cancer, SCCHN, DLBCL, clear cell RCC, and 2 cohorts of subjects with NSCLC based on PD-L1 expression.

10.2.2. Amendment 1 to Amendment 2

The purpose of SAP Amendment 2 is to coincide with changes in Protocol Amendments 6 and 7: to add MSI-high CRC, gastric cancer, and HCC expansion cohorts to Phase 2 of the study. Additionally, the list of sponsor-defined AEOSIs was updated.

10.2.3. Amendment 2 to Amendment 3

The main purpose of SAP Amendment 3 is to coincide with changes in Protocol Amendments 8 and 9: to add melanoma (primary refractory) and melanoma (relapsed) expansion cohorts to Phase 2 of the study. The list of sponsor-defined AEOSIs and ECIs were updated. Some treatment-related safety tables have been removed. Additionally, the subgroup analyses were modified per each tumor type.

10.2.4. Amendment 3 to Amendment 4

The purpose of SAP Amendment 4 is to reflect changes in wording from Protocol Amendment 10, remedy sections with lack of clarity on Protocol-defined analyses, reflect updates to the overall AE summary table, and make transparent what will be reported in the abbreviated CSR. Additionally, the list of sponsor-defined AEOSIs was updated.

A population PK model of epacadostat has been developed based on data from multiple epacadostat Phase 1, 2, and 3 studies (DMB-18.142.1). [redacted]

11. REFERENCES

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Food and Drug Administration (FDA). Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. 2007. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf. Accessed July 22, 2016.

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APPENDIX A. CLINICAL LABORATORY TESTS

<table>
<tr><th>Serum Chemistry</th><th>Hematology</th><th>Other</th></tr>
<tr><td rowspan="3">Albumin
Alkaline phosphatase
ALT
AST
Amylase
Bicarbonate
Blood urea nitrogen
Calcium
Chloride
Creatinine
Glucose
Iron
Lactate dehydrogenase
Phosphorus
Potassium
Serum or plasma lipase
Sodium
Total bilirubin
Direct bilirubin (if total bilirubin is elevated above ULN)
Total protein
Uric acid</td><td rowspan="3">Complete blood count, including:
• Hemoglobin
• Hematocrit
• Platelet count
• Red blood cell count
• Reticulocyte count
• White blood cell count

Differential count, including:
• Basophils
• Eosinophils
• Lymphocytes
• Monocytes
• Neutrophils</td><td>Serology:
Hepatitis B surface antigen
Hepatitis B surface antigen antibody
Hepatitis B core antibody
Hepatitis C virus antibody
HCV-RNA
HBV-DNA</td></tr>
<tr><td>Pregnancy test:
Female subjects of childbearing potential only require a serum test at screening.
Pregnancy tests (serum or urine) should be repeated if required by local regulations.</td></tr>
<tr><td>Urinalysis with microscopic examination:
Color and appearance
pH and specific gravity
Bilirubin
Glucose
Ketones
Leukocytes
Nitrite
Occult blood
Protein
Urobilinogen

Coagulation:
PT
aPTT
INR</td></tr>
<tr><th>Lipid Panel</th><th>Standard LFT Monitoring</th><th>Endocrine Monitoring</th></tr>
<tr><td>Total cholesterol
Triglycerides
LDL
HDL
CRP</td><td>Alkaline phosphatase
ALT
AST
Total bilirubin</td><td>ACTH
Serum cortisol (9 AM)[a]
LH[b]
Prolactin
TSH
Free thyroxine (T4)
Total triiodothyronine (T3)
Serum testosterone (9 AM)[c]</td></tr>
</table>

ACTH = adrenocorticotropic hormone; ALT = alanine aminotransferase; aPTT = partial thromboplastin time; AST = aspartate aminotransferase; CRP = C-reactive protein; DLCO = diffuse lung capacity for carbon monoxide; $FEF_{25\%-75\%}$ = forced expiratory flow 25% to 75%; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HBV-DNA = hepatitis B virus deoxyribonucleic acid; HCV-RNA = hepatitis C virus ribonucleic acid; HDL = high-density lipoprotein; IgG = immunoglobin G; INR = international normalized ratio; LDL = low-density lipoprotein; LFT = liver chemistry tests; LH = luteinizing hormone; PEF = peak expiratory flow; PT = prothrombin time; TSH = thyroid-stimulating hormone; ULN = upper limit of normal; VA = alveolar volume.

[a] Serum cortisol ideally should be drawn close to 9 AM but can be done any time before noon.

