Clinical Study Protocol

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 Cancers

Product:	**INCB024360 and MK-3475**
IND Number:	**121,704**
Phase of Study:	**1/2**
Sponsor:	**Incyte Corporation 1801 Augustine Cut-Off Wilmington, DE 19803**
Date of Original Protocol (Version 0):	**03 MAR 2014**
Date of Amendment (Version) 1:	**03 APR 2014**
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Date of Amendment (Version) 6:	**12 JUL 2016**
Date of Amendment (Version) 7:	**15 FEB 2017**
Date of Amendment (Version) 8:	**30 AUG 2017**
Date of Amendment (Version) 9:	**24 JAN 2018**
Date of Amendment (Version) 10:	**02 JUL 2018**

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

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochures for MK-3475 and INCB024360. I have read the INCB 24360-202 Protocol Amendment 10 (Version 10 dated 02 JUL 2018) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

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(Printed Name of Investigator)

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(Signature of Investigator) (Date)

SYNOPSIS

Name of Investigational Products: MK-3475 (pembrolizumab) and INCB024360 (epacadostat)

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

Protocol Number: INCB 24360-202	**Study Phase:** 1/2

Primary Objectives:

- 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 subjects with 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 diffuse large B-cell lymphoma (DLBCL).

Secondary Objectives (Phase 2):

- 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, progression-free survival (PFS), and duration of disease control as measured by irRECIST v1.1 for solid tumors or 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 criteria
  - 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.

[redacted]

Overall Study Design:

Note: Amendment 10 will serve to close the study to future enrollment. The primary purpose of the amendment is to provide guidance for handling subjects still on study.

This is a Phase 1/2 study, with Phase 1 being a dose-escalation of INCB024360 in combination with MK-3475 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 INCB024360 in combination with MK-3475 in subjects with the following selected solid tumors: Stage IIIB, Stage IV, or recurrent NSCLC, melanoma, transitional cell 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) 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, microsatellite-instability (MSI) high colorectal cancer (CRC), DLBCL, gastric cancer, and hepatocellular carcinoma (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) $\geq$ 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-naïve (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.

Phase 1 Dose Escalation:

Phase 1 is the dose-escalation phase, which will include cohorts of subjects treated with INCB024360 BID at initial doses of 25 mg BID, 50 mg BID, and 100 mg BID in combination with MK-3475 2 mg/kg every 3 weeks (Q3W), and INCB024360 300 mg BID in combination with MK-3475 200 mg Q3W. Interim dose levels of 75 mg QD (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 INCB024360 for at least 80% of the doses during the 42-day DLT observation period, and must have received 2 doses of MK-3475 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 MK-3475 200 mg Q3W.

3 + 3 + 3 Design: The dose of INCB024360 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 INCB024360 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 MK-3475 2 mg/kg, other alternative dose schedules (ie, intermittent dosing) of INCB024360 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 INCB024360 according to the table below will proceed with MK-3475 2 mg/kg Q3W. The cohorts and dose levels are shown in the tables below.

Dose Escalation:

Daily Dose[a] of INCB024360	Dose of MK-3475 (Once 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 QD (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 INCB024360 300 mg BID may be evaluated but will be tested with the flat dose of MK-3475 200 mg.

Safety Expansions:

Daily Dose of INCB024360	Dose of MK-3475 (Once 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 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 Adjustments section of the Protocol. However, dose adjustments should not be made during the DLT observation period without discussion with the medical monitor. Intrasubject dose escalation is not permitted.

Phase 2 Cohort Expansions:

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-naïve, 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.

Tumor Type	Approximate No. of Subjects Enrolled
NSCLC high positive (PD-L1 TPS ≥ 50%)[a]	42
NSCLC low/negative or indeterminate (PD-L1 TPS 0%-49% or indeterminate)[b]	25
Melanoma (immune checkpoint naïve)	40
Transitional cell carcinoma of the GU tract	36
TNBC	32
Ovarian cancer	33
SCCHN	32
DLBCL[a]	37
RCC	36
MSI high CRC[a]	29
Gastric cancer	27
HCC[a]	32
Melanoma (primary refractory)[a]	27[c]
Melanoma (relapsed)[a]	18[c]
Total	446[d]

[a] These cohorts were discontinued before full enrollment.

[b] Subjects whose biopsies are PD-L1 indeterminate will not be excluded from the study, with the exception as noted in inclusion criterion 10a. They will be enrolled under the PD-L1 low/negative group but will be analyzed separately. This may require additional enrollment into the PD-L1 low/negative group to ensure that 25 PD-L1 low/negative subjects are enrolled. Low/negative is defined as TPS of 0% to 49%.

[c] These 2 cohorts will use a Simon 2-stage design. These numbers represent the maximum total sample size for each cohort. The actual sample size may be smaller.
[d] Closing of cohorts before full enrollment will result in fewer than 446 subjects.

For all subjects enrolled in this study (Phase 1 and Phase 2), participation has 5 components:

Screening: Up to 28 days.

Treatment: The treatment period with the combination therapy (MK-3475 + INCB024360) will continue every 21 days for up to 24 months (35 administrations of MK-3475). After completion of 24 months of combination treatment, the option for treatment with monotherapy INCB024360 is available for up to 12 months for subjects who are receiving benefit from treatment and have not had disease progression or met any criteria for study withdrawal, or they may stop both INCB024360 and MK-3475. **Note:** As of Amendment 10, INCB024360 administration is removed from the regimen for melanoma cohorts (except with medical monitor approval). Ongoing subjects with melanoma will be instructed to stop taking INCB024360 and to continue on MK-3475 alone (for up to the 35 infusions) or to stop treatment if on INCB024360 monotherapy unless medical monitor approval has been received to continue for the Protocol-specified interval (up to 12 months). Treatment with INCB024360 monotherapy and as part of combination therapy during the re-treatment periods is removed for subjects who have not already initiated such treatment. For those subjects who have already initiated INCB024360 monotherapy treatment or re-treatment and who do not have melanoma, treatment is limited to 12 months.

Safety/Survival Follow-Up: Safety follow-up visits will occur 42 to 49 days after the last dose of INCB024360 is taken and survival/safety follow-up visit at 90 days after the last dose of INCB024360.

Combination Therapy, Dosage, and Mode of Administration:

Note: As of Amendment 10, subjects in the melanoma cohorts will no longer receive INCB024360 (except with medical monitor approval).

INCB024360 will be self-administered orally BID and continued BID during the 21-day cycle for an every-3-week dose schedule of MK-3475. The RP2D of INCB024360 (or PAD) defined during Phase 1 as 100 mg BID will be used for Phase 2.

All BID doses will be taken morning and evening, approximately 12 hours apart without respect to food. If a dose is missed by more than 4 hours, that dose should be skipped and should be resumed at the scheduled time.

MK-3475 is an investigational agent and will be administered at 2 mg/kg or 200 mg intravenously (IV) over a 30-minute period on Day 1 of an every-3-week cycle.

Duration of Participation: Subject participation is expected to average approximately 6 months.

Study Population:

Phase 1: Subjects with Stage IIIB, Stage IV, or recurrent NSCLC, melanoma, transitional cell carcinoma of the GU tract, RCC, TNBC, adenocarcinoma of the endometrium, and SCCHN who have received at least 1 line of prior therapy and are refractory or for which no curative treatment is available will be enrolled.

Phase 2 expansion cohorts: Subjects with melanoma, transitional cell carcinoma of the GU tract, SCCHN, ovarian cancer, TNBC, and DLBCL, NSCLC, MSI high CRC, clear cell RCC, gastric cancer, and HCC will be enrolled.

Key Inclusion Criteria:

- Male or female subjects, age 18 years or older.
- Willingness to provide written informed consent/assent for the study.
- For Phase 1: Histologically or cytologically confirmed NSCLC, melanoma, transitional cell carcinoma of the GU tract, clear cell RCC, TNBC, adenocarcinoma of the endometrium, or SCCHN

- For Phase 2: Histologically or cytologically confirmed melanoma, transitional cell carcinoma of the GU tract, SCCHN, ovarian cancer, TNBC, DLBCL, NSCLC, MSI high CRC, clear cell RCC, gastric cancer, and HCC.
- Life expectancy > 12 weeks.
- ECOG performance status 0 to 1.
- Presence of measurable disease per RECIST v1.1 for solid tumors or The Lugano Classification (Cheson et al 2014) for subjects with DLBCL.
- Laboratory and medical history parameters within Protocol-defined range. NOTE: If the screening laboratory tests below were conducted > 7 days prior to treatment initiation, they will need to be repeated on Day 1 before initiation of treatment. Hematology and coagulation testing are central testing; therefore, central laboratory results should be used to determine eligibility for those relevant analytes below unless central laboratory results are not available at the time of enrollment or are not within the 7-day window before Cycle 1 Day 1. In this case, local laboratory results may be used to confirm eligibility. Chemistry testing is local testing; therefore, local results should be used for those relevant analytes below.
  - Absolute neutrophil count $\geq 1.5 \times 10^9$/L (for subjects with DLBCL, in no case $< 1.0 \times 10^9$/L)
  - Platelets $\geq 100 \times 10^9$/L (for subjects with DLBCL or HCC in no case $< 50 \times 10^9$/L).
  - Hemoglobin ≥ 9 g/dL or ≥ 5.6 mmol/L (transfusion is acceptable to meet this criterion).
  - Serum creatinine $\leq 1.5 \times$ institutional upper limit of normal (ULN) OR measured or calculated creatinine clearance (glomerular filtration rate can also be used in place of creatinine or CrCl) ≥ 50 mL/min for subjects with creatinine levels $> 1.5 \times$ institutional ULN.
  - Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) $< 2.5 \times$ ULN OR $\leq 5 \times$ ULN for subjects with liver metastases. For subjects with HCC: AST/ALT $< 5 \times$ ULN. For other specific exceptions medical monitor approval is required.
  - Total bilirubin $\leq 1.5 \times$ ULN **OR** direct bilirubin $\leq$ ULN for subjects with total bilirubin $> 1.5 \times$ ULN).
    - If there is no institutional normal range available for the direct bilirubin, the direct bilirubin should be < 40% of the total bilirubin.
    - In no case can total bilirubin exceed $3.0 \times$ ULN.
  - International normalized ratio (INR) or prothrombin time (PT) $\leq 1.5 \times$ ULN unless subject is receiving anticoagulant therapy as long as PT or INR is within therapeutic range of intended use of anticoagulants. Subjects with HCC must have INR ≤ 2.3.
  - Activated partial thromboplastin time (aPTT) $\leq 1.5 \times$ ULN unless subject is receiving anticoagulant therapy, as long as PTT is within therapeutic range of intended use of anticoagulants.
- For Phase 1: Subjects who have advanced or metastatic disease as noted above who have received at least 1 prior therapy for their disease under study or have advanced or metastatic disease for which no curative treatment is available.
- For Phase 2 expansion cohorts: Subjects with NSCLC, melanoma, transitional cell carcinoma of the GU tract, SCCHN, ovarian cancer, DLBCL, TNBC, MSI high CRC, clear cell RCC, gastric cancer, and HCC.
  - Phase 2 expansion: NSCLC (PD-L1 positive and PD-L1 low/negative or indeterminate cohorts)
    - Subjects who have received at least 1 prior systemic chemotherapy regimen for Stage IIIB, Stage IV, or recurrent NSCLC (not including neoadjuvant and/or adjuvant therapy except as described below)

- One prior systemic regimen must include a platinum-based therapy. Investigational agents used in combination with standard therapies are allowed. Subjects who have a non–platinum-based regimen may be enrolled with medical monitor approval.

– Documentation of mutation status. Tumors with driver mutations (eg, epidermal growth factor receptor mutation positive or anaplastic lymphoma kinase fusion oncogene positive) treated with a targeted therapy are permitted; however, subjects should have progressed or be intolerant to the targeted therapy.

- Subjects who completed and progressed on a platinum-containing regimen as adjuvant, neoadjuvant, or part of a course of chemoradiation therapy within the 6 months before screening would be counted as having received 1 prior platinum-containing regimen and therefore would not require re-treatment with a platinum-containing regimen for Stage IIIB, Stage IV, or recurrent disease.
- Subjects must **not** have received immunotherapy with PD-1 or cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) targeted therapy.

– Subjects whose PD-L1 status is indeterminate from biopsy sample collected may be enrolled in the PD-L1 low/negative cohort until the cohort is full, at which time subjects whose sample is indeterminate may be eligible for repeat biopsy to determine PD-L1 status and, if positive, may be enrolled in the PD-L1-positive cohort if that cohort has not been filled. PD-L1 results from prior testing with the FDA-approved assay (PD-L1 IHC 22C3 pharmDX) are acceptable.

- Phase 2 expansion: Melanoma

– Documentation of V600E-activating BRAF mutation status or consent to BRAF V600E mutation testing during the screening period. **Note:** Testing should be performed in a Clinical Laboratory Improvement Amendments–certified laboratory. BRAF mutation status determined as part of a panel of genetic tests performed in a gene expression analysis will also satisfy the inclusion criteria for BRAF mutation testing.

– Prior systemic therapy requirements:

- Melanoma immune checkpoint-I cohort: Subjects must not have received immunotherapy with anti–PD-1, anti–PD-L1, or anti–CTLA-4 therapy. **Exception:** Prior anti–CTLA-4 in the adjuvant setting would be permitted.
- Primary refractory cohort: Subjects must have received prior treatment with anti–PD-1 or anti–PD-L1 therapy (alone or as part of a combination) in the advanced or metastatic setting and have PD as their best response to treatment that is confirmed at least 4 weeks later (no less than 28 days).
  - Subjects must have received at least 2 doses of a prior anti–PD-1 or anti–PD-L1 agent.
  - Progressive disease must also be at least 12 weeks from first dose of anti–PD-1 or anti–PD-L1 therapy and confirmed 4 weeks (no less than 28 days) later.
  - No more than 1 prior line of therapy is permitted and must have contained anti–PD-1 or anti–PD-L1 therapy (alone or as part of a combination) with the exception of targeted therapy for subjects who have tumors that are BRAF mutant.
    – For subjects with BRAF-mutant tumors, treatment with a targeted therapy is required, and subjects should have progressed or been intolerant to the targeted therapy to be eligible.
    – For subjects who progressed on BRAF targeted therapy, lactate dehydrogenase must be $< 2 \times$ ULN.

- Relapsed cohort: Subjects must have received prior anti–PD-1 or anti–PD-L1 therapy (alone or as part of a combination) in the advanced or metastatic setting and achieved partial response [PR]/CR but later have confirmed PD (PD confirmed at least 4 weeks [no less than 28 days] later).
  - For subjects enrolling in the primary refractory or relapsed melanoma cohorts: Willing to undergo mandatory pretreatment and on-treatment core or excisional tumor biopsies. **Note:** In all cases, biopsies will be confirmed to contain adequate tumor tissue by a local pathology review. If a subject is assessed by the interventional radiologist as having inaccessible lesions, subject may be enrolled with medical monitor approval. In this case submission of archived tumor tissue may be acceptable.
  - Ocular melanoma is excluded.

- Phase 2 expansion: Transitional cell carcinoma of the GU tract
  - Histologically or cytologically confirmed transitional cell carcinoma of the bladder, ureter, or renal pelvis, or mixed histology bladder cancer.
  - Metastatic or locally advanced and not amendable to curative therapy transitional cell carcinoma of the GU tract cancer with disease progression on or after platinum-based chemotherapy or alternative therapy if platinum-based therapy is not appropriate.
  - Prior PD-1 or CTLA-4 targeted therapies are excluded.
- Phase 2 expansion: SCCHN
  - Histologically confirmed metastatic or recurrent squamous cell carcinoma not amenable to local therapy with curative intent (surgery or radiation with or without chemotherapy). Carcinoma of the nasopharynx, salivary gland, or nonsquamous histologies are excluded.
  - Subjects must have received at least 1 prior systemic regiment that must have included a platinum-based therapy. Investigational agents used in combination with standard therapies are allowed. Subjects who relapse within 6 months of adjuvant therapy, including a platinum-containing regimen, may enroll.
  - Prior PD-1 or CTLA-4 targeted therapies are excluded.
- Phase 2 expansion: Ovarian cancer
  - Subjects with FIGO Stage Ic, Stage II, Stage III, Stage IV, recurrent, or persistent (unresectable) histologically confirmed epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube carcinoma.
  - Subjects must have received a platinum-taxane-based regimen as first-line therapy.
  - Subjects who received maintenance paclitaxel, bevacizumab, or alternative maintenance therapy (eg, vaccines) are eligible for enrollment provided they have discontinued therapy at least 4 weeks for prior taxane, at least 4 weeks for bevacizumab, or received medical monitor approval for time lapse from alternative maintenance therapy prior to enrollment and recovered from toxicities to less than Grade 2.
  - Prior PD-1 or CTLA-4 targeted therapies are excluded
  - Borderline, low-malignant-potential epithelial carcinoma per histopathology is excluded.
- Phase 2 expansion: Relapsed or refractory DLBCL
  - Prior allogeneic stem-cell transplantation is excluded.
  - Must have received ≥ 1 prior treatment regimen.
  - Not a candidate for curative therapy or hematopoietic stem-cell transplantation (either due to disease burden, fitness, or preference).

- Prior PD-1 or CTLA-4 targeted therapies are excluded.
- Fluorodeoxyglucose-avid disease (based on local evaluation) per the Lugano Classification (Cheson et al 2014). Fluorodeoxyglucose-avid disease is defined as disease with a 5-point scale score of 4 or 5.

- Phase 2 expansion: TNBC
  - Histologically confirmed breast adenocarcinoma that is unresectable loco-regional, or metastatic.
  - Pathologically confirmed as triple negative, source documented, defined as both of the following:
    - Estrogen receptor (ER) and progesterone receptor (PgR) negative: < 1% of tumor cell nuclei are immunoreactive in the presence of evidence that the sample can express ER or PgR (positive intrinsic controls).
    - Human epidermal growth factor receptor 2 (HER2) negative as per American Society of Clinical Oncology/College of American Pathologists guidelines i. immunohistochemistry (IHC) 0 or 1 fluorescence in situ hybridization (FISH) negative (or equivalent negative test). ii. Subjects with IHC 2 must have a negative by FISH (or equivalent negative test).
  - Subjects with breast cancer history of different phenotypes (ie, ER/PgR/HER2 positive) must have pathologic confirmation of triple negative disease in at least one of the current sites of metastasis
  - Subject must have received at least 1 prior systemic regimen for advanced or metastatic disease.
  - Prior PD-1 or CTLA-4 targeted therapies are excluded.
- Phase 2 expansion: RCC
  - Subjects with histological or cytological confirmation of clear cell RCC.
  - Not curable by surgery.
  - Subjects must have received prior antiangiogenic therapy or refused standard therapy.
  - Subjects must not have received prior immunotherapy with anti–PD-1, anti–PD-L1, or anti–CTLA-4 therapy.
- Phase 2 expansion: MSI high CRC
  - Subjects with histological confirmation of locally advanced unresectable or metastatic MSI high CRC.
  - Mismatch repair (MMR) or MSI status is, respectively, determined by examining either CRC tumor: protein expression by immunohistochemistry of 4 MMR enzymes (MLH1/MSH2/MSH6/PMS2) OR 3 to 5 tumor microsatellite loci using polymerase chain reaction (PCR)-based assay. Tumors are classified as MSI high when at least 2 allelic shifts among the 3 to 5 analyzed microsatellite markers are detected by PCR or absence of at least 1 of 4 MMR protein expression is detected by IHC.
  - Subjects may have received no more than 2 lines of prior therapy for advanced disease (if a subject progressed within 6 months of completing adjuvant therapy, this would count as a prior line of therapy).
- Phase 2 expansion: Gastric Cancer
  - Must have histologically or cytologically confirmed diagnosis of gastric or gastroesophageal junction adenocarcinoma.
  - Must have progression on or after therapy containing platinum/fluoropyrimidine or refused standard therapy.

- Documentation of HER2/neu status. Subjects who are HER2/neu-positive must be treated with a HER2/neu inhibitor, and subjects should have progressed on or be intolerant to the targeted therapy or refused standard therapy.
- Subjects may have received no more than 2 lines of prior therapy for the advanced disease (if a subject progressed within 6 months of completing adjuvant therapy, this would count as a prior line of therapy).

• Phase 2 expansion: HCC

- Must have histologically or cytologically confirmed diagnosis of hepatocellular carcinoma.
- Child-Pugh score of A.
- Subjects may have received no more than 2 lines of prior therapy for the advanced disease (If a subject progressed within 6 months of completing adjuvant therapy, this would count as a prior line of therapy).
- Must have progressed on, refused, or were intolerant of sorafenib.
  - Intolerant is defined as any Grade ≥ 2 drug-related AE that, despite supportive therapy, recurred after sorafenib treatment interruption of at least 7 days and dose reduction resulting in the subject requesting or the physician recommending discontinuation due to toxicity.
- The following are excluded: Subjects with liver transplants, clear invasion of the bile duct or main portal branch(es), or hepatorenal syndrome, or subjects who have required esophageal variceal ablation within 28 days of starting study treatment.
- Subjects with controlled (treated) hepatitis B will be allowed if they meet the following criteria:
  - Antiviral therapy for hepatitis B virus (HBV) must be given for at least 12 weeks, and HBV viral load must be < 100 IU/mL before the first dose of study drug. Subjects on active HBV therapy with viral loads < 100 IU/mL should stay on the same therapy throughout study treatment.
  - Subjects who are anti-HBc positive, negative for HbsAg, negative for anti-HBs, and have an HBV viral load < 100 IU/mL do not require HBV antiviral prophylaxis.
- Subjects with history of hepatitis C virus (HCV) who have had successful treatment, defined as undetectable HCV RNA more than 12 weeks after treatment (these subjects may be HCV antibody positive, but will not have detectable RNA). Also subjects with untreated HCV and those who failed treatment are permitted. However, for those with untreated HCV and those who have failed treatment, HCV viral load will be monitored every cycle.
- Blood pressure must be adequately controlled.

• Fresh baseline tumor biopsies (defined as a biopsy specimen with adequate tumor tissue taken since completion of the most recent prior systemic regimen) are required. If a subject has inaccessible lesions, such as in ovarian cancer, or highly vascular lesions, such as RCC, HCC, or gastric cancer, enrollment may be considered with medical monitor approval. In this case, submission of archived tumor tissue may be acceptable.

- Fresh formalin-fixed or formalin-fixed paraffin-embedded tumor tissue blocks are preferred. If a block is not available, a minimum 20 unstained freshly cut slides may be submitted to the testing laboratory per the specifications in the laboratory manual.

• Women of childbearing potential and males who use adequate birth control through 120 days after the last dose of study treatment.

Key Exclusion Criteria:

- Participated in any other study in which receipt of an investigational study drug or device occurred within 2 weeks or 5 half-lives (whichever is longer) before first dose. For investigational agents with long half-lives (eg, > 5 days), enrollment before the fifth half-life requires medical monitor approval.
- Diagnosis of immunodeficiency or is receiving systemic steroid or any other form of immunosuppressive therapy within 7 days before the first dose of study treatment.
- Prior monoclonal antibody within 4 weeks or 5 half-lives (whichever is shorter) before study Day 1 or not recovered (≤ Grade 1 or at baseline) from adverse events (AEs) due to agents administered more than 4 weeks earlier. An exception to this rule would be use of denosumab.
- Prior chemotherapy or targeted small molecule therapy within 2 weeks before study Day 1 or not recovered (≤ Grade 1 or at baseline) from AEs due to previously administered agents.
  - Note: Subjects with ≤ Grade 2 neuropathy or alopecia are an exception and may enroll.
  - Note: If subject received major surgery, he or she must have recovered adequately from the toxicity and/or complications from the intervention before starting therapy.
- Prior therapy with an anti–PD-1, anti–PD-L1, anti–PD-L2, anti–CD137, or anti–CTLA-4 (including ipilimumab or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways). **Exception:** Prior anti–CTLA-4 in the adjuvant setting for subjects with melanoma would be permitted.
- Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.
- Known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks before the first dose of study treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and have not required steroids for at least 7 days before study treatment.
  - Subjects with evidence of cerebral edema will be excluded from participation. In addition, subjects will be excluded from participation in the study if it has been < 8 weeks since radiation therapy was delivered to the CNS.
- Active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc) is not considered a form of systemic treatment.
- History of (noninfectious) pneumonitis that required steroids, or current pneumonitis.
- Prior radiotherapy within 2 weeks of therapy (exception for radiation to CNS, which requires ≥ 8-week washout). Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation to non-CNS disease with medical monitor approval.
- Active infection requiring systemic therapy.
- Known HBV or HCV viremia or at risk for HBV reactivation. Exception for subjects enrolled in the HCC cohort (see details in Section 3 under the HCC-specific inclusion/exclusion criteria).
  - HBV DNA and HCV RNA must be undetectable.
  - At risk for HBV reactivation is defined as: hepatitis B surface antigen positive or anti–hepatitis B core antibody positive. (Testing required and may be performed locally.). Results for

anti-HBV/HCV antibodies must be available before treatment. If negative, subjects may be enrolled before DNA/RNA results with medical monitor approval.