[b] Not needed in women, surgically castrated men, or men taking LH-releasing hormone agonist therapy.

[c] Not needed in subjects taking testosterone replacement therapy.

APPENDIX B. LABORATORY GRADING

Laboratory	Grade 1	Grade 2	Grade 3	Grade 4
Haptoglobin decreased	< LLN	-	-	-
Hemoglobin decreased	< LLN - 100 g/L	< 100 - 80 g/L	< 80 g/L	-
Hemoglobin increased	Increase in > 0 - 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in > 2 - 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in > 4 gm/dL above ULN or above baseline if baseline is above ULN	-
Lymphocyte count decreased	< LLN - 0.8 × 10^9/L	< 0.8 - 0.5 × 10^9/L	< 0.5 - 0.2 × 10^9/L	< 0.2 × 10^9/L
Lymphocyte count increased	-	> 4000/mm^3 - 20,000/mm^3	> 20,000/mm^3	-
Neutrophil count decreased	< LLN - 1.5 × 10^9/L	< 1.5 - 1.0 × 10^9/L	< 1.0 - 0.5 × 10^9/L	< 0.5 × 10^9/L
Platelet count decreased	< LLN - 75.0 × 10^9/L	< 75.0 - 50.0 × 10^9/L	< 50.0 - 25.0 × 10^9/L	< 25.0 × 10^9/L
White blood cell decreased	< LLN - 3.0 × 10^9/L	< 3.0 - 2.0 × 10^9/L	< 2.0 - 1.0 × 10^9/L	< 1.0 × 10^9/L
Activated partial thromboplastin time prolonged	> ULN - 1.5 × ULN	> 1.5 - 2.5 × ULN	> 2.5 × ULN	-
INR increased	> 1 - 1.5 × ULN	> 1.5 - 2.5 × ULN	> 2.5 × ULN	-
Alanine aminotransferase increased	> ULN - 3.0 × ULN	> 3.0 - 5.0 × ULN	> 5.0 - 20.0 × ULN	> 20.0 × ULN
Alkaline phosphatase increased	> ULN - 2.5 × ULN	> 2.5 - 5.0 × ULN	> 5.0 - 20.0 × ULN	> 20.0 × ULN
Aspartate aminotransferase increased	> ULN - 3.0 × ULN	> 3.0 - 5.0 × ULN	> 5.0 - 20.0 × ULN	> 20.0 × ULN
Blood bilirubin increased	> ULN - 1.5 × ULN	> 1.5 - 3.0 × ULN	> 3.0 - 10.0 × ULN	> 10.0 × ULN
CD4 lymphocytes decreased	< LLN - 0.5 × 10^9/L	< 0.5 - 0.2 × 10^9/L	< 0.2 - 0.05 × 10^9/L	< 0.05 × 10^9/L
Cholesterol high	> ULN - 7.75 mmol/L	> 7.75 - 10.34 mmol/L	> 10.34 - 12.92 mmol/L	> 12.92 mmol/L
CPK increased	> ULN - 2.5 × ULN	> 2.5 - 5 × ULN	> 5 - 10 × ULN	> 10 × ULN
Creatinine increased	> 1 - 1.5 × baseline; > ULN - 1.5 × ULN	> 1.5 - 3.0 × baseline; >1.5 - 3.0 × ULN	> 3.0 baseline; > 3.0 - 6.0 × ULN	> 6.0 × ULN
Fibrinogen decreased	< 1.0 - 0.75 × LLN or < 25% decrease from baseline	< 0.75 - 0.5 × LLN or 25 - < 50% decrease from baseline	< 0.5 - 0.25 × LLN or 50 - < 75% decrease from baseline	< 0.25 × LLN or 75% decrease from baseline or absolute value < 50 mg/dL
GGT increased	> ULN - 2.5 × ULN	> 2.5 - 5.0 × ULN	> 5.0 - 20.0 × ULN	> 20.0 × ULN
Lipase increased	> ULN - 1.5 × ULN	> 1.5 - 2.0 × ULN	> 2.0 - 5.0 × ULN	> 5.0 × ULN
Serum amylase increased	> ULN - 1.5 × ULN	> 1.5 - 2.0 × ULN	> 2.0 - 5.0 × ULN	> 5.0 × ULN
Serum albumin decreased	< LLN - 30 g/L	< 30 - 20 g/L	< 20 g/L	-

Laboratory	Grade 1	Grade 2	Grade 3	Grade 4
Serum calcium decreased	< LLN - 2.0 mmol/L	< 2.0 - 1.75 mmol/L	< 1.75 - 1.5 mmol/L	< 1.5 mmol/L
Serum calcium increased	> ULN - 2.9 mmol/L	> 2.9 - 3.1 mmol/L	> 3.1 - 3.4 mmol/L	> 3.4 mmol/L
Serum glucose decreased (fasting)	< LLN - 3.0 mmol/L	< 3.0 - 2.2 mmol/L	< 2.2 - 1.7 mmol/L	< 1.7 mmol/L
Serum glucose increased (fasting)	> ULN - 8.9 mmol/L	> 8.9 - 13.9 mmol/L	> 13.9 - 27.8 mmol/L	> 27.8 mmol/L
Serum magnesium decreased	< LLN - 0.5 mmol/L	< 0.5 - 0.4 mmol/L	< 0.4 - 0.3 mmol/L	< 0.3 mmol/L
Serum magnesium increased	> ULN - 1.23 mmol/L	-	> 1.23 - 3.30 mmol/L	> 3.30 mmol/L
Serum phosphate decreased	< LLN - 0.8 mmol/L	< 0.8 - 0.6 mmol/L	< 0.6 - 0.3 mmol/L	< 0.3 mmol/L
Serum potassium decreased	< LLN - 3.0 mmol/L	-	< 3.0 - 2.5 mmol/L	< 2.5 mmol/L
Serum potassium increased	> ULN - 5.5 mmol/L	> 5.5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L
Serum sodium decreased	< LLN - 130 mmol/L	-	< 130 - 120 mmol/L	< 120 mmol/L
Serum sodium increased	> ULN - 150 mmol/L	> 150 - 155 mmol/L	> 155 - 160 mmol/L	> 160 mmol/L
Serum triglycerides increased	1.71 - 3.42 mmol/L	> 3.42 - 5.7 mmol/L	> 5.7 - 11.4 mmol/L	> 11.4 mmol/L
Serum uric acid increased	> ULN - 0.59 mmol/L	-	> ULN - 0.59 mmol/L	> 0.59 mmol/L;

CPK = creatine phosphokinase; GGT = gamma glutamyl transferase; INR = international normalized ratio; LLN = lower limit of normal; ULN = upper limit of normal.