- Pregnant or nursing women or subjects expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of study treatment.
- Known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies).
- Live attenuated vaccine within 30 days before the first dose of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
- Monoamine oxidase inhibitors within the 21 days before screening or any concurrent use of a prohibited medication listed in Section 5.13.
- Any history of serotonin syndrome after receiving 1 or more serotonergic drugs.
- Presence of a gastrointestinal condition that may affect drug absorption.
- History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
- Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study.
- Immediate family member (self, spouse, or child) who is investigational site or sponsor staff directly involved with this study, unless prospective institutional review board approval (by chair or designee) is given allowing exception to this criterion for a specific subject.
- Known allergy or reaction to any component of either study drug or formulation components, including severe (≥ Grade 3) hypersensitivity to pembrolizumab and/or any of its excipients.
- Subjects with HCC who meet the following criteria are excluded:
  - Has had esophageal or gastric variceal bleeding within the last 6 months. All subjects will be screened for esophageal varices, unless such screening has been performed in the past 12 months before first dose of treatment. If varices are present, they should be treated according to institutional standards before starting study treatment.
  - Portal vein invasion at the main portal (Vp4), inferior vena cava, or cardiac involvement of HCC based on imaging.
  - Has had clinically diagnosed hepatic encephalopathy in the last 6 months. Subjects on rifaximin or lactulose to control their hepatic encephalopathy are not allowed.
  - Had a solid organ or hematologic transplant.
  - Has received locoregional therapy to liver (transcatheter chemoembolization, transcatheter embolization, hepatic arterial infusion, radiation, radioembolization, or ablation) within 4 weeks before the first dose of study drug. Subject is not eligible if aforementioned treatments were administered between the last dose of sorafenib and first dose of study medication.
  - Has dual active HBV infection (HbsAg positive and/or detectable HBV DNA) and HCV infection (anti-HCV antibody positive and detectable HCV RNA) at study entry.

Study Schedule/Procedures:

Subjects will have regularly scheduled study visits at the clinical site on Day 1 of every cycle (CXD1), where laboratory assessments, vital sign collection, and physical examinations will be performed. Assessments for ascites and for encephalopathy should be documented at each visit for subjects with HCC. Liver function test monitoring will occur weekly during the first 6 weeks of study treatment during Phase 1 and then will be tested Q3W thereafter and in Phase 2 for subjects who remain on study treatment. Assessment of tumor size (by magnetic resonance imaging or computed tomography scan) will be performed at screening or baseline (before beginning therapy, including baseline brain MRIs), every 9 weeks for 18 months, and then every 12 weeks thereafter until disease progression. **Note:** As of Amendment 10, tumor size assessments will be performed every 9 weeks for the first 2 assessments (Week 9 and Week 18) then every 12 weeks thereafter. 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 where feasible, and where subjects are clinically stable, defined as the following: absence of signs and symptoms (including worsening of laboratory values) indicating disease progression, no decline in ECOG performance status, absence of rapid progression of disease, and absence of progressive tumors at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention. Subjects will be followed for up to 90 days from last dose for safety and survival. This follow-up may occur through a phone call, email, or visit by the subject or the subject's caretaker.

Tumor biopsies will be required at baseline for all subjects and optional any time after C1D14 or with confirmed response or progression in subjects with accessible tumors [redacted]. Biopsy specimens obtained to evaluate toxicities will also be collected to evaluate target-related expression. For subjects in the melanoma primary refractory and relapsed cohorts, a fresh tumor biopsy will be required during screening and on treatment. On-treatment biopsy samples will be collected between Days 8 and 15 of Cycle 3 (Study Days 50 and 57). **Note:** As of Amendment 10, no new subjects in the melanoma primary refractory and relapsed cohorts will be enrolled. The preceding text is retained as it refers to ongoing subjects only.

Primary Endpoints:

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

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 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]

Planned Number of Subjects: Overall study accrual will be approximately 508 subjects. This includes approximately 62 subjects enrolled in the Phase 1 dose-escalation portion of the study, followed by approximately 446 for the Phase 2 expansion portion of the study depending on screen failure rate. Additional subjects may be screened and potentially enrolled in each cohort to ensure a minimum number of subjects are enrolled. Phase 2 cohorts may be closed before full enrollment, resulting in fewer than 446 subjects.

Planned Number of Study Sites: Approximately 6 sites for the Phase 1 dose-escalation portion, and approximately 30 sites for Phase 2.

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

Estimated Study Duration: 54 months

Estimated date first subject enrolled: July 2014 (FPI)

Estimated date last subject completed: January 2019 (LPLV)

Statistical Methods:

Phase 1

Descriptive statistics (eg, mean, standard deviation, range) will be derived where appropriate. Subject enrollment, disposition, demographics, and medical history will be summarized at baseline. The rate of DLTs will be summarized for each cohort. Dose exposure and density will be calculated for each cohort. Safety and disease response data will be compared over time to assess change from baseline, during treatment, and follow-up. [redacted]

Phase 2 expansion cohorts

During cohort expansion, approximately 18 to 42 subjects are expected to be enrolled in each of the 14 expansion cohorts (NSCLC [2 cohorts], melanoma [3 cohorts], transitional cell carcinoma of the GU tract, TNBC, ovarian cancer, SCCHN, DLBCL, MSI high CRC, clear cell RCC, gastric cancer, and HCC) and treated at the previously determined RP2D that is not to exceed the MTD. Assuming a 1-sided alpha of 5% and 10% lost to follow-up, the sample size yields a power of 80% to detect an increase in ORR by 20% from historical response rate of each tumor type. The proportion of subjects with ORR by irRECIST v1.1 and Lugano Classification (Cheson et al 2014) will be tabulated by tumor type (cohort). The PFS and OS will be analyzed by the Kaplan-Meier method. Descriptive statistics (eg, median and range) will be summarized for duration of response and duration of disease control for each tumor type.

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

Term	Explanation
AE	adverse event
AFP	alpha fetoprotein
AHSCT	autologous hematopoietic stem cell transplant
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ALP	alkaline phosphatase
ANOVA	analysis of variance
BCG	Bacillus Calmette–Guérin vaccine
BID	twice daily
BMI	body mass index
CA19-9	cancer antigen 19-9
CEA	carcinoembryonic antigen
CFR	Code of Federal Regulations
CI	confidence interval
CNS	central nervous system
CP	Child-Pugh (score)
CR	complete response
CRC	colorectal cancer
eCRF	electronic case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated antigen-4
DC	dendritic cell
DLBCL	diffuse large B-cell lymphoma
DLCO	diffuse lung capacity for carbon monoxide
DLT	dose-limiting toxicity
EBV	Epstein-Barr virus
ECG	electrocardiogram

Term	Explanation
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EOT	end of treatment
ER	estrogen receptor
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FIGO	International Federation of Gynecology and Obstetrics
FISH	fluorescence in situ hybridization
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GU	genitourinary
HBc	hepatitis B core antibody
HbeAg	hepatitis Be antigen
HBs	hepatitis B surface antibody
HbsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCC	hepatocellular carcinoma
HER2	human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HPV	human papillomavirus
IC_{50}	half maximal inhibitory concentration
iIB	INCB024360 Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDO1	indoleamine 2,3 dioxygenase-1
IEC	independent ethics committee
Ig	immunoglobulin
IHC	immunohistochemistry
IN	Investigator Notification

Term	Explanation
INR	international normalized ratio
irAE	immune-related adverse event
irRC	immune response criteria
irRECIST	modified Response Evaluation Criteria In Solid Tumors
IRB	institutional review board
IRT	interactive response technology
ITT	intent to treat
IV	intravenous
LFT	liver function (chemistry) test
LH	luteinizing hormone
MAOI	monoamine oxidase inhibitors
MedDRA	Medical Dictionary for Regulatory Activities
mIB	MK-3475 Investigator's Brochure
MMR	mismatch repair
MRI	magnetic resonance imaging
MSI	microsatellite-instability
MSKCC	Memorial Sloan Kettering Cancer Center (score)
MTD	maximum tolerated dose
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PAD	pharmacologically active dose
PCR	polymerase chain reaction
PD	[redacted] progressive disease
PD-1	programmed death receptor 1
PD-L1	programmed death ligand 1
PET	positron emission tomography
PFS	progression-free survival
PgR	progesterone receptor
PR	partial response
PK	pharmacokinetic

Term	Explanation
PT	prothrombin time
Q2W	every 2 weeks
Q3W	every 3 weeks
RCC	renal cell carcinoma
RECIST v1.1	Response Evaluation Criteria In Solid Tumors Version 1.1
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SNRI	serotonin/norepinephrine reuptake inhibitors
SS	serotonin syndrome
SSRI	serotonin reuptake inhibitors
SUSAR	suspected unexpected serious adverse reaction
T1DM	Type 1 diabetes mellitus
TNBC	triple negative breast cancer
TPS	tumor proportion score
Treg	regulatory T cell
ULN	upper limit of normal

1. INTRODUCTION

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, 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, microsatellite-instability (MSI) high colorectal cancer (CRC), diffuse large B-cell lymphoma (DLBCL), gastric cancer, and hepatocellular carcinoma (HCC). INCB024360 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 (DCs). MK-3475 is a potent and highly selective humanized monoclonal antibody of the immunoglobulin (Ig)G4/kappa isotype directed against programmed death receptor 1 (PD-1). For a thorough discussion of the pharmacology of MK-3475 and INCB024360, refer to the INCB024360 Investigator's Brochure (iIB) and the MK-3475 Investigator's Brochure (mIB).

1.1. Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades (Disis 2010). The inability of the immune system to control tumor growth does not appear to result from an inability to recognize the tumor as foreign. Tumor cells have been shown to evade immune destruction despite displaying recognizable antigens on their surface and despite the presence of high avidity T cells that are specific for these antigens (Boon and Van der Bruggen 1996, Ercolini et al 2005). Histologic evaluation of many human cancers show extensive infiltration by inflammatory and immune cells (Galon et al 2006), suggesting that the immune system responds less effectively to malignancy. These observations have led to the hypothesis that dominant mechanisms of immune tolerance or immune suppression are responsible for the immune system's inability to effectively respond in a way that consistently results in rejection.

There are a number of inhibitory mechanisms that have been identified to be involved in tumor-mediated immune suppression and include expression of the programmed death ligand 1 (PD-L1), which can engage the inhibitory receptor PD-1 on activated T cells; the presence of the tryptophan-catabolizing enzyme IDO1, which exploits the exquisite sensitivity of T cells to tryptophan depletion and tryptophan metabolites; and infiltration with $FoxP3^+$ regulatory T cells (Treg), which can mediate extrinsic suppression of effector T-cell function. Therefore, agents that target these negative regulatory pathways and thereby allow the expansion of effector T cells present in the tumor may be beneficial in the clinic.

1.1.1. Inhibition of PD-1 as a Target for Cancer

The PD-1 receptor-ligand interaction is a major pathway stimulated by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to CD28 and cytotoxic T-lymphocyte-associated antigen-4

(CTLA-4), which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (Talmadge et al 2007, Usubütün et al 1998). The mechanism by which PD-1 down modulates T-cell responses is similar to but distinct from that of CTLA-4, as both molecules regulate an overlapping set of signaling proteins (Hiraoka 2010, Nobili et al 2008). PD-1 has been shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, Tregs, and natural killer cells (Hodi and Dranoff 2010, Kloor 2009). Expression has also been shown during thymic development on CD4-CD8- (double negative) T cells as well as subsets of macrophages and dendritic cells (Hillen et al 2008). The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including nonhematopoietic tissues as well as in various tumors (Lee et al 2008, Leffers et al 2009, Nishimura et al 2000, Hiraoka 2010). Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various nonhematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues (Hiraoka 2010). Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (Liotta et al 2010). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

MK-3475 (pembrolizumab [Keytruda (US)]), a humanized monoclonal antibody against the PD-1 protein, has been developed by Merck & Co for the treatment of patients with cancer. Pembrolizumab is approved for treatment of patients with melanoma in several countries; in the US and EU it is approved for the treatment of patients with advanced (unresectable or metastatic) melanoma in adults. Pembrolizumab has also been approved for treatment of patients with NSCLC in several countries; in the US it is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. Patients with NSCLC and epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should also have disease progression on FDA-approved therapy for these aberrations before to receiving pembrolizumab. Pembrolizumab has also been approved in combination with pemetrexed and carboplatin as first-line treatment of patients with metastatic nonsquamous NSCLC. This indication is approved under accelerated approval based on tumor response rate and progression-free survival (PFS). Pembrolizumab has most recently been approved as therapy for patients with recurrent or metastatic SCCHN and classical Hodgkin lymphoma. For SCCHN, it was approved specifically for patients with SCCHN with disease progression on or after platinum-containing chemotherapy. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. For Hodgkin lymphoma it has been approved for the treatment of adult and pediatric patients with refractory classical Hodgkin lymphoma, or who have relapsed after 3 or more prior lines of therapy. This indication is also approved under accelerated approval based on tumor response

rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.1.2. Inhibition of Indoleamine 2,3–Dioxygenase as a Target for Cancer

Recent interest has focused on the role of indoleamine 2,3–dioxygenase (IDO1) as a mechanism of induction of tolerance to malignancy (Godin-Ethier et al 2011). IDO1 is a heme-containing, monomeric oxidoreductase that catalyzes the degradation of the essential amino acid tryptophan to N-formyl-kynurenine. Kynurenine can be subsequently metabolized through a series of enzymatic steps to nicotinamide adenine dinucleotide. IDO1 is the first rate-limiting enzyme in one of the breakdown pathways of tryptophan. In another pathway, tryptophan hydroxylase catalysis of tryptophan leads to the formation of serotonin and melatonin.

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

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

The biological relevance of IDO1 inhibition to immune tolerance was first demonstrated when it was shown that treating mice with a small molecule inhibitor of the IDO1 pathway, 1-methyl-tryptophan, could break the tolerogenic state that protects allogeneic concepti from the maternal immune system (Munn et al 1998). A critical role for IDO1 in immunomodulation has been confirmed in numerous animal models, including models of allograft tolerance, inflammation, and cancer (Mellor and Munn 2004). While IDO1 inhibition can exacerbate disease in models of autoimmune disorders (Mellor and Munn 2004), IDO1 null mice show no evidence of susceptibility to developing spontaneous autoimmunity or alterations in immune system development (Mellor et al 2003), suggesting that IDO1 inhibition, in a therapeutic setting, may produce minimal side effects in subjects without pre-existing autoimmune conditions.

Within the context of cancer, there are several lines of evidence to suggest that IDO1 is a key regulator of the immunosuppressive mechanisms responsible for tumor escape from immune surveillance. Several groups have demonstrated that blockade of IDO1 activity can directly influence the ability of tumor-bearing animals to reject tumors (Uyttenhove et al 2003, Muller et al 2005). In addition, studies with 1-methyl-tryptophan, demonstrate that IDO1

inhibition dramatically increases the efficacy of various chemotherapeutic agents (eg, platinum compounds, taxane derivatives, cyclophosphamide) without increased toxicity (Muller et al 2005). Although the specific mechanisms responsible for this potentiation remain to be fully elucidated, the effects were not observed in T-cell–deficient animals, suggesting that the results may be the consequence of the disablement of immunosuppressive mechanisms that exist within the tumor microenvironment.

Based on studies examining serum levels of tryptophan and kynurenine, IDO1 appears to be chronically activated in subjects with cancer, and IDO1 activation correlates with more extensive disease (Huang et al 2010, Weinlich et al 2007). IDO1 has subsequently been found to be overexpressed by a wide variety of human tumor cell types as well as by the DCs that localize to the tumor draining lymph nodes (Uyttenhove et al 2003, Munn et al 2004). Increased expression of IDO1 in tumor cells has been shown to be an independent prognostic variable for reduced overall survival (OS) in subjects with melanoma, ovarian, colorectal, and pancreatic cancers (Okamoto et al 2005, Brandacher et al 2006, Ino et al 2006, Nakamura et al 2007, Witkiewicz et al 2008, Hamid et al 2009).

Together, these results suggest that the IDO1 pathway is a key regulatory element responsible for the induction and maintenance of tumor immune tolerance. Small molecule inhibitors of IDO1 may provide an innovative and tractable method to treat advanced malignancies either alone or in combination with chemotherapeutics and/or immunotherapy-based strategies.

1.1.3. Rationale for Studying Immunotherapy in Advanced or Metastatic Cancers

Cancer immunotherapies have recently have been approved by the US FDA in several tumor indications to date, such as melanoma and NSCLC. The efficacy of MK-3475 was investigated in a multicenter, open-label, randomized (1:1), dose study in subjects with unresectable or metastatic melanoma with progression of disease; refractory to 2 or more doses of ipilimumab (3 mg/kg or higher) and, if BRAF V600 mutation-positive, a BRAF or MEK inhibitor; and disease progression within 24 weeks following the last dose of ipilimumab. There were 173 subjects enrolled and the objective response rate (ORR) was 24%, with 8 subjects with ongoing responses of 6 months or longer. There were also objective responses in subjects with and without BRAF V600 mutation-positive melanoma (Pembrolizumab 2017). Similarly, nivolumab demonstrated activity when given alone in subjects with progression of disease on or following ipilimumab treatment and, if BRAF V600 mutation-positive, a BRAF inhibitor. The study enrolled 120 subjects and the ORR was 32%, with 13 subjects with ongoing responses of 6 months or longer. There were also objective responses in subjects with and without BRAF V600 mutation-positive melanoma (Nivolumab 2017). More recently, nivolumab was tested in previously untreated melanoma without BRAF mutation, which similarly showed good response rates and improvement in OS when compared to dacarbazine. At 1 year, the overall rate of survival was 72.9% (95% confidence interval [CI], 65.5 to 78.9) in the nivolumab group, as compared with 42.1% (95% CI, 33.0 to 50.9) in the dacarbazine group (hazard ratio for death, 0.42; 99.79% CI, 0.25 to 0.73; $p < 0.001$). The ORR was 40.0% (95% CI, 33.3 to 47.0) in the nivolumab group versus 13.9% (95% CI, 9.5 to 19.4) in the dacarbazine group (odds ratio, 4.06; $p < 0.001$) (Robert et al 2015a).

Nivolumab was also recently approved as a single agent for the treatment of subjects with metastatic squamous NSCLC with progression on or after platinum-based chemotherapy based

on demonstration of superior overall survival versus docetaxel, with 41% reduction in risk of death in a prespecified interim analysis of a Phase 3 clinical study. The median OS was 9.2 months in the nivolumab group and 6 months in the docetaxel group (Opdivo 2017).

In addition, on 02 OCT 2015 pembrolizumab was granted accelerated approval for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Approval was based on demonstration of a durable ORR in an activity-estimating subgroup within a study by Merck & Co. (Trial P001). This prospectively identified and retrospectively analyzed subgroup included 61 patients with NSCLC, PD-L1 expression tumor proportion score (TPS) of ≥ 50% tumor cells, and disease progression on or after platinum-containing chemotherapy, and, if appropriate, targeted therapy for anaplastic lymphoma kinase or epidermal growth factor receptor mutations. The ORR for the 61 patients was 41.0% (95% CI: 28.6%, 54.3%). The median response duration was not yet reached at the analysis time. Safety data were evaluated in 550 patients with NSCLC receiving at least 1 dose of pembrolizumab 10 mg/kg every 2 or every 3 weeks, or 2 mg/kg every 3 weeks. The most common (≥ 20%) adverse reactions included fatigue, decreased appetite, dyspnea, and cough. The most frequent (≥ 2%) serious adverse drug reactions were pleural effusion, pneumonia, dyspnea, pulmonary embolism, and pneumonitis. Clinically significant immune-mediated adverse reactions included pneumonitis, colitis, hypophysitis, and thyroid disorders. An FDA-approved companion diagnostic, PD-L1 IHC 22C3 pharmDx, to determine PD-L1 expression is now available (Pembrolizumab 2017).

This approval of pembrolizumab in NSCLC was followed 1 week later on 09 OCT 2015 with the approval of nivolumab for the treatment of patients with metastatic NSCLC with progression on or after platinum-based chemotherapy. This approval was based on demonstration of an improvement in OS comparing nivolumab to docetaxel in patients with metastatic nonsquamous NSCLC with progression on or after platinum-based chemotherapy. The study demonstrated improvement in OS with a hazard ratio of 0.73 (95% CI: 0.60, 0.89; $p < 0.002$). The median OS was 12.2 months in patients treated with nivolumab and 9.4 months in patients treated with docetaxel. The study also demonstrated a significant improvement in ORR (19% vs 12%) in the nivolumab and docetaxel groups, respectively; the median response duration was 17 months in the nivolumab group and 6 months in the docetaxel group. There was no significant difference in PFS.

On 24 OCT 2016, the FDA approved pembrolizumab for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test for first-line treatment of lung cancer. This approval also expands the indication in second-line treatment of lung cancer to include all patients with PD-L1-expressing NSCLC (Pembrolizumab 2017).

First-line data in advanced or metastatic melanoma with pembrolizumab versus ipilimumab was recently presently at the annual meeting of the American Association for Cancer Research, with an estimated 46.4% 6-month PFS rate for pembrolizumab 2 mg/kg every 3 weeks (Q3W) versus 26.5% for ipilimumab. The ORR was 32.9% for pembrolizumab 2 mg/kg Q3W versus 11.9% for ipilimumab. Responses were ongoing in 96.7% of subjects after a median follow-up of 7.9 months (Robert et al 2015b). Median PFS was 4.1 months for pembrolizumab versus 2.8 months for ipilimumab. The hazard ratio for the disease progression for pembrolizumab

Q3W versus ipilimumab was 0.58 (95% CI, 0.47 to 0.72; $p < 0.001$). At the time of the data cutoff for the second interim analysis in this study, which was driven by a minimum follow-up duration of 12 months for all subjects, 289 deaths occurred. One-year estimates of survival for subjects receiving pembrolizumab Q3W was 68.4% as compared with ipilimumab 58.2% (hazard ratio for death as compared with ipilimumab group 0.69; 95% CI, 0.52 to 0.90; $p = 0.0036$). Because the OS results were superior to those for the ipilimumab group, the independent Data Monitoring Committee recommended stopping the study early to allow subjects in the ipilimumab group the option of receiving pembrolizumab (Robert et al 2015b).

In 38 subjects with previously treated advanced NSCLC treated with MK-3475 at a dose of 10 mg/kg Q3W, an ORR of 24% as measured by the immune response criteria (irRC) was observed (Wolchok et al 2009), with similar results using RECIST v1.1 (21%). Most responses were observed by the first planned assessment at Week 9. Median duration of response by irRC has not been reached with a median duration of follow-up of 62 weeks. The median OS for all 38 subjects treated with MK-3475 was 51 weeks.

An immunohistochemistry assay was used to evaluate PD-L1 expression in subject's baseline tumor biopsies. A modified H-score scoring system of PD-L1 expression was established for NSCLC by analyzing tumor specimens from resected NSCLC specimens. This scoring system was then applied to the samples from this portion of the study. Pretreatment tumor PD-L1 expression was a statistically significant predictor of response. In subjects with evaluable tumor PD-L1 expression, the majority of confirmed responses by RECIST v1.1 (and irRC) occurred in subjects with tumors strongly positive for PD-L1. A total of 35 subjects from this study had evaluable tumor samples and a clinical response assessed. Seven of the 35 subjects had a clinical response (20%) by investigator-assessed irRC. Six responders (26%) were observed among the 23 subjects whose tumors expressed PD-L1. Of note, these 6 responders clustered at the higher end of the modified H-score. Six of 9 subjects (67%) whose tumors expressed PD-L1 to an extent above the preliminary cutpoint had a clinical response. Only 1 response was noted among the 12 subjects whose tumors did not express PD-L1.

A training set comprising approximately 140 tumor samples and their associated clinical outcome data were used to assess an optimal cutpoint for PD-L1 positivity. An optimal PDL1 cutpoint was identified by receiver operator characteristic curve analyses and by considering clinical implications of false-positive and false-negative results. Cutpoints were identified based on a proportions score method of immunohistochemistry (IHC) analysis, with the tumors expressing at or greater than the highest cutpoint (proportions score $\geq 50\%$) referred to as PD-L1 strong tumors, and tumors expressing $> 1\%$ but $< 50\%$ referred to as the PD-L1 weak tumors. Outcomes based in irRC were used as the primary outcome for the analysis. Based on the training set, the positive predictive value for subjects in the strong category was 42%, while maintaining a negative predictive value of 92% for subjects in the weak or null category (Garon et al 2013). This study completed, and a total of 495 subjects received pembrolizumab either 2 mg/kg every 2 weeks (Q2W) or 10 mg/kg Q3W or 10 mg/kg Q2W, and 182 subjects were assigned to the training group or a validation group (313 subjects). Among all subjects, the ORR was 19.4%, and the median duration of response was 12.5 months. The median duration of PFS was 3.7 months, and the median duration of OS was 12.0 months. PD-L1 expression in at least 50% of tumor cells was selected as the cutoff from the training group. Among subjects with a proportion score of at least 50% in the validation group, the response rate was 45.2%. Among all subjects with a proportion score of at least 50%, median PFS was 6.3 months; median

OS was not reached. In summary, pembrolizumab had an acceptable side-effect profile and showed antitumor activity in subjects with advanced non–small cell lung cancer. PD-L1 expression in at least 50% of tumor cells correlated with improved efficacy of pembrolizumab (Garon et al 2015).

In an open-label, Phase 1b study, the safety, tolerability, and antitumor activity of pembrolizumab were assessed in subjects with recurrent or metastatic urothelial cancer in the KEYNOTE-012 study (Clinicaltrials.gov: NCT01848834). In this study, archival or newly obtained tumor samples from subjects with advanced carcinoma of the renal pelvis, ureter, bladder, or urethra were screened for PD-L1 expression using a prototype immunohistochemistry assay. PD-L1 expression in stroma or ≥ 1% of tumor cells was required for study entry. Subjects received pembrolizumab 10 mg/kg Q2W until complete response (CR), progression, or unacceptable toxicity. A total of 33 subjects were enrolled, including 30 with transitional cell histology and 3 with nontransitional cell or mixed histology. Fifty-two percent of subjects received ≥ 2 prior therapies for advanced disease, and 21% had liver metastases. Twenty-nine had a baseline scan with measurable disease and were evaluable for response. Objective response rate by RECIST v1.1 central review was 24%. The most common adverse events (AEs) included fatigue (n = 6), peripheral edema (n = 4), and nausea (n = 3); 4 subjects (12%) reported Grade 3-4 drug-related AEs, with only rash seen in > 1 subject (n = 2).