APPENDIX C. SPONSOR-DEFINED IMMUNE-RELATED ADVERSE EVENTS OF SPECIAL INTEREST

AEOSI Category	Preferred Terms
Pneumonitis	Acute interstitial pneumonitis, Interstitial lung disease, Pneumonitis, Idiopathic pneumonia syndrome, Organising pneumonia, Autoimmune lung disease
Colitis	Colitis, Colitis microscopic, Enterocolitis, Enterocolitis haemorrhagic, Necrotising colitis, Colitis erosive, Autoimmune colitis
Hepatitis	Hepatitis, Immune-mediated hepatitis, Autoimmune hepatitis, Hepatitis acute, Hepatitis fulminant, Drug-induced liver injury
Nephritis	Nephritis, Autoimmune nephritis, Chronic autoimmune glomerulonephritis, Fibrillary glomerulonephritis, Focal segmental glomerulosclerosis, Glomerulonephritis, Glomerulonephritis acute, Glomerulonephritis membranoproliferative, Glomerulonephritis membranous, Glomerulonephritis minimal lesion, Glomerulonephritis proliferative, Glomerulonephritis rapidly progressive, Mesangioproliferative glomerulonephritis, Nephritis haemorrhagic, Tubulointerstitial nephritis, Nephrotic syndrome
Adrenal insufficiency	Adrenal insufficiency, Adrenocortical insufficiency acute, Secondary adrenocortical insufficiency
Hypophysitis	Hypophysitis, Hypopituitarism, Lymphocytic hypophysitis
Hyperthyroidism	Hyperthyroidism, Basedow's disease, Thyrotoxic crisis
Hypothyroidism	Hypothyroidism, Hypothyroidic goitre, Myxoedema, Myxoedema coma, Primary hypothyroidism
Thyroiditis	Thyroid disorder, Thyroiditis, Autoimmune thyroiditis, Thyroiditis acute, Silent thyroiditis, Autoimmune thyroid disorder
Type 1 diabetes mellitus	Diabetic ketoacidosis, Diabetic ketoacidotic hyperglycaemic coma, Fulminant type 1 diabetes mellitus, Latent autoimmune diabetes in adults, Type 1 diabetes mellitus, Euglycaemic diabetic ketoacidosis, Diabetic ketosis, Ketosis-prone diabetes mellitus
Severe skin reactions including Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN): Any grade from Severe cutaneous reactions SMQ narrow	Dermatitis bullous, Dermatitis exfoliative, Dermatitis exfoliative generalised, Epidermal necrosis, Erythema multiforme, Exfoliative rash, Pemphigoid, Pemphigus, Skin necrosis, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Toxic skin eruption;
Severe Skin (continued): If Grade 3 or higher:	Rash, Rash erythematous, Rash generalised, Rash maculo-papular, Rash pruritic, Rash pustular, Pruritus, Pruritus generalised, and Pruritus genital
Uveitis	Iritis, Uveitis, Cyclitis, Autoimmune uveitis, Iridocyclitis, Vogt-Koyanagi-Harada syndrome
Pancreatitis	Pancreatitis, Autoimmune pancreatitis, Pancreatitis acute, Pancreatitis haemorrhagic, Pancreatitis necrotising
Myositis	Myositis, Necrotising myositis, Polymyositis, Immune-mediated necrotising myopathy, Rhabdomyolysis, Myopathy, Dermatomyositis
Guillain-Barre syndrome	Demyelinating polyneuropathy, Guillain-Barre syndrome, Axonal neuropathy, Multifocal motor neuropathy, Polyneuropathy idiopathic progressive, Miller Fisher syndrome, Subacute inflammatory demyelinating polyneuropathy
Myocarditis	Myocarditis, Autoimmune myocarditis, Hypersensitivity myocarditis
Encephalitis	Encephalitis, Encephalitis autoimmune, Limbic encephalitis, Noninfective encephalitis
Sarcoidosis	Sarcoidosis, Cutaneous sarcoidosis, Ocular sarcoidosis, Pulmonary sarcoidosis
Infusion reactions	Hypersensitivity, Drug hypersensitivity, Anaphylactic reaction, Anaphylactoid reaction, Cytokine release syndrome, Serum sickness, Serum sickness–like reaction, Infusion-related reaction
Myasthenic syndrome	Myasthenic syndrome, Myasthenia gravis, Myasthenia gravis crisis, Ocular myasthenia

APPENDIX D. SPONSOR-DEFINED EVENTS OF CLINICAL INTEREST

Hy's Law definition:

Any subject with:

- An elevated AST value that is greater than or equal to 3 × ULN or
- An elevated ALT value that is greater than or equal to 3 × ULN
- And with an elevated total bilirubin value that is ≥ 2 × ULN
- And with an alkaline phosphatase value that is < 2 × ULN

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

Overdose and Serotonin Syndrome

Adverse Event Preferred Term	Note
Overdose[a]	Any grade
Accidental overdose	Any grade
Intentional overdose	Any grade
Prescribed overdose	Any grade
Serotonin syndrome	Any grade

[a] Overdose of study drug (pembrolizumab and/or epacadostat) – an overdose is any dose ≥ 1000 mg (5 times the dose) of pembrolizumab or ≥ 1000 mg of epacadostat daily.

APPENDIX E. PLANNED TABLES AND LISTINGS

This appendix provides a list of the planned tables and listings for the Clinical Study Report. Standard tables will follow the conventions in the Standard Safety Tables initial version.

Tables

Table No.	Title	Population	Standard
Baseline and Demographic Characteristics			
1.1 Disposition			
1.1.1	Analysis Populations	Safety Evaluable	X
1.1.2	Summary of Subject Disposition	Safety Evaluable	X
1.1.3	Summary of Number of Subjects Enrolled By Country and Site	Safety Evaluable	X
1.1.4	Summary of Protocol Deviations	Safety Evaluable	X
1.2 Demography			
1.2.1	Summary of Demographic and Baseline Disease Characteristics	Safety Evaluable	X
1.3 Baseline Characteristics			
1.3.1.1	Summary of Baseline Disease Characteristics	Safety Evaluable Hepatocellular Carcinoma	X
1.3.1.2	Summary of Baseline Disease Characteristics	Safety Evaluable Breast Cancer	X
1.3.1.3	Summary of Baseline Disease Characteristics	Safety Evaluable Melanoma	X
1.3.1.4	Summary of Baseline Disease Characteristics	Safety Evaluable NSCLC	X
1.3.1.5	Summary of Baseline Disease Characteristics	Safety Evaluable Renal Cell Carcinoma	X
1.3.1.6	Summary of Baseline Disease Characteristics	Safety Evaluable Squamous Cell Carcinoma of the Head and Neck	X
1.3.1.7	Summary of Baseline Disease Characteristics	Safety Evaluable Transitional Carcinoma of the GU Tract	X
1.3.1.8	Summary of Baseline Disease Characteristics	Safety Evaluable Ovarian	X
1.3.1.9	Summary of Baseline Disease Characteristics	Safety Evaluable Gastric	X
1.3.1.10	Summary of Baseline Disease Characteristics	Safety Evaluable Colorectal	X
1.3.1.11	Summary of Baseline Disease Characteristics	Safety Evaluable DLBCL	X
1.3.1.12	Summary of Baseline Disease Characteristics	Safety Evaluable Adenocarcinoma of the Endometrium	X
1.4 Prior Medication and Concomitant Medication			
1.4.1	Summary of Prior Medications	Safety Evaluable	X
1.4.2	Summary of Concomitant Medications	Safety Evaluable	X
1.5+ Others			
1.5.1	Summary of General Medical History	Safety Evaluable	X
1.6.1	Summary of Prior Medications for Cancer	Safety Evaluable	X
1.7.1	Summary of Study Medication Compliance	Safety Evaluable	X

Table No.	Title	Population	Standard
Efficacy			
2.1 Primary Efficacy			
2.1.1.1	Summary of Best Overall Response by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Hepatocellular Carcinoma Phase 2 only	
2.1.1.2	Summary of Best Overall Response by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Breast Cancer Phase 2 only	
2.1.1.3	Summary of Best Overall Response by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Immune Checkpoint-naïve Melanoma Phase 2 only	
2.1.1.3.1	Summary of Best Overall Response by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Primary Refractory Melanoma Phase 2 only	
2.1.1.3.2	Summary of Best Overall Response by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Relapsed Melanoma Phase 2 only	
2.1.1.4	Summary of Best Overall Response by irRECIST Criteria by TPS Score	Efficacy Evaluable NSCLC Phase 2 only	
2.1.1.5	Summary of Best Overall Response by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Renal Cell Carcinoma Phase 2 only	
2.1.1.6	Summary of Best Overall Response by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Squamous Cell Carcinoma of the Head and Neck Phase 2 only	
2.1.1.7	Summary of Best Overall Response by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Transitional Carcinoma of the GU Tract Phase 2 only	
2.1.1.8	Summary of Best Overall Response by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Ovarian Phase 2 only	
2.1.1.9	Summary of Best Overall Response by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Gastric Cancer Phase 2 only	
2.1.1.10	Summary of Best Overall Response by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Colorectal Phase 2 only	
2.1.1.11	Summary of Best Overall Response by Modified Lugano Criteria by PD-L1 Status	Efficacy Evaluable DLBCL Phase 2 only	
2.2 Secondary Efficacy			
2.2.1.1	Summary of Duration of Response by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Hepatocellular Carcinoma Phase 2 only	
2.2.1.2	Summary of Duration of Response by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Breast Cancer Phase 2 only	

Table No.	Title	Population	Standard
2.2.1.3	Summary of Duration of Response by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Immune Checkpoint-naïve Melanoma Phase 2 only	
2.2.1.3.1	Summary of Duration of Response by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Primary Refractory Melanoma Phase 2 only	
2.2.1.3.2	Summary of Duration of Response by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Relapsed Melanoma Phase 2 only	
2.2.1.4	Summary of Duration of Response by irRECIST Criteria by TPS Score	Efficacy Evaluable NSCLC Phase 2 only	
2.2.1.5	Summary of Duration of Response by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Renal Cell Carcinoma Phase 2 only	
2.2.1.6	Summary of Duration of Response by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Squamous Cell Carcinoma of the Head and Neck Phase 2 only	
2.2.1.7	Summary of Duration of Response by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Transitional Carcinoma of the GU Tract Phase 2 only	
2.2.1.8	Summary of Duration of Response by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Ovarian Phase 2 only	
2.2.1.9	Summary of Duration of Response by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Gastric Cancer Phase 2 only	
2.2.1.10	Summary of Duration of Response by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Colorectal Phase 2 only	
2.2.1.11	Summary of Duration of Response by Modified Lugano Criteria by PD-L1 Status	Efficacy Evaluable DLBCL Phase 2 only	
2.2.2.1	Summary of Duration of Disease Control by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Hepatocellular Carcinoma Phase 2 only	
2.2.2.2	Summary of Duration of Disease Control by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Breast Cancer Phase 2 only	
2.2.2.3	Summary of Duration of Disease Control by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Immune Checkpoint-naïve Melanoma Phase 2 only	
2.2.2.3.1	Summary of Duration of Disease Control by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Primary Refractory Melanoma Phase 2 only	
2.2.2.3.2	Summary of Duration of Disease Control by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Relapsed Melanoma Phase 2 only	