Another cohort from the KEYNOTE-012 study included subjects with SSCHN. In this cohort, pembrolizumab 10 mg/kg was given Q2W. Sixty-one subjects were enrolled (23 human papillomavirus [HPV]+, 37 HPV−). After a median follow-up of 10.2 months, 15 subjects (25%) remained on pembrolizumab. The ORR per RECIST v1.1 by investigator review was 20%, and response duration ranged from 8+ to 41+ weeks (median not reached). The ORR was similar in HPV+ and HPV− subjects, whereas PFS and OS were longer in HPV+ subjects. PD-L1 expression was positively correlated with ORR (p = 0.018) and PFS (p = 0.024). The ORR was 50% in the 12 subjects with high PD-L1 expression. Drug-related AEs of any grade occurred in 58% of subjects (Grade ≥ 3 in 17%). The most common drug-related AEs were fatigue (18%), pruritus (10%), and nausea (8%). There were no drug-related deaths.

The safety, tolerability, and antitumor activity of pembrolizumab were also assessed in subjects with TNBC in another group in the KEYNOTE-012 study. PD-L1 expression in ≥ 1% tumor cells or in stroma was required for study entry. A total of 32 subjects were enrolled. Most of these subjects had received and progressed on multiple lines of therapy for advanced disease (the median number of prior treatments in the metastatic setting was 3). According to data through 06 NOV 2014, in 27 subjects with central imaging vendor–confirmed measurable disease, the ORR was 18.5%. The median duration of response had not been reached (range 15 to 40+ weeks). Also according to data through 06 NOV 2014, 5 subjects (15.6%) experienced at least 1 drug-related serious AE (SAE); each of 4 subjects experienced one of the following: Grade 3 anemia, headache, aseptic meningitis, or pyrexia, and a fifth subject experienced Grade 5 disseminated intravascular coagulation with thrombocytopenia and decreased blood fibrinogen.

On 05 AUG 2016, the FDA approved pembrolizumab for the treatment of some patients with an advanced form of head and neck cancer. The approval is for patients with recurrent or metastatic head and neck squamous cell carcinoma that has continued to progress despite standard-of-care treatment with chemotherapy (Pembrolizumab 2017).

Also, as part of KEYNOTE-012 pembrolizumab was tested in subjects with PD-L1–positive recurrent or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction. Subjects received intravenous pembrolizumab at 10 mg/kg once every 2 weeks. From 23 OCT 2013 to 05 MAY 2014, 39 subjects were enrolled. Thirty-six subjects were evaluable for response by central assessment. Eight subjects (22%, 95% CI 10-39) were judged to have had an objective response; all responses were partial. All 39 subjects were included in the safety analyses. Five subjects (13%) had a total of 6 Grade 3 or 4 treatment-related AEs, consisting of 2 cases of Grade 3 fatigue; 1 case each of Grade 3 pemphigoid, Grade 3 hypothyroidism, and Grade 3 peripheral sensory neuropathy; and 1 case of Grade 4 pneumonitis. No treatment-related deaths occurred (Muro et al 2016).

In patients with hematologic malignancies such as DLBCL, autologous hematopoietic stem cell transplant (AHSCT) results in remodeling of the immune system in the context of minimal residual disease, suggesting that PD-1 inhibition may be particularly effective in this setting. To test this hypothesis, Armand et al (2013) evaluated the safety and activity of pidilizumab, an anti-PD1 antibody that has shown antitumor activity in preclinical models and Phase 1 studies, in 66 subjects with DLBCL who received AHSCT. Pidilizumab was well tolerated and did not induce autoimmune toxicity or treatment-related mortality. The proportion of subjects who experienced a 16-month interval of PFS was 0.72, and the proportion of subjects who experienced a 16-month interval of overall survival was 0.85. Among 35 subjects with measurable disease after AHSCT, pidilizumab resulted in complete remission in 34% and partial remission in 17%, corresponding to an overall response rate of 51% and a median time to response of 30 weeks (Armand et al 2013).

Overexpression of PD-L1 in HCC has a poor prognosis. Safety and preliminary antitumor efficacy of nivolumab was evaluated in a Phase 1/2 study in subjects with HCC. The study evaluated 41 subjects with a Child-Pugh (CP) score of 5 (n = 35) or 6 (n = 6), ECOG score of 0 (n = 26) or 1 (n = 15), 73% with extrahepatic metastasis and/or portal vein invasion, and 77% with prior sorafenib use. The best overall response was 23% (9/39) in 39 evaluable subjects, 31.5% (6/19) in viral-infected subjects, and 15% (3/20) in uninfected subjects, including 2 CRs in this group. Drug-related AEs of any grade occurred in 29 subjects (71%; 17% Grade 3/4), with ≥ 10% of subjects experiencing aspartate aminotransferase (AST) increase and rash (each 17%), alanine aminotransferase(ALT) and lipase increase (each 15%), and amylase increase (12%). Grade 3 and 4 AEs ≥ 5% were AST increase (12%), ALT increase (10%), and lipase increase (5%). Also, no cases of viral reactivation have been seen to date (El-Khoueiry et al 2015).

1.1.4. Combined Immune Checkpoint Inhibition

Blockade of immune inhibitory pathways is emerging as an important therapeutic modality for the treatment of cancer as evidenced by the clinical responses observed with antibodies to CTLA-4 and PD-1/PD-L1. Ipilimumab, a fully human, IgG1 monoclonal antibody blocking CTLA-4, improved OS in patients with advanced melanoma (Hodi et al 2010, Robert et al 2011). Nivolumab, a fully human IgG4 antibody blocking PD-1, produced durable objective responses in patients with melanoma, renal cell cancer, and NSCLC (Topalian et al 2012, Hamid et al 2013, Wolchok et al 2013). Although these single agents have antitumor activity, multiple immune inhibitory mechanisms are present concurrently within the tumor

microenvironment, suggesting that combination therapies may be required for optimal therapeutic effect (Quezada and Peggs 2013).

For example, CTLA-4 and PD-1 appear to play complementary roles in regulating adaptive immunity. Whereas PD-1 contributes to T-cell exhaustion in peripheral tissues, CTLA-4 inhibits at earlier points in T-cell activation. In preclinical models, combined blockade of PD-1 and CTLA-4 achieved more pronounced antitumor activity than blockade of either pathway alone (Curran et al 2010, Selby et al 2013).

On the basis of these observations, a Phase 1 study was conducted to investigate the safety and efficacy of combined CTLA-4 and PD-1 blockade (with the use of ipilimumab and nivolumab, respectively) in patients with advanced melanoma. The ORR (according to modified World Health Organization criteria) for all patients in the concurrent-regimen group was 40%. Evidence of clinical activity (conventional, unconfirmed, or immune-related response or stable disease [SD] for ≥ 24 weeks) was observed in 65% of subjects. In 17 subjects treated at the maximum doses that were associated with an acceptable level of AEs, 53% of subjects had an objective response compared with ipilimumab monotherapy (10.9%), all with tumor reduction of ≥ 80%. Grade 3 or 4 AEs related to therapy occurred in 53% of subjects in the concurrent-regimen group but were qualitatively similar to previous experience with monotherapy and were generally reversible. Among subjects in the sequenced-regimen group, 18% had Grade 3 or 4 AEs related to therapy and the ORR was 20%. Grade 3 or 4 AEs, regardless of attribution, were observed in 72% of subjects, and Grade 3 or 4 treatment-related AEs were noted in 53%. Serious AEs related to the treatment were reported in 49% of patients in the concurrent regimen group. Common Grade 3 or 4 selected AEs that were related to the therapy included hepatic events (15%), gastrointestinal events (9%), and renal events (6%). Isolated cases of pneumonitis and uveitis were observed. In both regimen groups, treatment-related AEs were manageable and generally reversible with the use of immunosuppressants (or hormone-replacement therapy for endocrinopathies) according to previously established algorithms (Yervoy 2017).

Recently the FDA granted accelerated approval to nivolumab in combination with ipilimumab for the treatment of patients with BRAF V600 wild-type, unresectable or metastatic melanoma. Approval was based on a study that demonstrated a significant improvement in ORR. The ORR was 60% (95% CI: 48, 71) in the nivolumab plus ipilimumab group (n = 72) and 11% (95% CI: 3, 25) in the ipilimumab group (n = 37), an improvement in ORR of 49% (95% CI: 31, 61; $p < 0.001$). In addition, there was a significant improvement in PFS for the combination group compared with the ipilimumab group (HR 0.40; 95% CI: 0.22, 0.71; $p < 0.002$), with an estimated median PFS of 8.9 and 4.7 months in the nivolumab plus ipilimumab and ipilimumab groups, respectively. Common adverse reactions (≥ 20%) in patients receiving nivolumab plus ipilimumab were rash, pruritus, headache, vomiting, and colitis. The most frequent Grade 3 and 4 laboratory abnormalities occurring in at least 5% of patients receiving the combination were increased ALT, increased AST, increased lipase, increased amylase, hyponatremia, and lymphopenia (Nivolumab 2017).

As described above, IDO1 is another negative regulatory mechanism that contributes to tumor-derived immune suppression. In preclinical models, IDO1 inhibition has been shown to synergize with blockade of either anti–CTLA-4 or anti–PD-1/PD-L1 in delaying tumor growth and increasing OS (Holmgaard et al 2013, Spranger et al 2013). This effect was shown to be

T-cell dependent, leading to enhanced T-cell proliferation and interleukin-2 production within the tumor and to a marked increase in the effector-to-regulatory T cell ratios in the tumors.

In a Phase 1 open-label dose-escalation study of INCB024360 with ipilimumab (3 mg/kg intravenously [IV]), daily doses of INCB024360 have been evaluated in 21-day cycles. A total of 48 subjects have been enrolled to date in 6 cohorts: 300 mg, 100 mg, 25 mg, 50 mg twice daily (BID); 75 mg total daily dose (50 mg qam and 25 mg qpm); and 50 mg BID intermittent dosing (2 weeks on and 1 week off). The initial evaluation of INCB024360 300 mg BID in combination with ipilimumab was terminated due to the occurrence of Grade 3 or 4 ALT/AST elevations in 5 of 7 subjects treated at this dose. These AEs were reversible in all subjects upon discontinuation of study therapy and institution of corticosteroids based on an established protocol for the management of immune toxicities related to ipilimumab therapy. Enrollment was restarted at 25 mg BID. Serious AEs were observed in the 300 mg BID, 25 mg BID, 75 mg total daily dose (50 mg qam and 25 mg qpm), and 50 mg BID intermittent dose groups. The system organ class with the most frequently reported SAEs was gastrointestinal disorders (8 subjects, 16.7%) followed by investigations (6 subjects, 12.5%). Treatment-emergent AEs were reported in 46 subjects (95.8%). Fatigue was the most frequently reported TEAE (29 subjects, 60.4%), followed by rash (27 subjects, 56.3%). As of ASCO 2014, 12 immunotherapy-naïve subjects were enrolled; 42% of those subjects achieved objective response, and 75% achieved disease control (both assessed by irRC) (Gibney et al 2014). INCB024360 at doses up to 50 mg BID with ipilimumab were generally well tolerated and immune-related AEs (irAEs) previously observed with ipilimumab were reversible with appropriate management. Tumor response and duration data suggest the potential for enhanced melanoma patient outcomes compared to ipilimumab monotherapy.

In this current, ongoing study (INCB 24360-202), enrollment is complete in the epacadostat 25 mg BID, 50 mg BID, and 100 mg BID cohorts with pembrolizumab 2 mg/kg IV Q3W as well as in the Phase 1 expansion cohorts of epacadostat 50 mg BID, 100 mg BID, and 300 mg BID with pembrolizumab 200 mg IV Q3W. The Phase 2 portion of the study is ongoing, in which the recommended Phase 2 dose of epacadostat 100 mg BID is being evaluated in combination with the fixed dose of pembrolizumab 200 mg IV Q3W. As of 27 FEB 2017, a total of 356 subjects have been enrolled. The update below includes safety in the combined Phase 1 and Phase 2 treatment groups treated with epacadostat 100 mg BID in combination with pembrolizumab in this study who had at least 1 month of safety data available.

Among the 294 subjects who have received epacadostat 100 mg BID in combination with pembrolizumab in Phase 2, the most frequently reported (≥ 10%) treatment-related AEs of any grade for the combined Phase 1 and Phase 2 treatment groups were fatigue (29%), rash (17%), nausea (11%), and pruritus (10%). Fatigue (29%) and rash (17%; including the preferred terms rash, rash maculopapular, rash generalized, rash macular, and rash pruritic) were the only treatment-related AEs reported in > 15% of subjects (Hamid et al 2017). Treatment-related AEs of rash were only reported in the Phase 2 group.

The ORR in 19 evaluable subjects with treatment-naïve metastatic melanoma was 53% (10/19), with disease control rate of 74% (14/19). Median PFS has not been reached and all responses are ongoing with minimum follow-up of 31.7 weeks. Objective responses were also seen in other tumor types enrolled in Phase 1 (Gangadhar et al 2015). Additional data were recently presented

confirming an ORR and DCR in subjects with treatment-naïve metastatic melanoma of 58% (11/19) and 74%, respectively (Gangadhar et al 2016).

In April 2018, eDMC review of ECHO-301/KEYNOTE-252 study, a phase 3 study evaluating pembrolizumab in combination with epacadostat versus pembrolizumab with placebo as first-line treatment in subjects with unresectable or metastatic melanoma, concluded that the co-primary endpoint of improvement in progression-free survival was not met (HR = 1.00; 95% CI 0.83 to 1.21) and that the co-primary endpoint of improvement in overall survival was also not expected to reach statistical significance (HR = 1.13; 95% CI: 0.86 to 1.49). Based on these results, and on the recommendation of the eDMC, the study was stopped. The safety profile observed in the ECHO-301/KEYNOTE-252 study was consistent with that observed in previously reported studies of epacadostat in combination with pembrolizumab (Long et al 2018).

In summary, both IDO1 and PD-1 have been shown to suppress T-cell–mediated antitumor immunity, and IDO1 and the PD-1 ligand PD-L1 have been shown to be coexpressed in multiple cancer types and to correlate with poor prognosis. Combined inhibition of both pathways may therefore lead to greater suppression of antitumor immunity and to increased efficacy. Preclinical and clinical data indicate that these pathways are important in melanoma as well as in other cancers, including NSCLC, SCCHN, ovarian cancer, transitional cell carcinoma of the GU tract, TNBC, MSI high CRC, and DLBCL.

1.1.5. Preclinical and Clinical Study Data

Refer to the Investigator's Brochures for MK-3475 (mIB) and INCB024360 (iIB) for preclinical and clinical study data.

1.2. Study Rationale

1.2.1. Rationale for Combining PD-1 Inhibitor and IDO1 Inhibitor in Advanced or Metastatic Cancers

The goal of cancer immunotherapy is to initiate or reinitiate a self-sustaining cycle of cancer immunity, enabling it to amplify and propagate. Cancer immunotherapies must overcome the negative feedback mechanisms inherent in most cancers. The current approach will attempt to further amplify an immune response by targeting multiple nonredundant immune checkpoints. Expression of IDO1 represents an early checkpoint that results in a diminished immune response and tolerance to tumor antigen.

Many recent clinical results suggest that another common rate-limiting step is the expression of PD-L1 as a distal immune modulator expressed in 20% to 50% of human cancer and even as high as 89% in ovarian cancer (Hiraoka 2010, Herbst et al 2013, Hamanishi et al 2007), including but not limited to the ones selected for investigation in the Phase 1 and cohort expansion portions of this study: advanced or metastatic NSCLC, melanoma, transitional carcinoma of the GU tract, renal cell cancer, TNBC, endometrial cancer, SCCHN, ovarian cancer, and DLBCL. Expression of IDO and PD-1/L1 have been found to be increased in NSCLC as the disease progresses, and expression of these markers in tumor cells has been associated with shorter subject survival (Iversen et al 2014). For NSCLC specifically, anti–PD-L1 and anti–PD-1 monotherapy response rates of 17% to 24% have been reported in refractory NSCLC (Garon et al 2013, Brahmer et al 2013) with survival medians of 8 to

18 months; however, MK-3475 has not yet reached the median in its study (Garon et al 2013). Thus, there is a strong rationale for therapies aimed at restoring antitumor immunocompetence in NSCLC and establishing a rationale for inhibiting IDO1 and the PD-1/L1 pathways in this disease.

In addition, there is strong rationale for testing the combination of 2 different mechanisms for overcoming tumor tolerance in many other tumor types as well. Targeting PD-1 assumes that the T cells are essentially exhausted (and thus tolerant of the tumor) and that this exhaustion may be reversed by blocking PD-1 signaling. Targeting IDO will concurrently decrease infiltration of regulatory CD4+ cells and immune-suppressive cytokines. This novel combination strategy has strong biologic rationale for a number of solid tumors as well as DLBCL, and may augment and deepen response rates over and above that demonstrated with single agent PD-1 blockade. Thus, there is a strong rationale for therapies aimed at restoring antitumor immunocompetence in not only NSCLC and melanoma, but also SCCHN, ovarian cancer, transitional cell carcinoma of the GU tract, ovarian cancer, MSI high CRC, and DLBCL, and establishing another rationale for inhibiting IDO1 and the PD-1/L1 pathways in these diseases.

Although results from the final PFS and interim OS analysis for the Phase 3 ECHO-301/KEYNOTE-252 study (as noted in Section 1.1.4) did not demonstrate an added benefit with the addition of INCB024360 in the setting of advanced or metastatic melanoma; the rationale remains for other tumor types and other combinations based on differences in cancer biology. In addition, the safety profile observed in the ECHO-301/KEYNOTE-252 study was consistent with that observed in previously reported studies of epacadostat in combination with pembrolizumab.

1.3. Potential Risks and Benefits of the Treatment Regimen

1.3.2. Risks From MK-3475

An open-label Phase I study (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose-escalation portion of this study evaluated 3 dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered Q2W in subjects with advanced solid tumors. All 3 dose levels were well tolerated and no DLTs were observed. Based on pharmacokinetic (PK) data showing a half-life of 21 days, the Protocol was amended to include a dosing frequency of Q3W in expansion cohorts. Of a total of 479 subjects who have received MK-3475 in Protocol 001, 466 (97.3%) experienced treatment-emergent AEs, of which 368 (76.8%) were considered drug-related. Serious AEs were reported in 30.1% of subjects, but SAEs that were attributed as potentially (possibly, probably, or definitely) drug-related by investigators were reported in 6.7% of subjects overall. Potentially irAEs have been observed, including pneumonitis in both melanoma and NSCLC cohorts. The most commonly reported treatment-emergent AEs experienced have been fatigue, nausea, cough, pruritus, diarrhea, and rash. Most subjects continued treatment despite of AEs, and only 4.2% of subjects discontinued study treatment because of an AE that was considered related to study treatment by investigators. Thus, the overall AE summary suggests that MK-3475 is generally tolerable, and AEs are generally manageable in subjects.

1.3.3. Risks for the Combination of INCB024360 and MK-3475

The combination of INCB024360 and MK-3475 has the potential to cause more frequent, more severe, and/or new immune-related toxicities as compared with each individually.

In this ongoing Phase 1/2 study combining pembrolizumab and epacadostat, preliminary data suggest that doses up to 300 mg BID of epacadostat are well tolerated with pembrolizumab 200 mg IV. While 300 mg BID did not exceed the MTD, preliminary analysis of 19 subjects suggested that there were higher rates of dose holds and reductions compared to 100 mg BID, supporting 100 mg BID as the Phase 2 dose (as detailed later in this section). In the Phase 1 portion of the study, a DLT of Grade 3 rash and Grade 3 arthralgia were seen in 2 of 19 evaluable subjects treated with epacadostat 50 mg BID; 2 DLTs in 15 evaluable subjects were seen with epacadostat 100 mg BID (Grade 3 AST and Grade 2 nervous system disorder,

other – ataxia), and 4 DLTs in 19 evaluable subjects were seen at 300 mg BID (Grade 1 erythema, 2 Grade 3 rashes and 1 nervous system disorder – other – vomiting without nausea).

Among the 294 subjects who have received epacadostat 100 mg BID in combination with pembrolizumab in Phase 2, the most frequently reported (≥ 5%) treatment-related AEs were fatigue (29%), rash (17%) nausea (11%), pruritus (10%), diarrhea (8%), decreased appetite (7%), and arthralgia (6%). Rash (17%) noted above includes the following preferred terms: rash, rash maculopapular, rash generalized, rash pruritic, and rash macular. Grade 3 or higher treatment-related AEs were reported in 18% of subjects. Treatment-related AEs leading to treatment discontinuations occurred in 11 subjects (4%); the most common were arthralgia and rash (n = 2 subjects each); others occurred in 1 subject each. There was 1 treatment-related death due to respiratory failure (secondary to aspiration pneumonia; pneumonitis could not be ruled out).

Any treatment-related Grade 3/4 AEs occurring in more than 1 subject included lipase increased (n = 12, 4%), rash (n = 9, 3.0%); fatigue, diarrhea, amylase increased (n = 4 each, 1%); ALT increased and AST increased (n = 2 each, 1%) (Hamid et al 2017).

As noted in Section 1.1.4, the eDMC review of the Phase 3 randomized study ECHO-301/KEYNOTE-252 study noted the safety profile observed was consistent with that observed in previously reported studies of INCB024360 in combination with MK-3475.

Additional details regarding specific benefits and risks for subjects participating in this clinical study are available in the iIB and mIB.

1.4. Justification for Treatment Regimen

The goal of the present study is to explore doses of the IDO1 inhibitor INCB024360 that may synergize or otherwise augment the efficacy observed with the PD-1 inhibitor MK-3475 in subjects with advanced cancer. MK-3475 regimens currently being studied in Phase 2 and Phase 3 include 2 mg/kg and 10 mg/kg Q2W or Q3W, and 200 mg Q3W. The optimal dose and schedule has not yet been established. The initial dose and schedule of MK-3475 to be tested in this study is 2 mg/kg Q3W and will be combined with doses of INCB024360 that provide partial and more complete IDO1 inhibition based on observations from the Phase 1 study (INCB 24360-101). The initial dose selected for INCB024360 in combination with MK-3475 is 25 mg BID with escalation up to 300 mg BID. This is based on the preliminary observation that the average kynurenine inhibition for INCB024360 25 mg BID and 100 mg BID is 66% and 89%, respectively, and the safety of these doses, as well as doses up to 700 mg BID in the Phase 1 study. Pharmacokinetic and PD observations from Studies INCB 24360-101 and INCB 24360-201 in cancer subjects support these doses, which provide a differential pharmacologic effect. Based on a 6-hour observation period at steady state on Day 15 after administration of INCB024360, kynurenine levels are incompletely inhibited (66%) compared to baseline levels in subjects treated with 25 mg BID but are nearly maximally inhibited (89%) in subjects treated with 100 mg BID. Doses of INCB024360 ≥ 300 mg BID are associated with > 94% average inhibition of kynurenine, and based on this small difference in the average kynurenine inhibition; a final escalation of INCB024360 to 300 mg BID will be evaluated.

In general, as single agents, INCB024360 and MK-3475 have been well tolerated in this study population that has significant comorbidities. However, the initial evaluation of INCB024360

300 mg BID in combination with ipilimumab was terminated because of the occurrence of Grade 3 or 4 ALT/AST elevation in 5 of 7 subjects treated at this dose. These AEs were reversible in all subjects upon discontinuation of study therapy and institution of corticosteroids based on an established protocol for the management of immune toxicities related to ipilimumab therapy. Of note, among the 43 subjects treated in Study INCB 24360-101 with INCB024360 monotherapy at doses of up to 700 mg BID, there was 1 report of Grade 3 liver function test (LFT) elevations in a subject with biliary obstruction from progressive cancer. Complete inhibition of the IDO1 target is not required for maximally effective activity in preclinical models. As monotherapy, maximally effective doses in nonclinical models result in exposures that are comparable to doses of 50 to 100 mg BID in humans. A 3 + 3 + 3 design is being utilized to further explore the safety of the combination beyond 3 + 3.

1.4.1. Rationale for Fixed Dose of MK-3475

The dose of pembrolizumab planned for this study going forward is 200 mg Q3W. This dose was recently approved in the United States for treatment of melanoma subjects. The dose of 2 mg/kg Q3W was the originally approved dose of pembrolizumab for the treatment of melanoma subjects in the United States. Information on the rationale for selecting 200 mg Q3W is summarized below.

An open-label Phase 1 study (KEYNOTE-001) is being conducted to evaluate the safety and clinical activity of single-agent pembrolizumab. The dose-escalation portion of this study evaluated 3 dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered Q2W, and the dose-expansion cohort evaluated 2 mg/kg Q3W and 10 mg/kg Q3W in subjects with advanced solid tumors. All dose levels were well tolerated, and no DLTs were observed. This first-in-human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels. No MTD has been identified.