Table No.	Title	Population	Standard
2.2.2.4	Summary of Duration of Disease Control by irRECIST Criteria by TPS Score	Efficacy Evaluable NSCLC Phase 2 only	
2.2.2.5	Summary of Duration of Disease Control by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Renal Cell Carcinoma Phase 2 only	
2.2.2.6	Summary of Duration of Disease Control by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Squamous Cell Carcinoma of the Head and Neck Phase 2 only	
2.2.2.7	Summary of Duration of Disease Control by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Transitional Carcinoma of the GU Tract Phase 2 only	
2.2.2.8	Summary of Duration of Disease Control by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Ovarian Phase 2 only	
2.2.2.9	Summary of Duration of Disease Control by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Gastric Cancer Phase 2 only	
2.2.2.10	Summary of Duration of Disease Control by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Colorectal Phase 2 only	
2.2.2.11	Summary of Duration of Disease Control by Modified Lugano Criteria by PD-L1 Status	Efficacy Evaluable DLBCL Phase 2 only	
2.2.3.1	Summary of Progression-Free Survival by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Hepatocellular Carcinoma Phase 2 only	
2.2.3.2	Summary of Progression-Free Survival by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Breast Cancer Phase 2 only	
2.2.3.3	Summary of Progression-Free Survival by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Immune Checkpoint-naïve Melanoma Phase 2 only	
2.2.3.3.1	Summary of Progression-Free Survival by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Primary Refractory Melanoma Phase 2 only	
2.2.3.3.2	Summary of Progression-Free Survival by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Relapsed Melanoma Phase 2 only	
2.2.3.4	Summary of Progression-Free Survival by irRECIST Criteria by TPS Score	Efficacy Evaluable NSCLC Phase 2 only	
2.2.3.5	Summary of Progression-Free Survival by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Renal Cell Carcinoma Phase 2 only	
2.2.3.6	Summary of Progression-Free Survival by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Squamous Cell Carcinoma of the Head and Neck Phase 2 only	

Table No.	Title	Population	Standard
2.2.3.7	Summary of Progression-Free Survival by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Transitional Carcinoma of the GU Tract Phase 2 only	
2.2.3.8	Summary of Progression-Free Survival by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Ovarian Phase 2 only	
2.2.3.9	Summary of Progression-Free Survival by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Gastric Cancer Phase 2 only	
2.2.3.10	Summary of Progression-Free Survival by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Colorectal Phase 2 only	
2.2.3.11	Summary of Progression-Free Survival by Modified Lugano Criteria by PD-L1 Status	Efficacy Evaluable DLBCL Phase 2 only	
2.2.4.1	Summary of Overall Survival by PD-L1 Status	Efficacy Evaluable Hepatocellular Carcinoma Phase 2 only	
2.2.4.2	Summary of Overall Survival by PD-L1 Status	Efficacy Evaluable Breast Cancer Phase 2 only	
2.2.4.3	Summary of Overall Survival by PD-L1 Status	Efficacy Evaluable Immune Checkpoint-naïve Melanoma Phase 2 only	
2.2.4.3.1	Summary of Overall Survival by PD-L1 Status	Efficacy Evaluable Primary Refractory Melanoma Phase 2 only	
2.2.4.3.2	Summary of Overall Survival by PD-L1 Status	Efficacy Evaluable Relapsed Melanoma Phase 2 only	
2.2.4.4	Summary of Overall Survival by TPS Score	Efficacy Evaluable NSCLC Phase 2 only	
2.2.4.5	Summary of Overall Survival by PD-L1 Status	Efficacy Evaluable Renal Cell Carcinoma Phase 2 only	
2.2.4.6	Summary of Overall Survival by PD-L1 Status	Efficacy Evaluable Squamous Cell Carcinoma of the Head and Neck Phase 2 only	
2.2.4.7	Summary of Overall Survival by PD-L1 Status	Efficacy Evaluable Transitional Carcinoma of the GU Tract Phase 2 only	
2.2.4.8	Summary of Overall Survival by PD-L1 Status	Efficacy Evaluable Ovarian Phase 2 only	
2.2.4.9	Summary of Overall Survival by PD-L1 Status	Efficacy Evaluable Gastric Cancer Phase 2 only	

Table No.	Title	Population	Standard
2.2.4.10	Summary of Overall Survival by PD-L1 Status	Efficacy Evaluable Colorectal Phase 2 only	
2.2.4.11	Summary of Overall Survival by PD-L1 Status	Efficacy Evaluable DLBCL Phase 2 only	
2.2.5.1	Summary of Best Ordinal Categorical Response Score by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Hepatocellular Carcinoma Phase 2 only	
2.2.5.2	Summary of Best Ordinal Categorical Response Score by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Breast Cancer Phase 2 only	
2.2.5.3	Summary of Best Ordinal Categorical Response Score by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Immune Checkpoint-naïve Melanoma Phase 2 only	
2.2.5.3.1	Summary of Best Ordinal Categorical Response Score by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Primary Refractory Melanoma Phase 2 only	
2.2.5.3.2	Summary of Best Ordinal Categorical Response Score by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Relapsed Melanoma Phase 2 only	
2.2.5.4	Summary of Best Ordinal Categorical Response Score by irRECIST Criteria by TPS Score	Efficacy Evaluable NSCLC Phase 2 only	
2.2.5.5	Summary of Best Ordinal Categorical Response Score by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Renal Cell Carcinoma Phase 2 only	
2.2.5.6	Summary of Best Ordinal Categorical Response Score by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Squamous Cell Carcinoma of the Head and Neck Phase 2 only	
2.2.5.7	Summary of Best Ordinal Categorical Response Score by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Transitional Carcinoma of the GU Tract Phase 2 only	
2.2.5.8	Summary of Best Ordinal Categorical Response Score by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Ovarian Phase 2 only	
2.2.5.9	Summary of Best Ordinal Categorical Response Score by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Gastric Cancer Phase 2 only	
2.2.5.10	Summary of Best Ordinal Categorical Response Score by irRECIST Criteria by PD-L1 Status	Efficacy Evaluable Colorectal Phase 2 only	
[redacted]			

[redacted]

Safety			
3.1 Dose Exposure			
3.1.1	Summary of Exposure and Duration of Exposure to INCB024360 and MK-3475	Safety Evaluable	X
3.2 Adverse Events			
3.2.1	Overall Summary of Treatment-Emergent Adverse Events	Safety Evaluable	X
3.2.2	Summary of Treatment-Emergent Adverse Events By MedDRA System Organ Class and Preferred Term	Safety Evaluable	X
3.2.3	Summary of Treatment-Emergent Adverse Events By MedDRA Preferred Term in Decreasing Order of Frequency	Safety Evaluable	X
3.2.6	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events By MedDRA System Organ Class and Preferred Term	Safety Evaluable	X

Table No.	Title	Population	Standard
3.2.7	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety Evaluable	X
3.2.8	Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety Evaluable	X
3.2.9	Summary of Serious Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety Evaluable	X
3.2.10	Summary of Treatment-Related (Epacadostat or Pembrolizumab) Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety Evaluable	X
3.2.11	Summary of Treatment-Related (Epacadostat or Pembrolizumab) Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety Evaluable	X
3.2.16	Summary of Treatment-Emergent Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term	Safety Evaluable	X
3.2.18	Summary of Treatment-Emergent Adverse Events Leading to Any Dose Reduction by MedDRA System Organ Class and Preferred Term	Safety Evaluable	X
3.2.19	Summary of Treatment-Emergent Adverse Events Leading to Any Dose Interruption by MedDRA System Organ Class and Preferred Term	Safety Evaluable	X
3.2.20	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Any Study Drug by MedDRA System Organ Class and Preferred Term	Safety Evaluable	X
3.2.27	Summary of Treatment-Emergent Adverse Events of Special Interest by Category and MedDRA Preferred Term	Safety Evaluable	X
3.3 Laboratory			
3.3.1.1	Summary of Laboratory Values - Hematology	Safety Evaluable	X
3.3.1.2	Summary of Laboratory Values - Chemistry	Safety Evaluable	X
3.3.1.3	Summary of Laboratory Values – Endocrine Monitoring	Safety Evaluable	X
3.3.2.1	Shift Summary of Hematology Values - to the Worst Abnormal Value	Safety Evaluable	X
3.3.2.2	Shift Summary of Chemistry Values - to the Worst Abnormal Value	Safety Evaluable	X
3.4 Vital Signs			
3.4.1	Summary of Systolic Blood Pressure	Safety Evaluable	X
3.4.2	Summary of Diastolic Blood Pressure	Safety Evaluable	X
3.4.3	Summary of Pulse	Safety Evaluable	X
3.4.4	Summary of Body Temperature	Safety Evaluable	X
3.4.5	Summary of Respiration Rate	Safety Evaluable	X
3.5 ECG			
3.5.9	Summary of Clinically Significant ECG Abnormality	Safety Evaluable	X