In KEYNOTE-001, 2 randomized cohort evaluations (Cohorts B2 and D) of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg Q3W versus 10 mg/kg Q3W have been completed, and 1 randomized cohort (Cohort B3) evaluating 10 mg/kg Q3W versus 10 mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy or safety profile at these doses. For example, in Cohort B2, advanced melanoma subjects who had received prior ipilimumab therapy were randomized to receive pembrolizumab at 2 mg/kg Q3W versus 10 mg/kg Q3W, and the ORR was 28% (22/79) in the 2 mg/kg Q3W group and 28% (21/76) in the 10 mg/kg Q3W group (per RECIST v1.1 by independent central review). The proportion of subjects with drug-related AEs, Grade 3-5 drug-related AEs, serious drug-related AEs, death, or discontinuation due to an AE was comparable between groups. Cohort D, which compared 2 mg/kg Q3W versus 10 mg/kg Q3W in advanced melanoma subjects naïve to ipilimumab, also demonstrated overall similarity in efficacy and safety profile between the 2 doses. In Cohort B3, advanced melanoma subjects (irrespective of prior ipilimumab therapy) were randomized to receive pembrolizumab at 10 mg/kg Q2W versus 10 mg/kg Q3W. The ORR was 35.0% (41/117) in the 10 mg/kg Q2W group and 30.8% (33/107) in the 10 mg/kg Q3W group (per RECIST v1.1 by independent central review; cutoff date of 18 APR 2014). The proportion of subjects with drug-related AEs, Grade 3-5 drug-related AEs, serious drug-related AEs, death, or discontinuation due to an AE was comparable between groups.

An integrated body of evidence suggests that 200 mg Q3W is expected to provide similar response to 2 mg/kg Q3W, 10 mg/kg Q3W, and 10 mg/kg Q2W. Previously, a flat pembrolizumab exposure-response relationship for efficacy and safety had been found in subjects with melanoma in the range of doses between 2 mg/kg and 10 mg/kg. Exposures for 200 mg Q3W are expected to lie within this range and will be close to those obtained with the 2 mg/kg Q3W dose. The 2 mg/kg Q3W dose is the approved dose for metastatic melanoma in the United States.

A population PK model that characterized the influence of body weight and other patient covariates on exposure has been developed using available data from 1139 subjects from KEYNOTE-001 (cutoff date of 18 APR 2014) and KEYNOTE-002 (cutoff date of 12 MAY 2014), of which the majority (94.6%; N = 1077) were subjects with advanced melanoma. The PK profile of pembrolizumab is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose and, importantly, will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. The slight increase in PK variability predicted for the fixed dose relative to weight-based dosing is not expected to be clinically important given that the range of individual exposures is well contained within the range of exposures shown in the melanoma studies of 2 and 10 mg/kg to provide similar efficacy and safety.

In translating to other solid tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in subjects with melanoma can be expected, as the antitumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in PK exposures obtained at tested doses among tumor types. Thus, the 200 mg Q3W fixed dose regimen is considered an appropriate fixed dose for other solid tumor indications as well.

Thus, with the newly available rationale for a fixed dose, MK-3475 200 mg Q3W may be explored in combination with INCB024360. Moreover, given the PK comparability of the 2 mg/kg and 200 mg fixed-dose regimens of MK-3475, dose finding for INCB024360, conducted in conjunction with MK-3475 at the 2 mg/kg dose, will be considered suitable for selecting a dose of INCB024360 in the Phase 2 portion of the study, where MK-3475 will be administered at the 200 mg fixed dose. An early safety evaluation will be performed to confirm the safety and tolerability of INCB024360 in this setting.

1.4.2. Rationale for Phase 2 Dose Selection of INCB024360

The preliminary epacadostat PK was evaluated in a total of 53 oncology subjects with evaluable PK data. These subjects received epacadostat dose regimens ranging from 25 mg BID to 300 mg BID, concomitant with pembrolizumab. Based on the trend of observed epacadostat plasma concentrations at the troughs following multiple dose administration, epacadostat steady-state PK likely was reached on or before Day 8 of dose administration. At the steady state, epacadostat systemic exposures (measured by C_{max} and $AUC_{0-\tau}$) were proportional to dose within the dose range of 25 to 300 mg BID. The PK parameters of epacadostat were similar for

subjects with melanoma or other cancer types, and generally comparable to those observed in other studies including monotherapy (INCB 24360-101) and in combination with ipilimumab (INCB 24360-201). There is no evidence of the PK of epacadostat being affected by concomitant pembrolizumab.

The dose selected for epacadostat for the current study was formed on the basis of having a well-tolerated safety profile as monotherapy and in combination with pembrolizumab, a robust ORR, and durable disease control rates, as well as providing optimal target inhibition of IDO1 based on nonclinical models. Doses of epacadostat of up to 700 mg BID as monotherapy have been well tolerated, and doses of 25 mg BID to 300 mg BID in combination with pembrolizumab, nivolumab, durvalumab, and atezolizumab are currently being evaluated in several ongoing Phase 2 studies. Doses of pembrolizumab 2 mg/kg and 200 mg flat dose have been studied in this ongoing Phase 1/2 study of pembrolizumab in combination with epacadostat.

In this ongoing Phase 1/2 study combining pembrolizumab and epacadostat, preliminary data suggest that doses up to 300 mg BID of epacadostat are well tolerated with pembrolizumab 200 mg IV. While 300 mg BID did not exceed the MTD, preliminary analysis of 19 subjects suggested that there were higher rates of dose holds and reductions compared to 100 mg BID, supporting 100 mg BID as the initial Phase 2 dose (as is detailed later in this section). In the Phase 1 portion of the study, a DLT of Grade 3 rash and Grade 3 arthralgia were seen in 2 of 19 evaluable subjects treated with epacadostat 50 mg BID; 2 DLTs in 15 evaluable subjects were seen with epacadostat 100 mg BID cohort (Grade 3 AST and Grade 2 nervous system disorder, other – ataxia), and 4 DLTs in 19 evaluable subjects were seen at 300 mg BID (Grade 1 erythema, 2 Grade 3 rashes and 1 nervous system disorder – other – vomiting without nausea).

In Phase 1, treatment-related AEs ≥ Grade 3 occurring in more than 1 subject included rash (5 subjects, 4.3%) and dehydration, lipase increased, AST increased, and nausea (2 subjects [1.7%] each). In subjects receiving epacadostat 300 mg BID, there was an observable trend in increased AEs of rash (total events as well as severity) and the number of required dose holds and dose reductions for epacadostat compared to subjects receiving 100 mg BID.

Although the rashes observed at the 300 mg BID dose level were reversible with dose interruptions and medical treatment, total dose interruptions were higher in the 300 mg BID group, with 5 of 19 subjects interrupting epacadostat and 3 requiring dose reductions due to AEs, compared to 1 subject in the 100 mg BID group requiring a dose interruption, 2 subjects in the 50 mg BID group, and 1 subject in the 25 mg BID group. Based on the risk for early progression during dose interruptions and dose reductions associated with epacadostat 300 mg BID in combination with pembrolizumab 200 mg IV Q3W, 100 mg BID was selected as the dose for use in the Phase 2 portion of this study.

Based on observed systemic exposures and a pharmacokinetic-pharmacodynamic model for epacadostat, all subjects who received 100 mg BID epacadostat in combination with pembrolizumab had time-averaged inhibition of IDO1 activity exceeding 50%, a level of PD activity associated with inhibition of tumor growth seen in nonclinical models. Administration of 100 mg BID and above exceeded the IC_{50} at trough in nearly all subjects (Gangadhar et al 2015); further, the majority of subjects had trough epacadostat exposures that were above the IC_{50} of IDO1 inhibition. Therefore, 100 mg BID was selected as the recommended Phase 2 dose for epacadostat in the current study (INCB 24360-202) because this regimen had better

tolerability as demonstrated by the Phase 1 safety data, including fewer dose modifications (interruptions and reductions), and resulted in consistent inhibition of IDO1.

1.5. Rationale for Endpoints

1.5.1. Efficacy Endpoints

The primary efficacy objective of this study is to evaluate ORR based on investigator review of MK-3475 + INCB024360 in subjects enrolled in Phase 2 with select cancers. Response rates per irRECIST v1.1 for solid tumors (Section 7.6.3.1) and the Lugano Classification (Cheson et al 2014) for DLBCL (Section 7.6.4) will be evaluated.

RECIST v1.1 will also be used by the local site to determine eligibility and make treatment decisions. RECIST v1.1 will be adapted to account for the unique tumor response characteristics seen with treatment of MK-3475. Immunotherapeutic agents such as MK-3475 may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST criteria may not provide a complete response assessment of immunotherapeutic agents such as MK-3475. Therefore, RECIST v1.1 will be used with the following adaptation.

If radiologic imaging shows initial progressive disease (PD), tumor assessment should be repeated ≥ 4 weeks later in order to confirm PD with the option of continuing assigned study treatment while awaiting radiologic confirmation of progression. If repeat imaging shows a reduction in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued /resumed. If repeat imaging confirms PD, subjects will be discontinued from study therapy. In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as nontarget lesions.

In subjects who have initial radiological evidence of PD, it is at the discretion of the treating physician whether to continue a subject on study treatment until repeat imaging is obtained a minimum of 4 weeks later. This clinical judgment decision should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data.

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

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

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

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

2. STUDY OBJECTIVES AND PURPOSE

2.1. Primary Objectives

- Phase 1: To evaluate the safety, tolerability, and 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 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 diffuse large B-cell lymphoma (DLBCL)

2.2. Secondary Objectives (Phase 2)

- 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, PFS, and duration of disease control as measured by irRECIST 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 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 per irRECIST v1.1
  - 5 = Progressive disease per irRECIST v1.1
- To evaluate the efficacy with respect to OS.
- To evaluate the safety and tolerability of INCB024360 in combination with MK-3475.

3. SUBJECT ELIGIBILITY

3.1. Study Population

Phase 1: Subjects with Stage IIIB, Stage IV, or recurrent NSCLC, melanoma, transitional cell carcinoma of the GU tract, RCC, TNBC, adenocarcinoma of the endometrium, and SCCHN who have received at least 1 line of prior therapy and are refractory or for which no curative treatment is available will be enrolled.

Phase 2 expansion cohorts: Subjects with melanoma, transitional cell carcinoma of the GU tract, SCCHN, ovarian cancer, TNBC, DLBCL, NSCLC, MSI high CRC, clear cell RCC, gastric cancer, and HCC.

3.2. Subject Inclusion Criteria

The following criteria are required for inclusion in the study:

1. Male or female subjects, age 18 years or older on day of signing consent.
2. Willingness to provide written informed consent/assent for the study.
3. For Phase 1: Histologically or cytologically confirmed Stage IIIB, Stage IV, or recurrent NSCLC, melanoma, transitional cell carcinoma of the GU tract, clear cell RCC, TNBC, adenocarcinoma of the endometrium, or SCCHN.
4. For Phase 2: Histologically or cytologically confirmed melanoma, transitional cell carcinoma of the GU tract, SCCHN, ovarian cancer, TNBC, DLBCL, NSCLC, MSI high CRC, clear cell RCC, gastric cancer, and HCC.
5. Life expectancy > 12 weeks.
6. ECOG performance status 0 to 1.
7. Presence of measurable disease per RECIST v1.1 for solid tumors or the Lugano classification (Cheson et al 2014) for subjects with DLBCL.
8. Laboratory and medical history parameters within Protocol-defined range. NOTE: If the screening laboratory tests below were conducted > 7 days prior to treatment initiation, they will need to be repeated on Day 1 before initiation of treatment. Hematology and coagulation testing are central testing; therefore, central laboratory results should be used to determine eligibility for those relevant analytes below unless central laboratory results are not available at the time of enrollment or are not within the 7-day window before Cycle 1 Day 1. In this case, local laboratory results may be used to confirm eligibility. Chemistry testing is local testing; therefore, local results should be used for those relevant analytes below.
    a. Absolute neutrophil count $\geq 1.5 \times 10^9$/L (for subjects with DLBCL, in no case $< 1.0 \times 10^9$/L).
    b. Platelets $\geq 100 \times 10^9$/L (for subjects with DLBCL or HCC in no case $< 50 \times 10^9$/L).
    c. Hemoglobin ≥ 9 g/dL or ≥ 5.6 mmol/L (transfusion is acceptable to meet this criterion).

d. Serum creatinine ≤ 1.5 × institutional upper limit of normal (ULN) OR measured or calculated creatinine clearance (glomerular filtration rate can also be used in place of creatinine or CrCl) ≥ 50 mL/min for subjects with creatinine levels > 1.5 × institutional ULN.

e. AST/ALT < 2.5 × ULN OR ≤ 5 × ULN for subjects with liver metastases. For subjects with HCC: AST/ALT < 5 × ULN. For other specific exceptions medical monitor approval is required.

f. Total bilirubin ≤ 1.5 × ULN **OR** direct bilirubin ≤ ULN for subjects with total bilirubin > 1.5 × ULN.)

- If there is no institutional normal range available for the direct bilirubin, the direct bilirubin should be < 40% of the total bilirubin.
- In no case can total bilirubin exceed 3.0 × ULN.

g. International normalized ratio (INR) or prothrombin time (PT) ≤1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or INR is within therapeutic range of intended use of anticoagulants. Subjects with HCC must have INR ≤ 2.3.

h. Activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN unless subject is receiving anticoagulant therapy, as long as PTT is within therapeutic range of intended use of anticoagulants

9. For Phase 1: Subjects who have advanced or metastatic disease as noted above who have received at least 1 prior therapy for their disease under study or have advanced or metastatic disease for which no curative treatment is available.

10. For Phase 2 expansion cohorts: Subjects with NSCLC, melanoma, transitional cell carcinoma of the GU tract, SCCHN, ovarian cancer, DLBCL, TNBC, MSI high CRC, clear cell RCC, gastric cancer, and HCC.

a. Phase 2 expansion: NSCLC (PD-L1 positive and PD-L1 low/negative or indeterminate cohorts).

- Subjects who have received at least 1 prior systemic chemotherapy regimen for Stage IIIB, Stage IV, or recurrent NSCLC (not including neoadjuvant and/or adjuvant therapy except as described below).
  - One prior systemic regimen must include a platinum-based therapy. Investigational agents used in combination with standard therapies are allowed. Subjects who have a non–platinum-based regimen may be enrolled with medical monitor approval.
- Documentation of mutation status. Tumors with driver mutations (eg, epidermal growth factor receptor mutation positive or anaplastic lymphoma kinase fusion oncogene positive) treated with a targeted therapy are permitted; however, subjects should have progressed on or be intolerant to the targeted therapy.
  - Subjects who completed and progressed on a platinum-containing regimen as adjuvant, neoadjuvant, or part of a course of chemoradiation therapy within the 6 months before screening would be counted as 1 prior platinum-containing regimen and therefore would not require re-treatment with a platinum-containing regimen for Stage IIIB, Stage IV, or recurrent disease.

- Subjects must not have received immunotherapy with PD-1 or CTLA-4 targeted therapy.

- Subjects whose PD-L1 status is indeterminate from biopsy sample collected may be enrolled in the PD-L1–low/negative cohort until the cohort is full, at which time subjects whose sample is indeterminate may be eligible for repeat biopsy to determine PD-L1 status and, if positive, may be enrolled in the PD-L1–positive cohort if that cohort has not been filled. PD-L1 results from prior testing with the FDA-approved assay (PD-L1 IHC 22C3 pharmDX) are acceptable.

b. Phase 2 expansion: Melanoma

- Documentation of V600E-activating BRAF mutation status or consent to BRAF V600E mutation testing during the screening period. **Note:** Testing should be performed in a Clinical Laboratory Improvement Amendments–certified laboratory. BRAF mutation status determined as part of a panel of genetic tests performed in a gene expression analysis will also satisfy the inclusion criteria for BRAF mutation testing.
- Prior systemic therapy requirements:
  - Melanoma immune checkpoint-naïve cohort: Subjects must not have received immunotherapy with anti–PD-1, anti–PD-L1, or anti–CTLA-4 therapy. **Exception:** Prior anti–CTLA-4 in the adjuvant setting would be permitted.
  - Primary anti–PD-1 or anti–PD-L1 refractory cohort (primary refractory): Subjects must have received prior treatment with anti–PD-1 or anti–PD-L1 therapy (alone or as part of a combination) in the advanced or metastatic setting and have PD as their best response to treatment that is confirmed at least 4 weeks later (no less than 28 days).
    - Subjects must have received at least 2 doses of a prior anti–PD-1 or anti–PD-L1 agent.
    - Progressive disease must also be at least 12 weeks from first dose of anti–PD-1 or anti–PD-L1 therapy and confirmed 4 weeks (no less than 28 days) later.
    - No more than 1 prior line of therapy is permitted and must have contained anti–PD-1 or anti–PD-L1 therapy (alone or as part of a combination) with the exception of targeted therapy for subjects who have tumors that are BRAF mutant.
      - For subjects with BRAF-mutant tumors, treatment with a targeted therapy is required, and subjects should have progressed or been intolerant to the targeted therapy to be eligible.
      - For subjects who progressed on BRAF targeted therapy, lactate dehydrogenase must be $< 2 \times$ ULN.
  - Anti–PD-1 or anti–PD-L1 relapsed cohort (relapsed): Subjects must have received prior anti–PD-1 or anti–PD-L1 therapy (alone or as part of a combination) in the advanced or metastatic setting and achieved PR/CR but later have confirmed PD (PD confirmed at least 4 weeks [no less than 28 days] later).

- For subjects enrolling in the primary refractory or relapsed melanoma cohorts: Willing to undergo mandatory pretreatment and on-treatment core or excisional tumor biopsies

  Note: In all cases, biopsies will be confirmed to contain adequate tumor tissue by a local pathology review. If a subject is assessed by the interventional radiologist as having inaccessible lesions, subject may be enrolled with medical monitor approval. In this case submission of archived tumor tissue may be acceptable. Also subjects with solitary target lesions should not be enrolled in either cohort.

- Ocular melanoma is excluded.

c. Phase 2 expansion: Transitional cell carcinoma of the GU tract
   - Histologically or cytologically confirmed transitional cell carcinoma of the bladder, ureter, or renal pelvis, or mixed histology bladder cancer.
   - Metastatic or locally advanced and not amenable to curative therapy transitional cell carcinoma of the GU tract cancer with disease progression on or after platinum-based chemotherapy or alternative therapy if platinum-based therapy is not appropriate.
   - Prior PD-1 or CTLA-4 targeted therapies are excluded

d. Phase 2 expansion: SCCHN
   - Histologically confirmed metastatic or recurrent squamous cell carcinoma not amenable to local therapy with curative intent (surgery or radiation with or without chemotherapy).
   - Carcinoma of the nasopharynx, salivary gland, or nonsquamous histologies are excluded.
   - Subjects must have received at least 1 prior systemic chemotherapy regimen that must have included a platinum-based therapy. Investigational agents used in combination with standard therapies are allowed. Subjects who relapse within 6 months of adjuvant therapy, including a platinum-containing regimen, may enroll.
   - Prior PD-1 or CTLA-4 targeted therapies are excluded.

e. Phase 2 expansion: Ovarian cancer
   - Subjects with FIGO Stage Ic, Stage II, Stage III, Stage IV, recurrent, or persistent (unresectable) histologically confirmed epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube carcinoma.
   - Subjects must have received a platinum-taxane–based regimen as first-line therapy.
   - Subjects who received maintenance paclitaxel, bevacizumab, or alternative maintenance therapy (eg, vaccines) are eligible for enrollment provided they have discontinued therapy at least 4 weeks for prior taxane, at least 4 weeks for bevacizumab, or received medical monitor approval for time lapse from alternative maintenance therapy prior to enrollment and recovered from toxicities to less than Grade 2.

- Prior PD-1 or CTLA-4 targeted therapies are excluded.
- Borderline, low-malignant-potential epithelial carcinoma per histopathology is excluded.

f. Phase 2 expansion: Relapsed or refractory DLBCL

- Prior allogeneic stem-cell transplantation is excluded.
- Must have received ≥ 1 prior treatment regimen.
- Not a candidate for curative therapy or hematopoietic stem-cell transplantation (either due to disease burden, fitness, or preference).
- Prior PD-1 or CTLA-4 targeted therapies are excluded.
- Fluorodeoxyglucose (FDG)-avid disease (based on local evaluation) per the Lugano Classification (Cheson et al 2014). Fluorodeoxyglucose-avid disease is defined as disease with a 5-point scale score of 4 or 5.

g. Phase 2 expansion: TNBC

- Histologically confirmed breast adenocarcinoma that is unresectable loco-regional, or metastatic.
- Pathologically confirmed as triple negative, source documented, defined as both of the following:
  1. Estrogen receptor (ER) and progesterone receptor (PgR) negative: < 1% of tumor cell nuclei are immunoreactive in the presence of evidence that the sample can express ER or PgR (positive intrinsic controls).
  2. Human epidermal growth factor receptor 2 (HER2) negative as per American Society of Clinical Oncology/College of American Pathologists guidelines i. IHC 0 or 1 fluorescence in situ hybridization (FISH) negative (or equivalent negative test), ii. Subjects with IHC 2 must have a negative by FISH (or equivalent negative test).
- Subjects with breast cancer history of different phenotypes (ie, ER/PgR/HER2 positive) must have pathologic confirmation of triple negative disease in at least one of the current sites of metastasis.
- Subject must have received at least 1 prior systemic regimen for advanced or metastatic disease.
- Prior PD-1 or CTLA-4 targeted therapies are excluded.

h. Phase 2 expansion: RCC

- Subjects with histological or cytological confirmation of clear cell RCC.
- Not curable by surgery.
- Subjects must have received prior antiangiogenic therapy or refused standard therapy.
- Subjects must not have received immunotherapy with anti–PD-1, anti–PD-L1, or anti–CTLA-4 therapy.

i. Phase 2 expansion: MSI high CRC
   - Subjects with histological confirmation of locally advanced unresectable or metastatic MSI high CRC.
   - Mismatch repair (MMR) or MSI status is, respectively, determined by examining either CRC tumor: protein expression by immunohistochemistry of 4 MMR enzymes (MLH1/MSH2/MSH6/PMS2) OR 3 to 5 tumor microsatellite loci using polymerase chain reaction (PCR)-based assay. Tumors are classified as MSI high when at least 2 allelic shifts among the 3 to 5 analyzed microsatellite markers are detected by PCR or absence of at least 1 of 4 MMR protein expression is detected by IHC.
   - Subjects may have received no more than 2 lines of prior therapy for advanced disease (if a subject progressed within 6 months of completing adjuvant therapy, this would count as a prior line of therapy).

j. Phase 2 expansion: Gastric cancer
   - Must have histologically or cytologically confirmed diagnosis of gastric or gastroesophageal junction adenocarcinoma.
   - Must have progression on or after therapy containing platinum/fluoropyrimidine or refused standard therapy.
   - Documentation of HER2/neu status. Subjects who are HER2/neu-positive must be treated with a HER2/neu inhibitor, and subjects should have progressed on or be intolerant to the targeted therapy or refused standard therapy.
   - Subjects may have received no more than 2 lines of prior therapy for the advanced disease (if a subject progressed within 6 months of completing adjuvant therapy, this would count as a prior line of therapy).

k. Phase 2 expansion: HCC
   - Must have histologically or cytologically confirmed diagnosis of HCC (fibrolamellar and mixed hepatocellular/cholangiocarcinoma subtypes are not eligible).
   - Barcelona Clinic Liver Cancer (BCLC) Stage C disease (Llovet et al 1999), or BCLC Stage B disease not amenable to locoregional therapy or refractory to locoregional therapy, and not amenable to a curative treatment approach.
   - CP score of A within 7 days of first dose of study drug (Appendix I).
   - Subjects may have received no more than 2 lines of prior therapy for the advanced disease (If a subject progressed within 6 months of completing adjuvant therapy, this would count as a prior line of therapy).
   - Must have progressed on, refused, or were intolerant of sorafenib. If the subject received sorafenib, it must be at least 14 days since prior treatment with sorafenib before first dose of study treatment.
     – Intolerant is defined as any Grade $\geq$ 2 drug-related AE that, despite supportive therapy, recurred after sorafenib treatment interruption of at least 7 days and dose reduction resulting in the subject requesting or the physician recommending discontinuation due to toxicity.

- The following are excluded: Subjects with liver transplants, clear invasion of the bile duct or main portal branch(es), or hepatorenal syndrome, or subjects who have required esophageal variceal ablation within 28 days of starting study treatment.
- Has been treated with anti–hepatitis B therapy. Subjects with controlled (treated) hepatitis B will be allowed if they meet the following criteria:
  - Antiviral therapy for hepatitis B virus (HBV) must be given for at least 12 weeks, and HBV viral load must be < 100 IU/mL before the first dose of study drug. Subjects on active HBV therapy with viral loads < 100 IU/mL should stay on the same therapy throughout study treatment.
  - Subjects who are anti-HBc positive, negative for HbsAg, negative for anti-HBs, and have an HBV viral load < 100 IU/mL do not require HBV antiviral prophylaxis.
- Subjects with history of hepatitis C virus (HCV) who have had successful treatment, defined as undetectable HCV RNA more than 12 weeks after treatment (these subjects may be HCV antibody positive, but will not have detectable RNA). Also subjects with untreated HCV and those who failed treatment are permitted. However, for those with untreated HCV and those who have failed treatment, HCV viral load (HCV RNA) will be monitored every cycle.
- Blood pressure must be adequately controlled (blood pressure medications have been stable for 1 month).
- Albumin ≥ 3.0 g/dL. NOTE: No albumin supplement (or BCAA) allowed within the last 14 days.