Listings

Listing No.	Title
2.1 Discontinued Subjects (Subject Disposition)	
2.1.1	Subject Enrollment and Disposition Status
2.2 Protocol Deviation	
2.2.1	Protocol Deviations
2.3 Data Excluded from [redacted] Efficacy, and/or Safety Analyses	
2.3.1	Analysis Populations
2.4 Demography and Baseline	
2.4.1	Demographic and Baseline Disease Characteristics
2.4.2.1	Oncology Disease History (Hepatocellular Carcinoma)
2.4.2.2	Oncology Disease History (Breast Cancer)
2.4.2.3	Oncology Disease History (Melanoma)
2.4.2.4	Oncology Disease History (NSCLC)
2.4.2.5	Oncology Disease History (Renal Cell Carcinoma)
2.4.2.6	Oncology Disease History (Squamous Cell Carcinoma of the Head and Neck)
2.4.2.7	Oncology Disease History (Transitional Carcinoma of the GU Tract)
2.4.2.8	Oncology Disease History (Ovarian)
2.4.2.9	Oncology Disease History (Gastric Cancer)
2.4.2.10	Oncology Disease History (Colorectal)
2.4.2.11	Oncology Disease History (DLBCL)
2.4.2.12	Oncology Disease History (Adenocarcinoma of the Endometrium)
2.4.3	Prior Radiation Treatment
2.4.4	Prior Medications for Cancer
2.4.5	Prior Surgery
2.4.6	Medical History
2.4.7	Prior and Concomitant Medication
2.5 Study Drug Administration	
2.5.1	Study Drug Administration – INCB024360
2.5.2	Study Drug Administration – MK-3475
2.5.3	Study Drug Administration for Subjects Who Entered Monotherapy Period – INCB024360
2.5.4	Study Drug Administration for Subjects Who Entered Retreatment Period – INCB024360
2.5.5	Study Drug Administration for Subjects Who Entered Retreatment Period – MK-3475
2.6 Efficacy	
2.6.1.1	Investigator-Reported Assessment by irRECIST Criteria (Phase 2 only, not including DLBCL)
2.6.1.2	Investigator-Reported Assessment by Modified Lugano Criteria (Phase 2 only, DLBCL only)
2.6.2.1	Duration of Response by irRECIST/Modified Lugano Criteria (Phase 2 only, all tumor types)
2.6.2.2	Duration of Disease Control by irRECIST/Modified Lugano Criteria (Phase 2 only, all tumor types)
2.6.2.3	Progression-Free Survival by irRECIST/Modified Lugano Criteria (Phase 2 only, all tumor types)
2.6.2.4	Overall Survival (Phase 2 only, all tumor types)
2.6.2.5	Target Lesions (Phase 2 only, not including DLBCL)
2.6.3.1	Investigator-Reported Assessment by RECIST Criteria (Phase 2 only, not including DLBCL)
2.6.3.2	Investigator-Reported Assessment by Lugano Criteria (Phase 2 only, DLBCL only)

Listing No.	Title
2.7 Adverse Events	
2.7.1	Adverse Events
2.7.3	Liver Function Laboratory Values in Subjects With Aminotransferase (ALT or AST) >=3 x ULN and Bilirubin >=2 x ULN and Alkaline Phosphatase <2 x ULN
2.7.4	Dose-Limiting Toxicities
2.7.5	Serious Adverse Events
2.7.6	Adverse Events Leading to Interruption, Reduction, or Discontinuation of Any Study Drug
2.7.7	Fatal Adverse Events
2.8 Laboratory Data	
2.8.1.1	Clinical Laboratory Values - Hematology
2.8.1.2	Clinical Laboratory Values - Chemistry
2.8.2	Abnormal Clinical Laboratory Values
2.9 Vital Signs	
2.9.1	Vital Sign Values
2.10 ECG	
2.10.1	12-Lead ECG Values
2.12+ Other Data	
2.12.1	PD-L1 Status

Signature Manifest

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