11. Fresh baseline tumor biopsies (defined as a biopsy specimen with adequate tumor tissue taken since completion of the most recent prior systemic regimen) are required. If a subject has inaccessible lesions, such as in ovarian cancer, HCC, or gastric cancer, or highly vascular lesions, such as RCC, enrollment may be considered with medical monitor approval. In this case, submission of archived tumor tissue may be acceptable.
    a. Fresh formalin-fixed or formalin-fixed paraffin-embedded tumor tissue blocks are preferred. If block is not available, a minimum 20 unstained freshly cut slides may be submitted to the testing laboratory per the specifications in the laboratory manual.
12. Female subjects of childbearing potential (defined as women who have not undergone surgical sterilization with a hysterectomy and/or bilateral oophorectomy, and are not postmenopausal, defined as ≥ 12 months of amenorrhea) must have a negative serum pregnancy test at screening. All female and male subjects of childbearing potential must agree to take appropriate precautions to avoid pregnancy or fathering children (with at least 99% certainty) from screening through 120 days after the last dose of study treatment. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subjects and their understanding confirmed.

3.3. Subject Exclusion Criteria

If met, any of the following criteria will lead to subject exclusion from the study:

1. Participation in any other study in which receipt of an investigational study drug or device occurred within 2 weeks or 5 half-lives (whichever is longer) before first dose. For investigational agents with long half-lives (eg, 5 days), enrollment before the fifth half-life requires medical monitor approval.
2. Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days before the first dose of study treatment.
3. Prior monoclonal antibody within 4 weeks or 5 half-lives (whichever is shorter) before study Day 1 or not recovered (≤ Grade 1 or at baseline) from AEs due to agents administered more than 4 weeks earlier. An exception to this rule would be use of denosumab.
4. Phase 2 expansion cohorts: For exclusion criteria specific to each tumor type, see Section 3.2.
5. Prior chemotherapy or targeted small molecule therapy within 2 weeks before study Day 1 or not recovered (≤ Grade 1 or at baseline) from AEs due to previously administered agents.
    a. Note: Subjects with ≤ Grade 2 neuropathy or alopecia are an exception and may enroll.
    b. Note: If subject received major surgery, he or she must have recovered adequately from the toxicity and/or complications from the intervention before starting therapy.
6. Prior therapy with an anti–PD-1, anti–PD-L1, anti–PD-L2, anti–CD137, or anti–CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways). **Exception:** See the inclusion criteria for the melanoma cohorts in Section 3.2 for specific requirements related to prior immune checkpoint inhibitor therapies.
7. Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.
8. Known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks before the first dose of study treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days before study treatment.
    a. Subjects with evidence of cerebral edema will be excluded from participation. In addition, subjects will be excluded from participation in the study if it has been < 8 weeks since radiation therapy was delivered to the CNS.

9. Active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc) is not considered a form of systemic treatment.
10. History of (noninfectious) pneumonitis that required steroids, or current pneumonitis.
11. Prior radiotherapy within 2 weeks of therapy (exception for radiation to CNS, which requires ≥ 8-week washout). Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation to non-CNS disease with medical monitor approval.
12. Active infection requiring systemic therapy.
13. Known HBV or HCV viremia or at risk for HBV reactivation. Exception for subjects enrolled in the HCC cohort (see details in the HCC-specific inclusion criteria 10k and exclusion criteria 26f for specific requirement for HCC subjects with HBV or HCV).
    a. HBV DNA and testing for HCV RNA must be undetectable.
    b. At risk for HBV reactivation is defined as hepatitis B surface antigen positive or anti–hepatitis B core antibody positive. (Testing required and may be performed locally.) Results for anti-HBV/HCV antibodies must be available before treatment. If negative, subjects may be enrolled before DNA/RNA results with medical monitor approval.
14. Pregnant or nursing women or subjects expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of study treatment.
15. Known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies).
16. Live attenuated vaccine within 30 days before the first dose of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
17. Monoamine oxidase inhibitors within the 21 days before screening or any concurrent use of a prohibited medication listed in Section 5.13.
18. Any history of SS after receiving 1 or more serotonergic drugs.
19. Presence of a gastrointestinal condition that may affect drug absorption.
20. Use of systemic corticosteroids. **Exceptions:** Doses ≤ 10 mg/day are permitted (see Section 5.12) and use for radiographic procedures is permitted.

21. History or presence of an abnormal electrocardiogram (ECG) which, in the investigator's opinion, is clinically meaningful. Subjects with screening QTc interval > 480 ms are excluded. For subjects with an intraventricular conduction delay (QRS interval 120 ms), the JTc interval may be used in place of the QTc with sponsor approval. Subjects with left bundle branch block are excluded. Subjects with QTc prolongation due to a pacemaker may enroll if the JT is normal or with medical monitor approval.
22. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
23. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study.
24. Immediate family member (self, spouse, or child) who is investigational site or sponsor staff directly involved with this study, unless prospective institutional review board (IRB) approval (by chair or designee) is given allowing exception to this criterion for a specific subject.
25. Known allergy or reaction to any component of either study drug or formulation components, including severe (≥ Grade 3) hypersensitivity to pembrolizumab and/or any of its excipients.
26. Subjects with HCC who meet the following criteria are excluded:
    a. Has had esophageal or gastric variceal bleeding within the last 6 months. All subjects will be screened for esophageal varices, unless such screening has been performed in the past 12 months before first dose of treatment. If varices are present, they should be treated according to institutional standards before starting study treatment.
    b. Portal vein invasion at the main portal (Vp4), inferior vena cava, or cardiac involvement of HCC based on imaging.
    c. Has had clinically diagnosed hepatic encephalopathy in the last 6 months. Subjects on rifaximin or lactulose to control their hepatic encephalopathy are not allowed.
    d. Had a solid organ or hematologic transplant.
    e. Has received locoregional therapy to liver (transcatheter chemoembolization, transcatheter embolization, hepatic arterial infusion, radiation, radioembolization, or ablation) within 4 weeks before the first dose of study drug. Subject is not eligible if aforementioned treatments were administered between the last dose of sorafenib and first dose of study medication.
    f. Has dual active HBV infection (HbsAg positive and/or detectable HBV DNA) and HCV infection (anti-HCV antibody positive and detectable HCV RNA) at study entry.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

Note: Amendment 10 will serve to close the study to future enrollment. The primary purpose of the amendment is to provide guidance for handling subjects still on study. The last study visit is the 90-day safety follow-up visit.

This is a Phase 1/2 study, with Phase 1 being a dose-escalation of INCB024360 in combination with MK-3475 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 MTD or PAD of INCB024360 in combination with MK-3475 in subjects with the following selected solid tumors: 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 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 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, RCC, MSI high CRC, DLBCL, gastric cancer, and HCC. There will be 2 NSCLC cohorts included in the Phase 2 expansion. For the NSCLC cohorts, 1 cohort will include subjects with PD-L1 high expression (defined as ≥ 50%) and a second cohort will include subjects with low/negative or indeterminate PD-L1 expression (low/negative is defined as TPS of 0%-49%). There will also be 3 melanoma cohorts; 1 cohort will include subjects who are prior checkpoint-naïve (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.

4.1.1. Phase 1 Dose-Escalation Design

Phase 1 is the dose-escalation phase, which will include cohorts of subjects treated with INCB024360 BID at initial doses of 25 mg BID, 50 mg BID, and 100 mg BID in combination with MK-3475 2 mg/kg Q3W, and INCB024360 300 mg BID in combination with MK-3475 200 mg/kg Q3W. Interim dose levels of 75 mg QD (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 of MK-3475 administered Q3W 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 INCB024360 for at least 80% of the doses during the 42-day DLT observation period, and must have received 2 doses of MK-3475 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 MK-3475 200 mg Q3W.

3 + 3 + 3 Design: The dose of INCB024360 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 INCB024360 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 MK-3475 2 mg/kg, other alternative dose schedules (ie, intermittent dosing) of INCB024360 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 INCB024360 according to Table 1 will proceed with MK-3475 2 mg/kg Q3W.

The cohorts and dose levels are shown in Table 1 for the dose escalations of INCB024360 with Q3W schedule of MK-347 and in Table 2 for the safety expansions cohorts.

Table 1: Phase 1 Dose-Escalation Schema for Daily INCB024360 in Combination With MK-3475 Once Every 3 Weeks

Daily Dose[a] of INCB024360	Dose of MK-3475 (Once 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 QD (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 INCB024360 300 mg BID may be evaluated but will be tested with the flat dose of MK-3475 200 mg.

Table 2: Phase 1 Safety Expansion for Daily INCB024360 in Combination With MK-3475 Once Every 3 Weeks

Daily Dose of INCB024360	Dose of MK-3475 (Once 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 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 Section 5.6. However, dose adjustments should not be made during the DLT observation period without discussion with the medical monitor. Intrasubject dose escalation is not permitted.

4.1.2. Phase 2 Cohort Expansions

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-naïve, 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 (see Section 9.6). 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 (Table 3).

Table 3: Phase 2 Cohort Expansions

Tumor Type	Approximate No. of Subjects Enrolled
NSCLC high positive (PD-L1 TPS ≥ 50%)[a]	42
NSCLC low/negative or indeterminate (PD-L1 TPS 0%-49% or indeterminate)[b]	25
Melanoma (immune checkpoint–naïve)	40
Transitional cell carcinoma of the GU tract	36
TNBC	32
Ovarian cancer	33
SCCHN	32
DLBCL[a]	37
RCC	36
MSI high CRC[a]	29
Gastric cancer	27
HCC[a]	32
Melanoma (primary refractory)[a]	27[c]
Melanoma (relapsed)[a]	18[c]
Total	446[d]

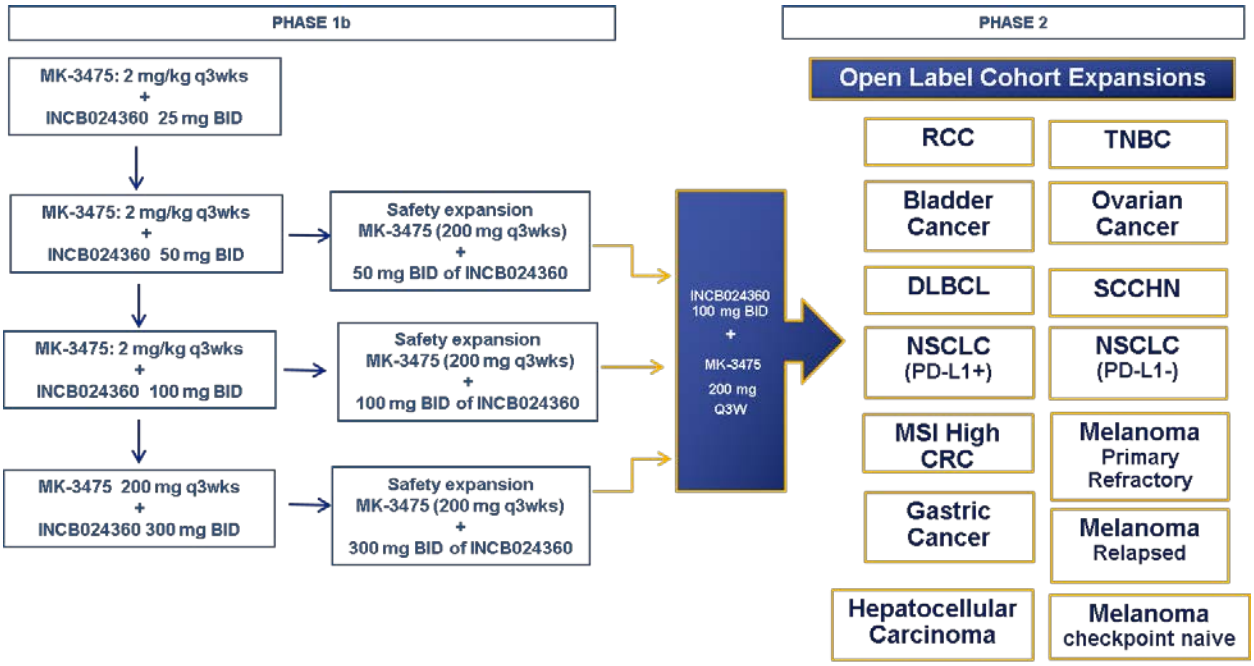
[a] These cohorts were discontinued before full enrollment.

[b] Subjects whose biopsies are PD-L1 indeterminate will not be excluded from the study, with the exception as noted in inclusion criterion 10a. They will be enrolled under the PD-L1 low/negative group but will be analyzed separately. This may require additional enrollment into the PD-L1 low/negative group to ensure that 25 PD-L1 low/negative subjects are enrolled. Low/negative is defined as TPS of 0% to 49%.

[c] These 2 cohorts will use a Simon 2-stage design. These numbers represent the maximum total sample size for each cohort. The actual sample size may be smaller.

[d] Closing of cohorts before full enrollment will result in fewer than 446 subjects.

Figure 1: Study Design



4.2. Study Endpoints

4.2.1. Primary Endpoints

- Phase 1: Safety and tolerability will be assessed by monitoring frequency, duration, and severity of AEs, through physical examinations, by evaluating changes in vital signs and electrocardiograms (ECGs), and through clinical laboratory blood and urine sample evaluations.
- Phase 2 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.

4.2.2. 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 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% ≤ 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 date of 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.

4.3. Measures Taken to Avoid Bias

The measurement of most toxicities using the CTCAE v4.0 and assessment of tumor size using the irRECIST v1.1 criteria or modified Lugano Classification (Cheson et al 2014) represent objective endpoints.

4.4. Number of Subjects

Overall study accrual will be approximately 508 subjects. This includes approximately 62 subjects enrolled in the Phase 1 dose-escalation portion of the study, followed by approximately 446 subjects for the Phase 2 expansion portion of the study depending on screen failure rate. Closing of Phase 2 cohorts before full enrollment will result in fewer than 446 subjects. Additional subjects may be screened and potentially enrolled in each cohort to ensure a minimum number of subjects are enrolled.

4.5. Study Termination

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

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

In addition, early study termination by the sponsor may occur based on clinical criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete;
2. Poor adherence to Protocol and regulatory requirements;
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects;
4. Plans to modify or discontinue the development of the study drug.

In the event of sponsor decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

5. TREATMENT OF SUBJECTS

5.1. Administration of Study Drug

5.1.1. INCB024360

Note: As of Amendment 10, INCB024360 administration is removed from the regimen for melanoma cohorts (except with medical monitor approval). Ongoing subjects with melanoma will be instructed to stop taking INCB024360 and to continue on MK-3475 alone (for up to the 35 infusions) or to stop treatment if on INCB024360 monotherapy unless medical monitor approval has been received to continue for the Protocol-specified interval (up to 12 months). Treatment with INCB024360 monotherapy and as part of combination therapy during the re-treatment periods is removed for subjects who have not already initiated such treatment. For those subjects who have already initiated INCB024360 monotherapy treatment or re-treatment and who do not have melanoma, treatment is limited to 12 months.

Subjects in Phase 1 will be administered study drug according to cohort enrollment (Table 1). Subjects in Phase 2 will be administered study drug at the dose or doses selected by the sponsor upon review of Phase 1 data.

All BID doses of INCB024360 will be taken orally morning and evening, approximately 12 hours apart without regard to food. If the morning or evening dose is missed by more than 4 hours, that dose should be skipped and the next scheduled dose should be taken at the usual time. Doses of INCB024360 will be self-administered except on the days scheduled to be given at the study clinic (see Section 7.8.1). INCB024360 will be given daily in combination with MK-3475 for approximately 24 months (35 administrations of MK-3475). After completion of 24 months of combination treatment, the option for treatment with INCB024360 monotherapy is available for up to 12 months for subjects who are receiving benefit from treatment and have not had disease progression or met any criteria for study withdrawal, or they may stop both INCB024360 and MK-3475. Monotherapy treatment is only available for subjects who have already initiated monotherapy at the time of implementation of Amendment 10. Medical monitor approval is required for monotherapy INCB024360 treatment beyond 12 months.

Subjects who complete 24 months (35 administrations) of MK-3475, continue on monotherapy INCB024360 for up to 12 months or stop both therapies, and later experience disease progression may be considered for re-treatment with the combination for an additional 12 months (17 administrations of MK-3475) followed by the option to continue monotherapy INCB024360 for up to 12 months as long as they are receiving benefit from treatment and have not met any criteria for study withdrawal, or to stop both therapies. Intrasubject dose escalation of INCB024360 is not permitted.

5.1.2. MK-3475

The treatment to be used in this study is outlined in Table 4.

Table 4: Dosage and Mode of Administration for MK-3475

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
MK-3475	2 mg/kg	Q3W	IV infusion	Day 1 of each cycle for approximately 24 months (35 administrations)	Experimental
MK-3475	200 mg	Q3W	IV infusion	Day 1 of each cycle for approximately 24 months (35 administrations)	Experimental

The dose amount required to prepare the MK-3475 infusion solution for a weight based dose will be based on the subject's weight in kilograms. Details on the dose calculation, preparation, and administration are provided in the Procedures Manual.

The dose of MK-3475 may be changed to 200 mg, as detailed in Section 4.1.1.

Note: The 24 months (35 administrations of MK-3475) of study drug is calculated from the date of first dose. Subjects who stop MK-3475 after 24 months may be eligible for up to 1 year (17 administrations of MK-3475) of additional study treatment if they experience disease progression after stopping study treatment provided they meet requirements detailed in Section 6.2.1.

Study treatment should begin on the day of enrollment or as close as possible to the date on which treatment is allocated/assigned.

5.1.2.1. Timing of Dose Administration of MK-3475

Study treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed in the schedule of assessments (Section 6). All study treatments will be administered on an outpatient basis.

MK-3475 will be administered as a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes -5 min/+10 min).

The Procedures Manual contains specific instructions for MK-3475 dose calculation, reconstitution, preparation of the infusion fluid, and administration.

5.2. Treatment Compliance

Treatment compliance with all study-related medications should be emphasized to the subject by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Subjects will bring all bottles of unopened, empty, and unused study drug with them to each study visit. Investigative site staff will perform a count of returned tablets to assess compliance, and this information will be entered into the electronic case report form (eCRF). Bottles of study drug, including all bottles of unopened, partially opened, or empty bottles cannot be destroyed or returned to the depot until a monitor reviews and verifies all tablet counts for compliance. Compliance with MK-3475 will also be documented in the medical record and monitored by the sponsor or its designee.

5.3. Randomization and Blinding

For Phase 1 and Phase 2 expansion cohorts, subjects will be allocated by nonrandom assignments and will occur centrally by an interactive response technology system (IRT). The assigned bottle numbers will be entered into the eCRF. At subsequent medication dispensing visits, the investigator or designee will follow the same procedures. Full details will be provided in the IRT manual.

5.4. Duration of Treatment and Subject Participation

Note: As of Amendment 10, the INCB024360 monotherapy, second course (re-treatment), and re-treatment monotherapy periods are removed. The option for INCB024360 monotherapy, re-treatment combination, and re-treatment monotherapy are only available for up to 12 months to subjects who have already initiated those therapies at the time of implementation of this amendment and who do not have melanoma. The last study visit is the safety follow-up visit.

Each subject enrolled in the study will continue receiving combination study treatment in continuous 21-day cycles for up to 24 months (35 administrations of MK-3475). After 24 months of combination treatment, the option for treatment with INCB024360 monotherapy is available for up to 12 additional months for subjects who are receiving benefit from treatment and have not had disease progression or met any criteria for study withdrawal, or they may stop both INCB024360 and MK-3475. Monotherapy treatment is only available for subjects who have already initiated monotherapy at the time of Amendment 10. Medical monitor approval is required for monotherapy INCB024360 treatment beyond 12 months. Subjects who complete 24 months of MK-3475 (35 administrations), continue on monotherapy INCB024360 for up to 12 months or stop both therapies, and later experience disease progression may be considered for re-treatment with the combination for an additional 12 months (17 administrations of MK-3475) followed by the option to continue monotherapy INCB024360 for up to 12 months as long as they are receiving benefit from treatment and have not met any criteria for study withdrawal, or to stop both therapies. If the subject discontinues all study treatment, the treatment period will end, and the subject will enter the follow-up period (see Section 6.4). Study participation is expected to average about 6 months.

5.5. Rationale for Dose Modification

The purpose of the dose-escalation portion of the study (Phase 1) is to establish a suitable dose of INCB024360 in combination with MK-3475. Thus, toxicities during the first 42 days of treatment will be used to define tolerability. Independent of the determination of tolerability during Phase 1 of the study, subjects may require individual modification of INCB024360 or MK-3475 if necessitated by drug-related AEs, including irAEs. Dose adjustments are summarized in Section 5.6.

5.5.1. Definition of Dose-Limiting Toxicities for Phase 1

A DLT will be defined as the occurrence of any treatment-emergent AE in Table 5 occurring up to and including Study Day 42 (6-week observation period). Dose-limiting toxicities include all treatment-emergent AEs 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 5: 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 MK-3475 or 14 days, whichever is longer. • Episcleritis, uveitis, or iritis of Grade 2 or higher
General: • If subjects are unable to receive 75% of INCB024360 or 2 doses of MK-3475 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.

5.5.2. Procedures for Cohort Review and Dose Escalation in Phase 1

Telephone conferences will be scheduled by the sponsor with Phase 1 investigators in order to review cohort-specific data, overall safety data from prior cohorts (if applicable), and to agree on dose escalation. For additional safety oversight, this group will review and adjudicate individual high-grade AEs as potentially dose-limiting and for guiding the study team on decisions regarding dose escalation and cohort expansion. The same method will be used for reviewing data at the end of Phase 1 to determine the recommended dose for Phase 2.

5.5.3. Procedures for Safety Review for Phase 2 Expansion Cohorts

Interim safety analyses are 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, 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 agents.

5.5.4. Follow-Up for Dose-Limiting Toxicities

Subjects whose treatment is discontinued because of a DLT must be followed until resolution or stabilization of the DLT event, whichever comes first.

5.6. Dose Adjustment of Study Drugs

5.6.1. Planned Dose Adjustments

Intrasubject dose escalations are not permitted. Subjects will remain on their cohort-assigned dose, or a lower dose if required because of AEs, throughout the treatment and extension portions.

5.6.2. Criteria and Procedures for Interruption

In some circumstances, it may be necessary to temporarily interrupt both study treatments as a result of AEs that may have an unclear relationship to study drug. Any interruptions of > 2 weeks or for LFT abnormalities must be discussed with the medical monitor before resuming treatment. Treatment with both study drugs should be withheld for drug-related Grade 4 hematologic toxicities, nonhematological toxicity ≥ Grade 3 (including laboratory abnormalities), and severe or life-threatening AEs (see Table 6). Table 6 summarizes the dosing actions for MK-3475 and INCB024360 that must be implemented with the indicated related AEs. Table 7 provides dose modification guidance for epacadostat. Additional information related to dose changes for INCB024360 and MK-3475 and guidance for immune-related toxicities can be found in Section 5.6.3 and for SS in Section 5.6.5.

Except in cases of emergency, it is recommended that the investigator consult with the sponsor's medical monitor (or other representative of the sponsor) before temporarily interrupting therapy for reasons other than Protocol-mandated medication hold. Additionally, the investigator must notify the sponsor's medical monitor and study project manager via email before restarting study drug that was temporarily interrupted because of an AE.

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (eg, elective surgery, unrelated medical events, subject vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the sponsor. The reason for interruption should be documented in the subject's study record.

Table 6: Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Grade	Hold Treatment (Y/N)	Timing for Treatment Restart	Dose/Schedule for Treatment Restart		Discontinue Subject (After Medical Monitor Consultation)
				INCB024360	MK-3475	
Hematologic toxicity	1, 2	No	N/A	N/A	N/A	N/A
	3	Yes	Toxicity resolves to ≤ Grade 1 or baseline	Restart at same dose	Restart at same dose and schedule. See Section 5.6.3 for recommendations regarding immune-mediated AEs.	Toxicity does not resolve within 12 weeks of last infusion.
	4	Yes	N/A	N/A	N/A	Permanently discontinue
Nonhematologic toxicity Note: Exception to be treated to similar Grade 1 toxicity: – Grade 2 alopecia – Grade 2 fatigue – **Grade 3 rash in the absence of desquamation, no mucosal involvement, does not require systemic steroids, and resolves to Grade 1 within 14 days** For additional information regarding AEs with potential immune etiology, see Section 5.6.3 or for subjects with HCC, refer to Appendix J for guidance related to hepatic adverse events.	1	No	N/A	N/A	N/A	N/A
	2	Consider holding for persistent symptoms	Toxicity resolves to ≤ Grade 1 or baseline	Restart at same dose	Restart at same dose and schedule. See Section 5.6.3 for recommendations regarding immune-mediated AEs.	Toxicity does not resolve within 12 weeks of last infusion
	3	Yes	Toxicity resolves to ≤ Grade 1 or baseline	Restart at 1 dose level lower.	Restart at same dose and schedule. See Section 5.6.3 for recommendations regarding immune-mediated AEs.	Toxicity does not resolve within 12 weeks of last infusion. Permanent discontinuation should be considered for any severe or life-threatening event.
	4	Yes	N/A	N/A	N/A	Permanently discontinue

Note: Subjects who experience a recurrence of the same severe or life-threatening AE at the same grade or greater with rechallenge of the combination should be discontinued from study treatment. For toxicities such as recurrent or intolerant rash with this combination, subjects may have the opportunity to resume treatment with MK-3475 alone with medical monitor approval.

In case toxicity does not resolve to Grade 0 to 1 within 12 weeks after last infusion of MK-3475, study treatment should be discontinued after consultation with the sponsor. With investigator and sponsor agreement, subjects with a laboratory AE still at Grade 2 after 12 weeks may continue treatment in the study only if asymptomatic and controlled. For information on the management of irAEs, see Section 5.6.3.

Table 7: Dose Modifications for INCB024360 (Epacadostat)

Current Dose	Dose Adjustment
300 mg BID	100 mg BID
100 mg BID	50 mg BID
50 mg BID	25 mg BID

A maximum of 2 dose reductions of INCB024360 are permitted. Twenty-five mg BID is the lowest dose of epacadostat in this Protocol. See the general instructions at the bottom of Table 8 for guidance regarding the re-occurrence of an AE when a subject has had his or her epacadostat dose reduced to 25 mg BID.

5.6.3. Procedures for Subjects Exhibiting Immune-Related Adverse Events

This section is meant to apply to suspected irAEs or events of clinical interest (ECIs) of a potential immunologic etiology from INCB024360, MK-3475 or the combination.

Events of clinical interest of a potential immunologic etiology or irAEs may be defined as an AE of unknown etiology, associated with drug exposure and consistent with an immune phenomenon. irAEs may be predicted based on the nature of the MK-3475 or INCB024360 compounds, their mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment. Of note, the requirement for reporting ECIs applies to all groups, including comparators, of MK-3475.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes before labeling an AE as an irAE. Subjects who develop a ≥ Grade 2 irAE should be discussed with the sponsor.

General recommendations to managing irAEs not detailed elsewhere in the Protocol are detailed in Table 8 and below.

Table 8: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events

Toxicity	Grade	Study Treatment	Action Taken	AE Management	Monitor, Follow-up and Restart Guidelines
Diarrhea/ Colitis	2-3	MK-3475	Withhold until toxicity resolves to Grade 0-1	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). • All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. • For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis. • If toxicity does not resolve within 12 weeks of last dose, or cannot taper below 10 mg or less of prednisone or equivalent within 12 weeks, must permanently discontinue. • Restart INCB024360 at same dose if event assessed as unrelated, decrease by 1 dose level if assessed as related.
		INCB024360	Withhold until toxicity resolves to Grade 0-1		
	4 or recurrent Grade 3	MK-3475	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). • All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. • For Grade 2 or higher diarrhea suspecting colitis, consider GI consultation and endoscopy to confirm or rule out colitis.
		INCB024360	Permanently discontinue		

Table 8: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events (Continued)

Toxicity	Grade	Study Treatment	Action Taken	AE Management	Monitor, Follow-up and Restart Guidelines
AST, ALT, or Increased Bilirubin	2	MK-3475	Withhold until toxicity resolves to Grade 0-1	Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme values return to baseline or are stable. • If toxicity does not resolve within 12 weeks of last dose, or cannot taper below 10 mg or less of prednisone or equivalent within 12 weeks, must permanently discontinue. • Restart INCB024360 at same dose if event assessed as unrelated, decrease by 1 dose level if assessed as related.
		INCB024360	Withhold until toxicity resolves to Grade 0-1		
	3-4	MK-3475	Permanently discontinue	Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper.	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme values return to baseline or are stable
		INCB024360	Permanently discontinue		
Type 1 diabetes mellitus (TIDM) (if new onset) or Hyper-glycemia[a]	T1DM or 3-4 hyper-glycemia associated with evidence of β-cell failure	MK-3475	Withhold until toxicity resolves to Grade 0-1	Initiate insulin replacement therapy for subjects with T1DM Administer anti-hyperglycemic in subjects with hyperglycemia	• Monitor subjects for hyperglycemia or other signs and symptoms of diabetes. • Resume MK-3475 when subjects are clinically and metabolically stable. • Resume INCB024360 when subjects are clinically and metabolically stable. • Restart INCB024360 at same dose if event assessed as unrelated, decrease by 1 dose level if assessed as related.
		INCB024360	Withhold until toxicity resolves to Grade 0-1		

Table 8: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events (Continued)

Toxicity	Grade	Study Treatment	Action Taken	AE Management	Monitor, Follow-up and Restart Guidelines
Hypophysitis	2	MK-3475	Withhold until toxicity resolves to Grade 0-1	Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency). • Restart INCB024360 at same dose if event assessed as unrelated, decrease by 1 dose level if assessed as related. • If toxicity does not resolve within 12 weeks of last dose, must permanently discontinue.
		INCB024360	Withhold until toxicity resolves to Grade 0-1		
	3-4	MK-3475	Withhold or permanently discontinue[b]	Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency). • Restart INCB024360 at same dose if event assessed as unrelated, decrease by 1 dose level if assessed as related • If toxicity does not resolve within 12 weeks of last dose, must permanently discontinue.
		INCB024360	Withhold or permanently discontinue[b]		
Hyper-thyroidism [a]	2	MK-3475	Continue	Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders. • If toxicity does not resolve within 12 weeks of last dose, must permanently discontinue.
		INCB024360	Continue		
	3-4	MK-3475	Withhold or permanently discontinue[b]	Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
		INCB024360	Withhold or permanently discontinue[b]		
Hypo-thyroidism[a]	2-4	MK-3475	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders. • If toxicity does not resolve within 12 weeks of last dose, must permanently discontinue.
		INCB024360	Continue		

Table 8: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events (Continued)

Toxicity	Grade	Study Treatment	Action Taken	AE Management	Monitor, Follow-up and Restart Guidelines
Pneumonitis	2	MK-3475	Withhold until toxicity resolves to Grade 0-1	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	• Monitor subjects for signs and symptoms of pneumonitis • Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections. • If toxicity does not resolve within 12 weeks of last dose, or cannot taper below 10 mg or less of prednisone or equivalent within 12 weeks, must permanently discontinue. • Restart INCB024360 at same dose if event assessed as unrelated, decrease by 1 dose level if assessed as related.
		INCB024360	Withhold until toxicity resolves to Grade 0-1		
	3-4 or recurrent Grade 2	MK-3475	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	• Monitor subjects for signs and symptoms of pneumonitis • Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
		INCB024360	Permanently discontinue		
Renal Failure or Nephritis	2	MK-3475	Withhold until toxicity resolves to Grade 0-1	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	• Monitor for changes in renal function. • If toxicity does not resolve within 12 weeks of last dose, or cannot taper below 10 mg or less of prednisone or equivalent within 12 weeks, must permanently discontinue. • Restart INCB024360 at same dose if event assessed as unrelated, decrease by 1 dose level if assessed as related.
		INCB024360	Withhold until toxicity resolves to Grade 0-1		
	3-4	MK-3475	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	• Monitor for changes in renal function.
		INCB024360	Permanently discontinue		

Table 8: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events (Continued)

Toxicity	Grade	Study Treatment	Action Taken	AE Management	Monitor, Follow-up and Restart Guidelines
Rash	1 or 2	MK-3475	Continue	Manage with topical steroids with or without drug interruption.	
		INCB024360	Continue		
	3 [c]	MK-3475	Withhold until toxicity resolves to Grade 0-1	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	• If toxicity does not resolve within 12 weeks of last dose, or cannot taper below 10 mg or less of prednisone or equivalent within 12 weeks, must permanently discontinue. • Restart INCB024360 at same dose if rash is mild and assessed as Grade 3 based only on body surface area and resolves without oral steroids. If oral steroids are required, or rash is severe, decrease by 1 dose level once resolved to Grade 0-1.
		INCB024360	Withhold until toxicity resolves to Grade 0-1		
	4	MK-3475	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	
		INCB024360	Permanently discontinue		

Table 8: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events (Continued)

Toxicity	Grade	Study Treatment	Action Taken	AE Management	Monitor, Follow-up and Restart Guidelines
Asymptomatic Amylase or Lipase Increased	3	MK-3475	May continue treatment with medical monitor approval		• Permanently discontinue if clinical signs and symptoms of pancreatitis develop (abdominal pain, nausea, vomiting). • If toxicity does not resolve within 12 weeks of last dose after an interruption, must permanently discontinue unless approved by the medical monitor to continue. • If Grade 4 lipase/amylase elevation is asymptomatic and abdominal imaging suggests no pathology, study drug administration dosing may continue with medical monitor approval.
		INCB024360	May continue treatment with medical monitor approval		
	4	MK-3475	Withhold until toxicity resolves to Grade 0-1		
		INCB024360	Withhold until toxicity resolves to Grade 0-1 Once resolved to Grade 0-1, may restart: Related: Reduce by 1 dose level. Not Related: Same dose level.		

Table 8: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events (Continued)

Toxicity	Grade	Study Treatment	Action Taken	AE Management	Monitor, Follow-up and Restart Guidelines
All Other Drug-Related Toxicity	Intolerable/ persistent Grade 2	MK-3475	Withhold until Grade 0-1	Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
		INCB024360	Withhold until Grade 0-1 Once resolved to Grade 0-1, may restart: Related: Reduce by 1 dose level. Not Related: Same dose level.		
	Grade 3	MK-3475	Withhold until Grade 0-1, or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre, encephalitis		
		INCB024360	Withhold until Grade 0-1 Once resolved to Grade 0-1, may restart: Related: Reduce by 1 dose level. Not Related: Same dose level. Events that require discontinuation include and not limited to: Gullain-Barre, encephalitis		
	Grade 4 or recurrent Grade 3	MK-3475	Permanently discontinue		
		INCB024360	Permanently discontinue		

Table 8: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events (Continued)

Toxicity	Grade	Study Treatment	Action Taken	AE Management	Monitor, Follow-up and Restart Guidelines
Myocarditis	Grade 1 or 2	MK-3475	Withhold until Grade 0	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
		INCB024360	Withhold until Grade 0		
	Grade 3 or 4	MK-3475	Permanently discontinue		
		INCB024360	Permanently discontinue		

General Instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where MK-3475 and INCB024360 have been withheld, MK-3475 and INCB024360 can be resumed after AE has been reduced to Grade 1 or 0, and corticosteroid has been tapered. MK-3475 and INCB024360 should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.
4. If the same AE that required INCB024360 dose reductions to the 25 mg BID dose level re-occurs, regardless of the causality to INCB024360, INCB024360 should be discontinued. If a participant who is being treated at INCB024360 25 mg BID has a different AE that is considered unrelated to INCB024360 by the investigator, the participant may resume study treatment at 25 mg BID after discussion with the study medical monitor.

NOTES:

a. For participants with Grade 3 or 4 immune-related endocrinopathy where withholding of MK-3475 and INCB024360 is required, MK-3475 and INCB024360 may be resumed when AE resolves to ≤Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM)
b. Withhold OR permanently discontinue MK-3475 + INCB024360 at the discretion of the Investigator.
c. Participants with Grade 3 rash in the absence of desquamation, no mucosal involvement, does not require systemic steroids, and resolves to Grade 1 within 14 days does not have to hold study treatment.

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

5.6.3.1. Procedures and Guidance for Infusion Reactions

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 9 shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 9: Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	Stop infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study treatment administration.	Subject may be premedicated 1.5 hours (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: • Diphenhydramine 50 mg orally (or equivalent dose of antihistamine). • Acetaminophen 500 to 1000 mg orally (or equivalent dose of antipyretic).

Table 9: Infusion Reaction Treatment Guidelines (Continued)

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or 83prague83te support indicated	**Stop infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further study treatment administration.**	No subsequent dosing.

NSAID = nonsteroidal anti-inflammatory drug.
Note: Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.

5.6.4. Treatment After Initial Evidence of Radiologic Evidence of Disease Progression

Immunotherapeutic agents such as MK-3475 and INCB024360 may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

If radiologic imaging shows PD, tumor assessment should be repeated ≥ 4 weeks later to confirm PD, with the option of continuing treatment per below while awaiting radiologic confirmation of progression. If repeat imaging shows a reduction in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued as per treatment calendar. If repeat imaging confirms PD, subjects will be discontinued from study therapy. In determining whether the tumor burden has increased or decreased, investigators should consider all target lesions as well as nontarget lesions.

When feasible, subjects should not be discontinued until progression is confirmed; however, the decision to continue study treatment after the first evidence of disease progression is at the investigator's discretion based on the clinical status of the subject as described in Table 10.

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

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

Table 10: Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD	Repeat imaging at ≥ 4 weeks to confirm PD	May continue study treatment at the investigator's discretion while awaiting confirmatory scan	Repeat imaging at ≥ 4 weeks to confirm PD if possible	Discontinue treatment
Repeat scan confirms PD	No additional imaging required	Discontinue treatment	No additional imaging required	N/A
Repeat scan shows SD, PR, or CR	Continue regularly scheduled imaging assessments every 9 weeks	Continue study treatment at the investigator's discretion	Continue regularly scheduled imaging assessments every 9 weeks	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion

5.6.5. Procedures for Subjects Exhibiting Serotonin Syndrome

As noted in Section 1.3, an uncommon risk of IDO1 inhibition is an increase in serotonin levels that could precipitate a cluster of AEs termed SS when administered alone or in combination with other serotonergic agents. This rare syndrome has been associated with some MAOIs and combinations of serotonergic drugs (Boyer and Shannon 2005). Serotonin reuptake inhibitors and serotonin/norepinephrine reuptake inhibitors (SNRIs) are permitted in the study. The following procedures will be implemented if subjects exhibit the signs/symptoms of SS described in Section 7.5.4, including tremor; hyperreflexia; spontaneous, ocular, or inducible clonus; together with agitation, fever, diaphoresis, or muscle rigidity:

- Immediately interrupt INCB024360 and MK-3475 administration.
- Immediately interrupt any SSRI or SNRI administration.
- Provide appropriate medical management of the subject until all signs/symptoms are resolved (eg, IV fluids and/or sympathomimetic amines for hypotension, benzodiazepines for agitation, administration of 5-hydroxytryptamine antagonists such as cyproheptadine).

- If etiologies other than SS are excluded, MK-3475 administration may be resumed unless other AE management guidelines apply for the specific event.
- If subject chooses to remain in the study, restart treatment with INCB024360 after the SSRI or SNRI has been discontinued, no sooner than 5 half-lives have elapsed for the specific SSRI or SNRI in question, and after resolution of signs/symptoms of SS. The SSRI or SNRI dosing MAY NOT be restarted.
- If subject chooses to withdraw from the study, or must restart treatment with SSRI or SNRI, the subject should be scheduled for a follow-up visit. Treatment with SSRI or SNRI may be initiated 2 weeks after resolution of signs and symptoms of SS.

5.7. Diet, Activity, and Other Considerations

5.7.1. Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

5.7.2. Contraception

Subjects should be informed that taking MK-3475 and INCB024360 may have unknown adverse effects on a fetus (unborn baby) in utero if pregnancy were to occur during the study. Furthermore, it is not known if MK-3475 or INCB024360 has transient adverse effects on the composition of sperm. Nonpregnant, non-breastfeeding women may be enrolled only if they are willing to agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through follow-up if of childbearing potential. (Note: Permitted methods that are at least 99% effective in preventing pregnancy are given in Appendix A). Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.
Note: Abstinence is acceptable if this is established and preferred contraception for the subject.

5.7.3. Use in Nursing Women

It is unknown whether MK-3475 or INCB024360 is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breastfeeding are not eligible for enrollment.

5.8. Criteria for Permanent Discontinuation of Study Drug

Subjects may withdraw consent at any time for any reason or be withdrawn from the study at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the sponsor if enrollment into the study is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.10.6, Withdrawal or Discontinuation.

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

- In the investigator's medical judgment, further participation would be injurious to the subject's health or well-being.
- The subject becomes pregnant.
- Consent is withdrawn by the subject or legal representative (such as parent or legal guardian).
- The study is terminated by the sponsor.
- The study is terminated by the local health authority or IRB/IEC.
- Confirmed radiographic progression of disease per irRECIST v1.1 (Appendix F) or Lugano Classification (Cheson et al 2014; Table 17).
  - Note: For unconfirmed radiographic disease progression, see Section 7.6.3.1.
  - Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved. See Section 7.6.
- The subject has experienced an unacceptable toxicity or a toxicity that does not recover in 4 weeks. Investigators who wish to continue treatment after a treatment delay of 4 weeks should consult with the sponsor's medical monitor for approval.
  - NOTE: For toxicities such as recurrent or intolerant rash with the combination, subjects may have the opportunity to resume treatment with pembrolizumab (MK-3475) alone with medical monitor approval.
- Noncompliance with study treatment or procedure requirements.
- The subject is lost to follow-up.
- Administrative reasons.

The end-of-treatment (EOT) and follow-up visit procedures are listed in Section 6 (Table 12 and Table 13). After the end of treatment, each subject will be followed for 42 days for AE monitoring (SAEs will be collected for 90 days after the end of treatment as described in Section 8.3.2).

5.8.1. Discontinuation of MK-3475 Treatment After Complete Response

Note: As of Amendment 10, the option for re-treatment is only available for subjects who have already initiated the re-treatment period. The text below applies to subjects who met criteria for re-treatment with MK-3475 before Amendment 10.

Discontinuation of MK-3475 treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with MK-3475 and had at least 2 treatments of MK-3475 beyond the date when the initial CR was declared. Subjects may continue on INCB024360 at this time or stop both therapies. Subjects who then experience radiographic disease progression will be eligible for re-treatment with MK-3475 at the discretion of the investigator if no cancer treatment was administered other than INCB024360, the subject

meets the safety parameters listed in the inclusion/exclusion criteria, and the study is open. Subjects will resume combination therapy as detailed in Section 6.2.1.

5.9. Study Completion

5.9.1. Study Completion Criteria

Subjects will be considered completing the study if they met any of the following criteria:

- Subject dies and a date of death is available.
- Subject is known to have died; however, the date of death cannot be obtained. (NOTE: Every effort must be made to obtain the date of death.)
- Consent is withdrawn for any further contact related to this study.
  - Subjects may choose to withdraw from the study at any time without penalty of jeopardizing their health care or loss of benefits to which the subject is otherwise entitled. Every reasonable effort should be made to determine the reason a subject withdraws prematurely, and this information should be recorded in the eCRF.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority or IRB or IEC.
- Data collection for all primary and secondary endpoints for a given tumor-specific cohort has been completed, as defined by the following:
  - The cohort is fully enrolled or closed to further enrollment.
  - The last subject in a given cohort has completed treatment (2 years on study treatment) or all subjects in a given cohort are off study treatment and completed the required 90-day safety follow-up assessments.

5.9.2. Withdrawal Procedures

In the event that any subject discontinues study drug and, subsequently, withdraws from the study before completion, regardless of reason, reasonable efforts should be made to have the subject return for the EOT procedures to be completed as described in Section 6.3. The date the subject was withdrawn from the study and the specific reason for withdrawal will be recorded in the eCRF.

If a subject is withdrawn from the study:

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

5.10. Beginning and End of the Study

The study begins when the first subject signs the informed consent. The end of the study may be designated as the timepoint when all subjects have discontinued the study or are a minimum of 6 months after initial study medication administration. If by the end of the study there remains at least 1 subject still on study treatment for at least 6 months, the subject(s) may enter additional treatment cycles. At this point a database lock of the study may occur to allow the analysis of the study data. Any remaining subjects may continue to receive study medication and be seen by the investigator per usual standard of care for this subject population. In addition, the investigator will be expected to monitor for and report any SAEs, ECIs, and pregnancies, as detailed in Section 8.3 (Serious Adverse Events). The subject is considered on study until such time that he/she meets any of the discontinuation criteria and written notification is given to the sponsor.

5.11. Concomitant Medications and Measures

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

5.11.1. Acceptable Concomitant Medications

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

All concomitant medications received within 28 days before the first dose of study treatment and 42 days after the last dose of study treatment should be recorded. Concomitant medications administered after 42 days after the last dose of study treatment should be recorded for SAEs and AEs as defined in Section 8.

5.11.1.1. Antiviral Therapies

Antiviral therapies for subjects with HCC with a history of HBV are permitted. The following antivirals have no known drug-drug interactions with pembrolizumab and epacadostat based on metabolism: adefovir, entecavir, lamivudine, telbivudine, and tenofovir.

5.12. Restricted Medications and Measures

- Systemic steroids may be used at doses ≤ 10 mg/day prednisone or equivalents or corticosteroids may be used for radiographic procedures.
- Use of coumarin-based anticoagulants (eg, warfarin) is discouraged. Low-dose warfarin (1 mg) is acceptable; however, doses that increase the INR are discouraged and may require dose modification. If an alternative to coumarin-based anticoagulants cannot be used, investigators should follow the guidelines in Table 11 and either closely monitor or closely monitor and reduce the subject's dose of coumarin-based anticoagulant upon initiating therapy with INCB024360. The INR should be monitored weekly for the first 4 weeks after initiation of therapy and upon discontinuation of INCB024360.

Table 11: Warfarin Dose Adjustment Recommendation When Initiating Concurrent INCB024360 (Epacadostat) Treatment

	INCB024360 (Epacadostat) Dose		
Stable INR	**≤ 100 mg BID**	**200 mg BID**	**300 mg BID**
INR ≤ 2.5	Close INR monitoring	Close INR monitoring	Reduce warfarin by ~33%
INR > 2.5	Close INR monitoring	Reduce warfarin by 20%-25%	Reduce warfarin by ~33%

5.13. Prohibited Medications and Measures

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

- Any investigational medication other than the study drugs.
- Any anticancer medications, including chemotherapy or biologic therapy other than the study medications.
- Any immunological-based treatment for any reason. (NOTE: Inhaled or topical steroids are allowed, and systemic steroids at doses ≤ 10 mg/day prednisone or equivalents or corticosteroid use for radiographic procedures are allowed as described in Section 5.12, and immune suppressants are allowed for treatment for immune toxicities.)
- Radiation therapy or surgery

  Note: In the presence of a mixed response (some lesions improving or stable and other lesions progressing), radiation therapy or surgery to a symptomatic solitary lesion or to the brain is allowed. No pembrolizumab infusions are permitted during radiation therapy or procedure and epacadostat should be stopped the day treatment begins. Study medications may be resumed as early as 1 week after treatment if the subject's symptoms are improving and not requiring corticosteroids for management. If study medications are not resumed within 4 weeks of completing treatment, the subject should discontinue study treatment permanently.

- Administration of live attenuated vaccines within 30 days before the first dose of study treatment and while participating in the study is prohibited. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
- Administration of an injectable influenza vaccine is prohibited during the DLT observation period (ie, 42 days after Cycle 1 Day 1).
- Any MAOI or drug associated with significant MAO inhibitory activity agents is prohibited from 21 days before Day 1 through 2 weeks after the final dose of INCB024360 has been taken (see Appendix D).
- Any UGT1A9 inhibitor, including: acitretin, amitriptyline, androsterone, cyclosporine, dasatinib, diclofenac, diflunisal, efavirenz, erlotinib, flutamide, gefitinib, gemfibrozil, glycyrrhetinic acid glycyrrhizin, imatinib, imipramine, ketoconazole (systemic), linoleic acid supplements, mycophenolic acid, niflumic acid, nilotinib, phenobarbital, phenylbutazone, phenytoin, probenecid, quinidine, ritonavir, sorafenib, sulfinpyrazone, valproic acid, and verapamil.

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

The exclusion criteria (Section 3.3) describes other medications that are prohibited during this study. There are no prohibited therapies during the post-treatment follow-up period.

5.13.1. Supportive Care Guidelines

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

- Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.
- Anti-infectives: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.
- Immune-related AEs: See Section 5.6.3 regarding diagnosis and management of adverse experiences of a potential immunologic etiology.
- Management of infusion reactions from MK-3475: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Table 9 shows treatment guidelines for subjects who experiences an infusion reaction associated with administration of MK-3475.

6. STUDY ASSESSMENTS

All study assessments will be performed as indicated in the schedules of assessments (Table 12 and Table 13). If a subject qualifies for re-treatment, all assessments as indicated in Table 12 and Table 13 should be performed. The order of assessments is suggested by the order of mention within the schedules. For instructions on each assessment, see Section 7. The required laboratory analytes are listed in Table 14.

Table 12: Schedule of Assessments

As of Amendment 10, for those subjects remaining on study, procedures are simplified. The Schedule of Assessment tables have been amended, and assessments that are no longer required have been deleted. For subjects who meet Amendment 10 criteria for re-treatment, the following Schedule of Assessments should be followed, except for the screening visit, which does not apply.

		Combination, Monotherapy, and Re-Treatment Period[a]					EOT	Follow-Up	
Visit Day (Range)	**Screening**	**C1D1**	**Weekly for First 6 Weeks (Phase 1 only)[b]**	**C2D1**	**Day 1 All Subsequent Cycles**	**Every 9-12 Weeks**	**Discontin-uation**	**Safety Follow-Up**	**Safety/Survival Follow-Up[c]**
Evaluation/Window	**Day -28 to Day -1**	**Day 1**	**± 3 Days**	**± 3 Days**	**± 3 Days**	**± 14 Days**	**+ 5 Days**	**42-49 Days After Last Dose of INCB024360[d] (+ 7 Days)**	**90 Days After Last Dose of Study Drug**
ADMINISTRATIVE PROCEDURES									
Informed consent	X								
Inclusion/exclusion criteria	X	X							
Contact IRT	X	X		X	X		X		
Prior medical and cancer history (tumor-specific)[e]	X								
Concomitant medications review	X	X		X	X		X	X	
Administer INCB024360 in clinic		X							
Administer MK-3475		X		X	X				
CLINICAL PROCEDURES AND ASSESSMENTS									
Comprehensive physical exam	X						X	X	
Targeted physical exam		X		X	X				
ECOG performance status	X						X		
Vital signs and weight (height at screening only)	X	X		X	X		X		
12-lead ECG	X						X		
AE assessment	X	X		X	X		X	X	X
Laboratory assessments	X	X	X	X	X	X	X	X	
Assess for ascites and encephalopathy (subjects with HCC only)	X	X		X	X		X	X	
Esophagogastroduodenoscopy (subjects with HCC only)	X[f]								

Table 12: Schedule of Assessments (Continued)

		Combination, Monotherapy, and Re-Treatment Period[a]					EOT	Follow-Up	
Visit Day (Range)	**Screening**	**C1D1**	**Weekly for First 6 Weeks (Phase 1 only)[b]**	**C2D1**	**Day 1 All Subsequent Cycles**	**Every 9-12 Weeks**	**Discontin-uation**	**Safety Follow-Up**	**Safety/Survival Follow-Up[c]**
Evaluation/Window	**Day -28 to Day -1**	**Day 1**	**± 3 Days**	**± 3 Days**	**± 3 Days**	**± 14 Days**	**+ 5 Days**	**42-49 Days After Last Dose of INCB024360[d] (+ 7 Days)**	**90 Days After Last Dose of Study Drug**
Fresh/archival tissue collection	X[g]	X[g]		X[h]					
Pathology review of tumor tissue	X[g]			X[h]					
EFFICACY MEASUREMENTS									
Radiologic tumor assessments[i]	X					X[j]	X[k]		X[k]
Bone marrow exam[l]	X[l]					X[l]			

[a] Treatment cycles are 3 weeks. Imaging should be performed every 9 weeks (63 days ± 5 days) regardless of any treatment delays for the first 2 assessments (Weeks 9 and 18), then every 12 weeks thereafter.

[b] Weekly LFTs are only required in Phase 1.

[c] Visit may occur through a phone call, email, or visit by the subject or the subject's caretaker.

[d] Subjects must be followed for AEs for 42 to 49 days after the last dose of study drug; however, subjects must be followed for 90 days for SAEs.

[e] For RCC: Memorial Sloan Kettering Cancer Center (MSKCC) score; for HCC: CP score, BCLC stage, and HCV/HBV status; for DLBCL: International Prognostic Index score; for gastric cancer: history of *H. pylori* and Epstein Barr virus (EBV).

[f] Esophagogastroduodenoscopy will only be required at screening for subjects with HCC to screen for varices. If esophagogastroduodenoscopy has been performed within the past 12 months before first dose of treatment it does not have to be repeated at screening.

[g] Archived tissue samples obtained since last treatment may be acceptable per Inclusion Criterion #11. Tissue should be submitted during screening but must be submitted before study drug administration on Cycle 1 Day 1. For subjects in the melanoma primary refractory and relapsed cohorts, fresh baseline tumor tissue is mandatory and confirmed by local pathologist review that sample in fact contains tumor tissue (unless medical monitor approval is received).

[h] An optional biopsy can be obtained any time after Cycle 1 Day 14, for safety or with confirmed response or progression. For subjects in the melanoma primary refractory and relapsed cohorts, tumor tissue is mandatory **during Cycle 3 anytime between Days 8 and 15 (Study Days 50 and 57)** and confirmed by local pathologist review that sample in fact contains tumor tissue (unless medical monitor approval is received). If the subject progresses before this timepoint then biopsy should be done at time of progression. Note: If the baseline tumor biopsy was found to be inadequate, the patient should not undergo an on treatment biopsy. Post-progression biopsy can still be optional.

[i] Initial tumor imaging will be performed within 28 days before the first dose of study treatment. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days before the first dose of study treatment (including PET imaging for subjects with DLBCL).

[j] On-study imaging will be performed every 9 weeks (± 5 days) after the first dose of study treatment for the first 2 assessments (Weeks 9 and 18) then every 12 weeks thereafter, should follow calendar days, and should not be adjusted for delays in cycle starts or extension of combination treatment cycle frequencies. The same imaging technique should be used in a subject throughout the study. Per the irRECIST v1.1 used in this Protocol, if imaging shows progressive disease, the imaging assessment should be performed at a minimum of 4 weeks later to confirm progressive disease as described in the Protocol.

[k] In subjects who discontinue study drug without confirmed disease progression, a radiological evaluation should be repeated at the time of treatment discontinuation (ie, date of discontinuation ± 4-week window).

[l] Bone marrow examination is only required for subjects with DLBCL. Exceptions include: 1) if a recent bone marrow biopsy was performed (within 60 days of Cycle 1 Day 1), a new bone marrow biopsy does not need to be repeated for screening, or 2) if bone marrow involvement is clearly evident or absent per PET/CT it also would not be required at screening. Subsequently, bone marrow biopsy will be performed only to confirm CR or as clinically indicated.

Table 13: Laboratory Assessments

As of Amendment 10, for those subjects remaining on study, procedures are simplified. The Schedule of Assessment tables have been amended, and assessments that are no longer required have been deleted. For subjects who meet Amendment 10 criteria for re-treatment, the following Schedule of Assessments should be followed, except for the screening visit, which does not apply.

		Combination, Monotherapy, and Re-Treatment Period[a]								EOT	Safety Follow-Up
Visit Day (Range)	**Screening**	**C1D1**	**Weekly for 6 Weeks (Phase 1 only)**	**C2D1**	**C4D1**	**C6D1 and C8D1**	**C12D1 and C16D1**	**Day 1 All Cycles**	**Every 9-12 Weeks**	**Discon-tinuation**	**42-49 Days After EOT or Last Dose of INCB024360**
Laboratory Assessment[b] /Window	**Day -28 to Day -1**	**Day 1**	**± 3 Days**	**± 3 Days**				**± 3 Days**	**± 14 Days**	**+ 5 Days**	**+ 7 Days**
Comprehensive serum chemistry	X[c]	X[d]		X	X	X	X	X		X	X
LFTs			X[e,f]	X[e]	X[e]	X[e]	X[e]	X[e]		X	X
Hematology with differential	X[c]	X[d]		X	X	X	X	X		X	X
Coagulation panel (PT, aPTT, INR)	X[c]	X[d,g]								X	
Endocrine function testing	X[c]	X[d]						X[h]		X	X
Tumor-specific history	X[i]										
PD-L1 Testing (NSCLC)	X[j]										
CA 125 testing (ovarian cancer only)	X								X[k]	X	
CA19-9 and CEA (gastric cancer only)	X								X[k]	X	
AFP tumor marker (HCC only)	X								X[k]	X	
If anti-HCV positive (HCC only):											
HCV genotype	X										
HCV viral load (HCV RNA)	X	X		X	X	X	X	X		X	

Table 13: Laboratory Assessments (Continued)

Visit Day (Range)	Screening	Combination, Monotherapy, and Re-Treatment Period[a]								EOT	Safety Follow-Up
		C1D1	Weekly for 6 Weeks (Phase 1 only)	C2D1	C4D1	C6D1 and C8D1	C12D1 and C16D1	Day 1 All Cycles	Every 9-12 Weeks	Discon-tinuation	42-49 Days After EOT or Last Dose of INCB024360
Laboratory Assessment[b]/Window	**Day -28 to Day -1**	**Day 1**	**± 3 Days**	**± 3 Days**				**± 3 Days**	**± 14 Days**	**+ 5 Days**	**+ 7 Days**
If (1) HbsAg+ or (2) anti-HBc+, anti-HBs-, HbsAg-, and viral load < 100 IU/mL (HCC only):											
Anti-HDV	X										
Anti-Hbe and HbeAg	X										
HbsAg and HBV viral load (HBV DNA)		X		X	X	X	X	X		X	
Anti-HBc (total), anti-Hbe, anti-HBs, and HbeAg								X		X	
Serum pregnancy test or urine	X[l]										
Serology	X										
Urinalysis	X							X			X

[a] If subjects are re-treated with MK-3475 as described in Section 6.2.1, subjects should follow this schedule of events.
[b] All laboratory analysis will be done locally unless otherwise noted.
[c] If screening laboratory testing occurs within 7 days of Cycle 1 Day 1, it is not required to be evaluated on Day 1 before treatment initiation. See required list of analytes for each panel in Table 14.
[d] Cycle 1 Day 1 laboratory tests (eg, serum chemistry, complete blood count, and coagulation panel) may be omitted IF the screening test was performed no more than 7 days prior.
[e] If LFTs are abnormal, then LFT should be monitored closely per standard of care until resolved to baseline.
[f] LFT testing is required weekly for the first 6 weeks during Phase 1 dose escalation. For Phase 2, weekly LFTs are not required and should be performed on Day 1 of each cycle.
[g] If a coumarin-based anticoagulant is given, monitor INR weekly for the first 4 weeks after initiation of therapy and upon discontinuation of INCB024360.
[h] To be repeated every 4 cycles (eg, Cycle 5 Day 1, Cycle 9 Day 1, Cycle 13 Day 1, Cycle 17 Day 1, etc).
[i] For subjects with SCCHN, HPV status; for NSCLC, EGFR status; for CRC, MSI status; for RCC, MSKCC score; for melanoma, BRAF status; for gastric cancer: CA19-9, EBV, *H. pylori*, CEA; for HCC, AFP, HCV/HBV status.
[j] PD-L1 testing for subjects with NSCLC may be performed locally using the PD-L1 IHC 22C3 pharmDX assay only. If local test results are unavailable, then tissue must be submitted for central testing before enrollment to determine appropriate cohort.
[k] Tumor markers should be performed every 9 weeks for the first 2 assessments (Weeks 9 and 18), then every 12 weeks thereafter.
[l] For women of child-bearing potential, a serum pregnancy test is required at screening but must be within 72 hours before first dose of study treatment. Pregnancy tests (serum or urine) should be repeated if required by local regulations.

Table 14: Laboratory Tests: Required Analytes

Serum Chemistry	Hematology	Other
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 IgG[a]	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	**Serology:** Hepatitis B surface antigen Hepatitis B surface antigen antibody Hepatitis B core antibody Hepatitis C virus antibody HCV-RNA HBV-DNA
		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.
		Urinalysis with microscopic examination: Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein Urobilinogen
		Coagulation: PT aPTT INR
		Tumor Specific: **Ovarian:** CA 125 testing **Gastric:** CEA **HCC:** AFP **HCC (if anti-HCV positive only):** HCV genotype, HCV viral load (HCV RNA) **HCC (if HbsAg+ or anti-HBc+, anti-HBs-, HbsAg- and viral load < 100 UI/mL):** Anti-HDV, anti-Hbe, HbsAg, HBV viral load (HBV DNA), anti-HBc (total), anti-HBs, and HbeAg
	Standard LFT Monitoring	**Endocrine Monitoring**
	Alkaline phosphatase ALT AST Total bilirubin	ACTH Serum cortisol (9 AM)[b] LH[c] Prolactin TSH Free thyroxine (T4) Total triiodothyronine (T3) Serum testosterone (9 AM)[b,d]

ACTH = adrenocorticotropic hormone; HDL = high-density lipoprotein; HS-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; LH = luteinizing hormone; PEF = peak expiratory flow; TSH = thyroid-stimulating hormone; VA = alveolar volume.

[a] Total IgG is obtained by an automated assay such as rate nephelometry. As long as the IgG is measured and not total immunoglobulin, institutional normal method of assessment is acceptable

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

[c] Not needed in subjects receiving testosterone therapy.

[d] Not needed in women, surgically castrated men, or men taking LHRH agonist therapy.

6.1. Screening Period

The screening period will be up to 28 days. Screening is the interval between the signing of the inform consent form (ICF) and the day the subject received the first dose of treatment in the study (Cycle 1 Day 1). Informed consent must be obtained before performing any study-specific procedures. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during this period.

Results from the screening visit evaluations will be reviewed to confirm subject eligibility before enrollment or the administration of study drug. Tests with results that fail eligibility requirements may be repeated once during the screening period if the investigator believes the results to be in error (eg, repeat biopsy allowed for subjects with a PD-L1 status of indeterminate when the PD-L1–low/negative NSCLC cohort is full, since the subject could be found to be PD-L1–positive with repeat biopsy). Additionally, a subject who fails screening may repeat the screening process 1 time if the investigator believes there has been a change in eligibility status (eg, after recovery from an infection).

6.2. Treatment Period

Note: As of Amendment 10, the option for monotherapy and re-treatment are only available to subjects who have already initiated monotherapy or re-treatment periods.

The treatment period with the combination therapy will continue every 21 days for up to 24 months, and then treatment with monotherapy INCB024360 may continue for up to 12 months if subjects are receiving benefit from treatment and have not had disease progression or met any criteria for study withdrawal, or subjects may stop both MK-3475 and INCB024360. Subjects who complete 24 months (35 administrations of MK-3475) of MK-3475, continue on monotherapy INCB024360 or stop both therapies, and later experience disease progression on INCB024360 monotherapy or off therapy may be considered for re-treatment with the combination for an additional 12 months (17 administrations of MK-3475) followed by the option to continue monotherapy INCB024360 for up to 12 months. Medical monitor approval is required for INCB024360 monotherapy treatment beyond 12 months.

6.2.1. Second Course Period (Re-Treatment Period)

Subjects who stop MK-3475 with SD or better may be eligible for up to 1 year of additional combination therapy if they experience disease progression after stopping the combination study treatment. This re-treatment is termed the second course period of this study and is only available if the study remains open and the subject meets either one of the following conditions.

1a. Stopped initial treatment of the combination after attaining an investigator-determined confirmed CR according to RECIST v1.1.

- Was treated for at least 24 weeks before discontinuing therapy.
- Received at least 2 cycles of the combination (2 doses of MK-3475 and at least 80% of the planned doses of INCB024360) beyond the date when the initial CR was declared.

OR

1b. Subject had SD, PR, or CR and stopped after 24 months (35 administrations of MK-3475) of study therapy for reasons other than disease progression or intolerability.

AND

2. Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with MK-3475.
3. Did not receive any anticancer treatment since the last dose of MK-3475 other than INCB024360.
4. Have an ECOG performance status of 0 or 1.
5. Demonstrate adequate organ function as detailed in study inclusion criteria (Section 3.2).
6. Female subject of childbearing potential should have a negative urine or serum pregnancy test within 72 hours before receiving re-treatment with study medication.
7. Female subjects of childbearing potential (defined as women who have not undergone surgical sterilization with a hysterectomy and/or bilateral oophorectomy, and are not postmenopausal, defined as ≥ 12 months of amenorrhea) must have a negative serum pregnancy test. All female and male subjects of childbearing potential must agree to take appropriate precautions to avoid pregnancy or fathering children (with at least 99% certainty) from screening through 120 days after the last dose of study treatment. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.
8. Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with participation for the full duration of the study or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Subjects who restart treatment will be re-treated with the 200 mg flat dose of MK-3475. For INCB024360, subjects should be treated at the same dose of INCB024360 they LAST received during the initial combination therapy (in particular, if a subject was dose reduced during initial combination therapy, he or she must resume second course at the same dose of INCB024360). Exceptions are noted below:

- If the subject was treated in Phase 1 with a dose lower than the recommended Phase 2 dose of INCB024360 (100 mg BID) as his or her initial treatment, AND did not require a dose reduction, he or she may begin second course treatment at 100 mg BID.

Treatment will be administered for up to 1 additional year.

Visit requirements are outlined in Table 12 and Table 13.

6.3. End of Treatment

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

6.4. Follow-Up Period

6.4.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled safety follow-up visit, which should occur 42 to 49 days after the EOT visit (or after the last dose of study drug if the EOT visit was not performed). Adverse events and SAEs must be reported up until at least 42 days (90 days for SAEs) after the last dose of study drug, the date of the follow-up visit, or until study drug–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. If a subject initiates a new anticancer therapy within 42 days after the last dose of study treatment, the 42-day safety follow-up visit must occur before the first dose of the new therapy. Reasonable efforts should be made to have the subject return for the follow-up visit and report any AEs that may occur during this period.

Subjects who are eligible for re-treatment with the combination therapy (as described in Section 6.2.1) may have up to 2 safety follow-up visits, 1 after the treatment period and 1 after the second course period.

6.4.2. Follow-Up

Note: As of Amendment 10, follow-up beyond the safety follow-up is discontinued. This section should be disregarded.

Subjects who discontinue study treatment for a reason other than disease progression will move into the follow-up period and should be assessed every 9 weeks (63 ± 5 days) by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new antineoplastic therapy, disease progression, death, and end of the study, or if the subject begins re-treatment with the combination therapy (MK-3475 and INCB024360) as detailed in Section 6.2.1. Information regarding poststudy antineoplastic treatment will be collected if new treatment is initiated.

[redacted]

Subjects who are eligible to receive re-treatment with MK-3475 and INCB024360 according to the criteria in Section 6.2.1 will move from the follow-up period to the second course period when they experience disease progression. Details are provided in Section 6 (Table 12 and Table 13).

6.4.3. Survival Follow-Up

Note: As of Amendment 10, long-term survival follow-up is discontinued. This section should be disregarded.

Once a subject has confirmed disease progression or starts a new anticancer therapy, the subject moves into the survival follow-up period and should be contacted by telephone, email, or visit every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

6.5. Unscheduled Visits

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

6.6. Early Termination

Not applicable.

7. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

7.1. Study Procedures

Section 6 summarizes the study procedures to be performed at each visit. Individual study procedures are described in detail below. It may be necessary to perform these procedures at unscheduled timepoints if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the sponsor and/or Merck for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C, etc), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.2. Administration of Informed Consent Form

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

7.3. Interactive Response Technology Procedure

The IRT will be contacted to obtain a subject identification number when a subject enters the screening period. Upon determining that the subject is eligible for study entry, the IRT will be contacted to obtain study drug assignment. Additionally, the IRT will be contacted at each regular study visit to update the study drug supply.

7.4. Demography and History

7.4.1. Demographics and Medical History

Demographic data and a complete medical and medication history will be collected at screening by the investigator or qualified designee and will include date of birth, race, ethnicity, medical and surgical history, and concurrent illnesses assessed using the NCI CTCAE v4.0 (NCI 2010).

Medical history should include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the investigator.

7.4.2. Tumor-Specific History

Details regarding the disease for which the subject has enrolled in the study (eg, date of diagnosis, primary tumor histology, prior systemic therapies, surgeries, radiation therapy, and stage of cancer) will be recorded separately and not listed in medical history. In addition, disease-relevant [redacted] information is required where available; for RCC, MSKCC score; for SCCHN, HPV status; for NSCLC, EGFR status; for melanoma, BRAF status; for CRC, MSI status; for gastric cancer, CA19-9, *H. pylori*, EBV, and CEA; for HCC, AFP, CP score, BCLC stage, and HCV/HBV status; and for DLBCL, International Prognostic Index score.

7.4.2.1. Esophagogastroduodenoscopy

Esophagogastroduodenoscopy will only be required at screening for subjects with HCC to screen for varices if it has not been performed within the past 12 months before first dose of study drug.

7.4.3. PD-L1 Testing (Phase 2 NSCLC Cohorts Only)

PD-L1 testing for subjects with NSCLC may be performed locally using the PD-L1 IHC 22C3 pharmDX assay only. If local test results are unavailable, then tissue must be submitted for central testing before enrollment to determine appropriate cohort placement. [redacted]

7.4.4. Prior Medications

Prior and ongoing medications will be reviewed to determine study eligibility. The investigator or qualified designee will review prior medication use, including any Protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the study. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

7.4.5. Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the study. Concomitant medications include any prescription, over-the-counter, or natural/herbal preparations taken or administered during the study period. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 8.1.

7.4.6. Poststudy Anticancer Therapy Status

The investigator or qualified designee will review all new antineoplastic therapy initiated after the last dose of study treatment. If a subject initiates a new anticancer therapy within 42 days after the last dose of study treatment, the 42-day safety follow-up visit must occur before the first dose of the new therapy.

7.5. Safety Assessments

7.5.1. Adverse Events

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

All AEs of unknown etiology associated with MK-3475 and INCB024360 exposure should be evaluated to determine if it is possibly an ECI of a potentially immunologic etiology (irAE).

Nonserious events of clinical interest identified from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, must be reported to the SPONSOR within 24 hours of the event, similar to standard SAE reporting guidelines, and either by electronic media or paper. Events of clinical interest that meet serious criteria must be reported within 24 hours as defined in Section 8.3.2. Sponsor contact information can be found in the regulatory binder.

Subjects should be assessed for possible irAEs prior to each dose. Laboratory results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an AE thought to be immune-related should have additional testing to rule out other etiologic causes. If laboratory results or symptoms indicate a possible irAE, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

7.5.2. Comprehensive Physical Examination

Physical examinations must be performed by a medically qualified individual such as a licensed physician, Physician's Assistant, or an advanced Registered Nurse Practitioner, as local law permits.

The comprehensive physical examination will include the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; lymph nodes; and a brief neurological examination. Before the first dose of study treatment, clinically significant abnormal findings should be recorded as medical history. After the first dose of study treatment, new clinically significant abnormal findings should be recorded as AEs.

7.5.3. Targeted Physical Examination

For cycles that do not require a full physical examination per the schedules of assessments (Table 12), the investigator or qualified designee will perform a directed physical examination as clinically indicated before study treatment administration. A targeted physical examination will be a symptom-directed evaluation conducted by the investigator or designee. The targeted physical examination will include assessment(s) of the body systems or organs, as indicated by

subject symptoms, AEs, or other findings. New clinically significant abnormal findings should be recorded as AEs.

7.5.4. Assessment of Serotonin Syndrome Symptoms

Note: As of Amendment 10, assessment for serotonin syndrome is no longer required. This section should be disregarded.

Subjects will be assessed for the presence of any of the following symptoms approximately 6 hours postdose at the Cycle 1 Day 1 visit and at any time on Day 1 of all subsequent cycles and at the EOT visit. Symptoms are based on the findings of Boyer and Shannon (2005; Appendix H) as indicated in Table 15.

Table 15: Serotonin Syndrome Symptoms

Tremor and hyperreflexia
Spontaneous clonus
Muscle rigidity, temperature > 38°C, and either ocular clonus or inducible clonus
Ocular clonus and either agitation or diaphoresis
Inducible clonus and either agitation or diaphoresis

7.5.5. Vital Signs

Vital sign measurements include blood pressure, pulse, respiratory rate, body temperature, and weight. Height will be measured at screening only.

7.5.6. Twelve-Lead Electrocardiograms

Baseline ECGs will be obtained at screening, at EOT, and as clinically indicated. Clinically significant abnormal findings prior to signing consent should be recorded as medical history. Clinically significant abnormal findings after signing consent should be recorded as an AE.

The 12-lead ECGs will be interpreted by the investigator at the site and will be used for immediate subject management. The decision to include or exclude a subject or withdraw a subject from the study based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the sponsor's medical monitor, as appropriate. The correction method (Fridericia or Bazett) used for calculating QTc will need to be provided in the eCRF.

7.5.7. Laboratory Assessments

Note: As of Amendment 10, all laboratory assessments will be performed locally unless otherwise specified.

Laboratory tests for screening or entry into the second course period should be performed within 7 days before the first dose of treatment. After Cycle 1, for local laboratories noted below, predose laboratory procedures can be conducted up to 72 hours before study drug administration. Results must be reviewed by the investigator or qualified designee and found to be acceptable before each dose of study treatment.

7.5.7.1. Hematology, Coagulation Panel, Serology, and Endocrine Function Testing

Hematology, coagulation panel, serology, and endocrine function will all be analyzed by a local laboratory.

7.5.7.2. Urinalysis

Urinalysis will be analyzed by the site local laboratory.

7.5.7.3. Serum Chemistry and Liver Function Tests

All serum chemistry testing (screening, Cycle 1 Day 1, and Day 1 of each cycle) as well as weekly LFTs for the first 6 weeks of study treatment (for Phase 1) then Q3W thereafter will be performed by the site's local laboratory, as well as more frequent LFT monitoring (per standard of care for elevations) if it is required. Throughout the Protocol, LFT refers specifically to liver chemistry testing, and required analytes for LFTs are listed in Table 14.

7.5.7.4. Pregnancy Testing

Serum pregnancy tests will be analyzed by the site laboratory during screening and must be within 72 hours before first dose of study treatment. Subsequently, pregnancy tests will be conducted only as medically indicated.

If a subject inadvertently becomes pregnant while on treatment with MK-3475 and INCB024360, the subject will immediately be withdrawn from the study. The site will contact the subject at least monthly and document the subject's status until the first well-baby visit to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. The outcome of the pregnancy will be reported to the sponsor without delay and within 24 hours if the outcome is an SAE (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the sponsor. If a male subject impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy reported to the sponsor and followed as described above and in Section 8.5.

7.5.7.5. Laboratory Assessments for Subjects With Hepatocellular Carcinoma

All testing noted in this section will be done locally. Anti-HBc (total), anti-HBs, HBV viral load (HBV DNA), HbsAg, hepatitis C virus antibody, and HCV RNA testing are required for all subjects with HCC at screening.

If (1) HbsAG+ or (2) anti-HBc+, anti-HBs-, HbsAg-, and viral load < 100 IU/mL, then the following testing will also be required:

- Anti-HDV, anti-Hbe, and HbeAg at screening.
- HbsAg and HBV viral load (HBV DNA) will be required at each cycle while on study treatment and at EOT.
- Anti-HBc (total), anti-Hbe, anti-HBs, and HbeAG will be required every 4 cycles while on study treatment and at EOT.

For all subjects who are anti-HCV positive:

- HCV genotype testing is required at screening along with HCV viral load (HCV RNA) testing. HCV viral load (HCV RNA) testing will also be required at each cycle while on study treatment and at EOT.

7.6. Efficacy Assessments

7.6.1. Initial Tumor Imaging

Initial tumor imaging must be performed within 28 days before the first dose of study treatment. The site study team must review prestudy images to confirm the subject has measurable disease per RECIST v1.1 for solid tumors or Lugano Classification (Cheson et al 2014) for DLBCL. A standard, full assessment for lesions should be conducted at baseline, including CT or MRI scans of chest, abdomen, and pelvis for solid tumors. Baseline imaging of the CNS (eg, MRI or contrast CT of the brain) should be performed for all subjects with previously treated brain metastases. Otherwise, baseline brain MRI is only indicated if there are symptoms consistent with CNS disease based on investigator assessment. The same modality (CT or MRI) should be used for follow-up assessments at Week 9, Week 18, and every 12 weeks, including radiological assessments of all sites of disease present at baseline. In addition to radiological monitoring, all other lesions observed at the screening visit should be followed.

Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days before the first dose of study treatment. **The same imaging technique should be used in a subject throughout the study.** Baseline scan must be a contrast computed tomography (CT) or magnetic resonance imaging (MRI), except in circumstances where there is a contrast allergy or with medical monitor approval. When the CT component of a positron emission tomography (PET)/CT uses higher energy and thinner slices, it may be acceptable (with medical monitor approval).

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

7.6.2. Tumor Imaging During the Study

Tumor imaging may be performed by CT or MRI, but the same imaging technique should be used in a subject throughout the study. Scans must be a contrast CT or MRI, except in circumstances where there is a contrast allergy or with medical monitor approval. When the CT component of a PET/CT uses higher energy and thinner slices, it may be acceptable (with medical monitor approval) if it was the same technique used for baseline. Imaging should be performed every 9 weeks (63 days ± 5 days) for the first 2 timepoints (Weeks 9 and 18), then every 12 weeks thereafter. More frequent imaging should be performed if clinically indicated. Imaging should not be delayed for delays in cycle starts or extension of combination treatment cycle intervals.

Per RECIST v1.1, response should be confirmed by a repeat radiographic assessment not less than 4 weeks from the date the response was first documented. The scan for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (9 or 12 weeks later), whichever is clinically indicated. Confirmation scans are considered interval scan and subjects need to stay on 9 or 12-week schedule from baseline (eg, imaging at Week 9 shows PR, confirmation scan done at Week 13, next scheduled scan should be Week 18 followed by Week 30, etc).

Imaging should continue to be performed until documented disease progression, the start of new anticancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first. Disease progression should be confirmed at least 4 weeks after the first scan indicating progressive disease in clinically stable subjects. Subjects who have unconfirmed disease progression may continue on treatment until progression is confirmed provided they have met the conditions detailed in Section 7.6.3.

7.6.3. Assessment of Disease

7.6.3.1. Assessment of Disease According to Modified RECIST v1.1 for Solid Tumors

RECIST v1.1 will be applied by the site as the primary measure for assessment of tumor response and as a basis for Protocol guidelines related to disease status (eg, discontinuation of study therapy). RECIST v1.1 will be adapted for defining PD as follows to account for the unique tumor response seen in this class of therapeutics.

If imaging shows PD, tumor assessment should be repeated ≥ 4 weeks later to confirm PD with the option of continuing treatment for clinically stable subjects (see Table 16). Clinically stable is defined by the following criteria:

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

Table 16: Imaging and Treatment After First Radiographic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD	Repeat imaging at ≥ 4 weeks to confirm PD	May continue study treatment at the investigator's discretion while awaiting confirmatory scan	Repeat imaging at ≥ 4 weeks to confirm PD if possible	Discontinue treatment
Repeat scan confirms PD	No additional imaging required	Discontinue treatment	No additional imaging required	N/A
Repeat scan shows SD, PR, or CR	Continue regularly scheduled imaging assessments every 12 weeks	Continue study treatment at the investigator's discretion	Continue regularly scheduled imaging assessments every 12 weeks	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion

In determining whether the tumor burden has increased or decreased, investigators should consider all target lesions as well as nontarget lesions. Subjects who are deemed clinically unstable are not required to have repeat imaging for confirmation. If radiologic progression is confirmed, then the subject will be discontinued from study treatment as specified in the Protocol, and the first radiographic evidence of PD should be the date of progression. If radiologic progression is not confirmed, then the subject should resume/continue study treatment and have their next scan according to the Protocol-specified schedule. If progression is not confirmed and the subject continues on treatment, the next scan that documents disease progression (and is confirmed by a second scan at least 4 weeks later), will be considered the date of disease progression.

NOTE: If a subject with confirmed radiographic progression (ie, 2 scans at least 28 days apart demonstrating progressive disease) is clinically stable or clinically improved, and there is no further increase in the tumor dimensions at the confirmatory scan, an exception may be considered to continue treatment upon consultation with the sponsor. Clinically stable subjects should also have at the confirmatory scan no further increase in the target lesions, no unequivocal increase in nontarget lesions, and no additional new lesions develop (nonworsening PD) to continue study treatment.

7.6.4. Assessment of Response for DLBCL by the Lugano Classification

An objective assessment of disease status is required using the Lugano Classification (Cheson et al 2014) and will be adapted for defining PD as noted in Section 7.6.3.1 to account for the unique tumor response seen in this class of therapeutics.

Details regarding response assessment per the Lugano Classification are presented in Table 17.

Positron emission tomography using [^{18}F] FDG, or combined PET-CT is required at screening. If imaging assessment was performed under standard of care prior to signing of the ICF but

within 30 days of Cycle 1 Day 1, the result of that assessment may be recorded in the CRF in lieu of a study-specific assessment. On-treatment assessments should be performed every 9 weeks following Cycle 1 Day 1. This assessment schedule also applies to those subjects who discontinue study treatment for reasons other than disease progression until disease progression, start of new anticancer therapy, withdrawal of consent, end of the study, or death, whichever comes first. Scheduled PET assessments should always be calculated from the first dose of study treatment. Imaging should not be delayed for delays in cycle starts. Results will be captured in the eCRF.

Table 17: Revised Criteria for Response Assessment (Lugano Classification)

Site	PET-CT–Based Response	CT-Based Response
Complete response		
Lymph nodes and extralymphatic sites	Score 1, 2, or 3 with or without a residual mass on 5PS[a].	Target nodes/nodal masses must regress to ≤ 1.5 cm in Ldi. No extralymphatic sites of disease.
Nonmeasured lesion	Not applicable.	Absent.
Organ enlargement	Not applicable.	Regress to normal.
New lesions	None.	None.
Bone marrow	No evidence of FDG-avid disease in marrow.	Normal by morphology; if indeterminate, IHC negative.
Partial response		
Lymph nodes and extralymphatic sites	Partial metabolic response: • Score 4 or 5[a] with reduced uptake compared with baseline and residual mass(es) of any size. • At interim, these findings suggest responding disease. • At EOT, these findings indicate residual disease.	Partial remission (all of the following): • ≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites. • When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value. • When no longer visible, 0 × 0 mm. For a node > 5 mm × 5 mm but smaller than normal, use actual measurement for calculation.
Nonmeasured lesions	Not applicable.	Absent/regressed, but no increase.
Organ enlargement	Not applicable.	Spleen must have regressed by > 50% in length beyond normal.
New lesions	None.	None.
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given for further evaluation with MRI or biopsy at interval scan.	Not applicable.

Table 17: Revised Criteria for Response Assessment (Lugano Classification) (Continued)

Site	PET-CT–Based Response	CT-Based Response
No response or stable disease		
Target nodes/nodal masses, extranodal lesions	No metabolic response. Score of 4 or 5[a] with no significant change in FDG uptake from baseline at interim or EOT.	Stable disease. < 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met.
Nonmeasured lesions	Not applicable.	No increase consistent with progression.
Organ enlargement	Not applicable.	No increase consistent with progression.
New lesions	None.	None.
Bone marrow	No change from baseline.	Not applicable.
Progressive disease		
Individual target nodes/nodal lesions	Progressive metabolic disease. Individual target nodes/nodal lesions: • Score 4 or 5[a] with an increase in intensity of uptake from baseline and/or • New FDG-avid foci consistent with lymphoma at interim or EOT assessment. Extranodal lesions: • New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment. New lesions: • New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered. Bone marrow: New or recurrent FDG-avid foci.	Progressive disease requires at least one of the following PPD progression: • An individual node/lesion must be abnormal with all of the following: – Ldi > 1.5 cm – Increase by ≥ 50% from PPD nadir – An increase in Ldi or Sdi from nadir ▪ 0.5 cm for lesions ≤ 2 cm ▪ 1.0 cm for lesions > 2 cm • In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. • New or recurrent splenomegaly. • New or clear progression of preexisting nonmeasured lesions. • Regrowth of any previously resolved lesions. • A new node > 1.5 cm in any axis. • A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma. • Assessable disease of any size unequivocally attributable to lymphoma. New or recurrent involvement of the bone marrow.

5PS = 5-point scale; Ldi = longest transverse diameter of lesion; PPD = cross product of the Ldi and perpendicular diameter; Sdi = shortest axis perpendicular to the Ldi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

[a] PET 5-point scale: 1, no uptake above background; 2, update ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

7.6.4.1. Bone Marrow Examination

Bone marrow examination is required as a baseline assessment for subjects with disease subtypes (DLBCL) that utilize bone marrow histology as part of the objective criteria for disease staging. Exceptions include: 1) if a recent bone marrow biopsy was performed (within 60 days of Cycle 1 Day 1), a new bone marrow biopsy does not need to be repeated for screening, or 2) if bone marrow involvement is clearly evident or absent per PET/CT it also would not be required at screening. Subsequently, bone marrow biopsy will be performed only to confirm CR or as clinically indicated.

Data from the pathology report resulting from the bone marrow examination will be captured in the CRF. Results of assessments performed under standard-of-care prior to the signing of informed consent may be used as the baseline assessment in lieu of a study-specific procedure IF performed within 60 days of the first dose of study drug (Cycle 1 Day 1).

All bone marrow examinations should include a unilateral aspiration and biopsy, when feasible. Subjects may be enrolled based on a biopsy only when a "packed marrow" precludes aspiration. An aspiration only may be performed at the discretion of the investigator.

Subsequently, bone marrow biopsy will be performed only to confirm CR or as clinically indicated. If the bone marrow does not have lymphoma involvement at baseline, a repeat bone marrow exam is not required to confirm indication of CR on imaging.

7.6.5. Tumor Markers

7.6.5.1. CA 125 Monitoring (Ovarian Cancer Only)

CA 125 monitoring will be performed locally for subjects with ovarian cancer only at screening, Week 9, then every 12 weeks until EOT.

7.6.5.2. CA19-9 and CEA Monitoring (Gastric Cancer Only)

CA19-9 and CEA monitoring will be performed locally for subjects with gastric cancer only at screening, Week 9, then every 12 weeks until EOT.

7.6.5.3. Alpha Fetoprotein Tumor Marker (HCC Only)

AFP monitoring will be performed locally for subjects with HCC only at screening, Week 9, Week 18, then every 12 weeks until EOT.

7.6.5.4. Assessments for Ascites and Encephalopathy (HCC Only)

Assessments for ascites and for encephalopathy should be documented at each visit for subjects with HCC only.

7.6.6. Tumor Biopsy

Fresh tumor biopsies (defined as a biopsy specimen taken since completion of the most recent prior systemic regimen) will be required (except as indicated in the inclusion criteria) at baseline. Optional tumor biopsy specimens on study may be obtained any time after C1D14 or with confirmed response or progression in subjects with accessible tumors [redacted]

[redacted] Biopsy specimens obtained to evaluate toxicities will also be collected to evaluate target-related expression.

Details and methods for obtaining, processing, and shipping the fresh tumor biopsy samples will be provided in the Laboratory Manual for the study. Archived tumor tissue should also be submitted if available. Details for processing and shipping the archived tumor tissue samples will be provided in the Laboratory Manual.

7.6.6.1. Tumor Biopsy in the Phase 2 Melanoma Primary Refractory and Relapsed Cohorts

Note: As of Amendment 10, the melanoma primary refractory and relapsed cohorts are closed to further enrollment. The following text applies to subjects enrolled before Amendment 10.

Pretreatment and on-treatment tumor biopsies are required for subjects enrolled in the Phase 2 primary refractory and relapsed melanoma cohorts. Subjects should have tumor lesions that are amenable to repeat percutaneous or endoscopic biopsy. Tumor biopsy samples will be collected at baseline (before Day 1 administration) and while the subject is receiving therapy as specified in the following:

- Screening: A fresh biopsy at baseline is required. Archival samples are not permitted in order to enable analysis of TIL infiltration into tumors during treatment.
- On-treatment biopsy: A biopsy will be collected during Cycle 3 between Days 8 and 15 (Study Days 50 and 57). The biopsy should be collected from the same lesion as the screening biopsy. If the subject progresses before this timepoint, then biopsy should be done at time of progression.

If a subject is scheduled to have a tumor biopsy for the purposes of this study and it is subsequently determined by the interventional radiologist that tumor tissue cannot safely be obtained, or if the biopsy does not meet the minimum standards for evaluation (as outlined in the Laboratory Manual), then the subject may still enroll in the cohort and will be followed for efficacy and safety. The subject may be replaced in order to enroll sufficient numbers of biopsy-evaluable subjects. Note: If the baseline tumor biopsy was found to be inadequate, the patient should not undergo an on treatment biopsy. Post-progression biopsy can still be optional.

Subjects with solitary target lesions should not be enrolled in either of these cohorts.

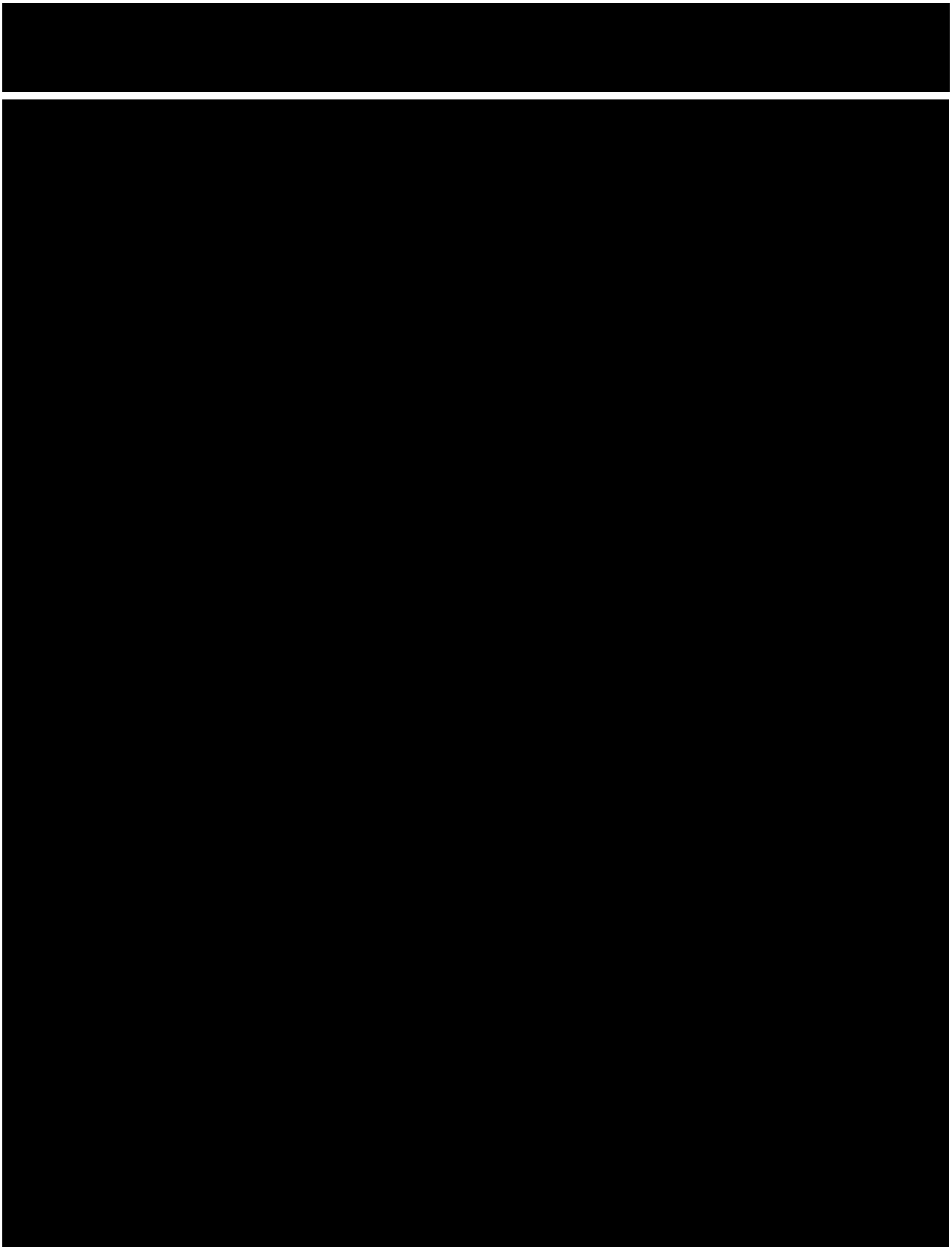
7.7. Performance and Quality of Life Assessments

7.7.1. Eastern Cooperative Oncology Group Performance Status

The investigator or qualified designee will assess ECOG performance status (Appendix C) at screening and before the administration of each cycle of study treatment and EOT as specified in the schedules of assessments (Table 12). No quality of life instrument will be used in this study.

[redacted]

[redacted]



7.10. Other Study Procedures

7.10.1. Study Compliance (Medication, Diet, Activity, Other)

Interruptions from the Protocol-specified treatment plan for > 12 weeks between MK-3475 and INCB024360 doses due to toxicity require consultation between the sponsor and investigator and written documentation of the collaborative decision on subject management.

7.10.2. Administration of MK-3475 and Compliance

Administration of MK-3475 (± 3 days) will be witnessed by the investigator and/or study staff. The total volume of study treatment infused will be compared to the total volume prepared to determine compliance with each dose administered.

The instructions for preparing and administering MK-3475 will be provided in the Procedures Manual.

7.10.3. Administration of INCB024360 and Compliance

Subjects will self-administer their dose of INCB024360 in the morning and evening, approximately 12 hours apart without regard to food.

INCB024360 compliance will be calculated by the sponsor based on the drug accountability documented by the site staff and monitored by the sponsor/designee (tablet counts). The objective is 100% compliance and investigators and their staff should evaluate compliance at each visit, and take appropriate steps to optimize compliance.

7.10.4. Dispensing of INCB024360

Site staff will contact the IRT to obtain the subject study drug assignment. The investigator or designee will select the assigned bottles from their stock that correspond to the number provided by the IRT and dispense the medication. The investigator will enter the bottle numbers in the eCRF. At subsequent medication dispensing visits, the investigator or designee will follow the same procedures as described above. Full details will be provided in the IRT Manual.

7.10.5. Distribution of Subject Reminder Cards and Diaries

Subjects will be provided with reminder cards at each visit. The subject reminder cards will indicate the date/time of the next visit. On Day 1 only subjects will also be given an SS information sheet for signs and symptoms of SS. This information sheet also instructs subjects to seek immediate medical care if any of these symptoms are observed.

7.10.6. Withdrawal or Discontinuation

When a subject discontinues or withdraws before study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Any AEs that are present at the time of discontinuation or withdrawal should be followed in accordance with the safety requirements outlined in Section 8.1.1. These subjects should return to the site for the safety follow-up visit (described in Section 6.4.1).

8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events

8.1.1. Definitions and Reporting

For the purposes of this Protocol, an AE is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after a subject provides informed consent. Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically meaningful, require therapy (eg, hematologic abnormality that requires transfusion), or require changes in the study drug(s).

Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events page of the eCRF. Conditions that were already present at the time of informed consent should be recorded on the Medical History page of the eCRF. Adverse event monitoring should be continued for at least 42 days after the last dose of study drug. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

Adverse events will be assessed according to the CTCAE v4.0. The CTCAE severity Grade 5 (death) will not be used in this study; rather, information about deaths will be collected as an outcome of the event.

If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity:

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

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

- The severity grade (CTCAE Grade 1 to 4).
- Reasonable possibility that the AE is related to the study treatment: unrelated (no) or related (yes).

  NOTE: Since this is a study of INCB024360 combined with MK-3475, the relationship to study drug can be assessed for INCB024360 alone, MK-3475 alone,

INCB024360 combined with MK-3475, or not related to either INCB024360 or MK-3475.

- Start and end dates, unless unresolved at final examination.
- Action taken with respect to study drug (eg, none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable).
- Outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- Whether it is serious, as per SAE definition provided in Section 8.3.1.

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

All AEs should be treated appropriately. If a concomitant medication or nondrug therapy is given, this action should be recorded on the AE and Prior/Concomitant medications pages of the eCRF.

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

The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition or considered to be treatment-related by the investigator, should not be reported as an adverse event.

Efficacy endpoints as outlined in Section 4 will not be reported as AE/SAEs, specifically, any event that is related to disease progression of the cancer under study. Unblinded aggregated efficacy endpoint events and safety data will be monitored to ensure the safety of the participants in the study. Any suspected endpoint that upon review is not progression of the cancer under study will be forwarded to Incyte Pharmacovigilance as a SAE within 24 hours of determination that the event is not progression of the cancer under study.

8.2. Laboratory Test Abnormalities

8.2.1. Definitions and Reporting

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

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A Grade 3 or 4 (severe) AE, as per CTCAE, does not automatically indicate an SAE unless it meets the definition of serious, as defined in Section 8.3.1, and/or per the investigator's discretion. A dose interruption or adjustment for the laboratory abnormality may be required (see Section 5.6.2) and should not contribute to the designation of a laboratory test abnormality as an SAE.

8.3. Serious Adverse Events

8.3.1. Definitions

A SAE is defined as an event that meets 1 of the following criteria:

- Is fatal or life-threatening (ie, immediate risk of dying).
- Results in persistent or significant disability or incapacity.
- Constitutes a congenital anomaly or birth defect.
- Is clinically meaningful (ie, defined as an event that jeopardizes the subject or requires potential medical or surgical intervention to prevent 1 of the outcomes listed above). Considered meaningful by the investigator as an important medical event that may not result in death, be life-threatening, or require hospitalization, but may be considered a SAE when, based upon appropriate medical judgment, it may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is a result of:
  - Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
  - Elective or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF.
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.
  - Social reasons and respite care, in the absence of any deterioration in the subject's general condition.
  - Any SAEs that are expected due to the condition being treated, including if the SAE is a primary outcome measure, or where there has been a clear agreement with regulators not to consider these as SAEs, provided the information is collected elsewhere.

8.3.2. Reporting

To ensure subject safety, every SAE, regardless of suspected causality, occurring after the subject has signed the ICF and up to 90 days after the subject has stopped study treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy,

whichever is earlier, must be reported to the sponsor (or designee) within 24 hours of learning of its occurrence. Any SAEs experienced after this period should be reported to the sponsor (or designee) only if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as the follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event. Previously planned (before providing informed consent) surgeries should not be reported as SAEs unless the underlying medical condition worsens over the course of the study.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to each specific study drug (if there is more than 1), complete the SAE Report Form in English, and send the completed, signed form by fax or emailed within 24 hours to the sponsor or its designee. The investigator must assess if there is a reasonable possibility that the SAE is related to the study treatment: unrelated (no) or related (yes).

Serious AEs related to unblinded comparator drugs or concomitant medications/drug delivery systems are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

The telephone, email, and facsimile number of the sponsor's contact persons, specific to the study, are listed in the investigator binder provided to each site. The original copy of the SAE Report Form and the fax or email confirmation sheet must be kept with the eCRF documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each recurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation, or if study drug was interrupted or discontinued.

If the SAE is not previously documented in the IB for the study drug (new occurrence) and is thought to be related to the sponsor's study drug, a sponsor's associate may urgently require further information from the investigator for reporting to health authorities.

The sponsor or its designee may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC, or as per national regulatory requirements in participating countries.

8.4. Emergency Unblinding of Treatment Assignment

Not applicable.

8.5. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study drug may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed, including the pregnancy of a male subject's female partner that occurs during the study, or within 120 days of completing the study or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, the following procedures should occur:

- The investigator must notify the sponsor or its designee immediately.
- The study drug must be discontinued immediately.
- The subject must be withdrawn from the study.
- The EOT visit evaluations must be performed.
- The investigator must complete and submit the Pregnancy Initial and Follow-Up Report forms to the sponsor or its designee.
- A serum pregnancy test must be performed to confirm the urine pregnancy test result. (The serum test should be performed at the investigative site to ensure the test will be performed promptly and the result available immediately for review.)

If a negative serum test does not confirm the urine pregnancy test result, then:

- The investigator will use his or her expert judgment, based on an assessment of the potential benefit/risk to the subject, to determine if it is in the subject's best interest to resume study drug and continue participation in the study.

To ensure subject safety, each pregnancy in a subject during maternal or paternal exposures to study drug must be reported within 24 hours of learning of its occurrence. Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation. Follow-up to each pregnancy should be conducted, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the sponsor's study drug of any pregnancy outcome and follow-up to the first well-baby visit. **Any SAE experienced during pregnancy must be reported on the SAE Report Form and to the sponsor or its designee.**

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

For this study, an overdose will be defined as ≥ 1000 mg (5 times the dose) of MK-3475 or > 1000 mg of epacadostat. No specific information is available on the treatment of overdose of MK-3475 or epacadostat. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an AE(s) is associated with ("results from") the overdose of study therapies the AE(s) is reported as an SAE, even if no other seriousness criteria are met.

If a dose of the study therapy (MK-3475) meeting the Protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a nonserious ECI using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an AE must be reported within 24 hours to the sponsor either by electronic media or paper.

8.7. Warnings and Precautions

No evidence available at the time of the approval of this study Protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided IB. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications (Ins). Any important new safety information should be discussed with the subject during the study as needed. If new, significant risks are identified, they will be added to the ICF.

8.8. Data Monitoring Committee

There will be no formal data monitoring committee for this open-label study. For Phase 1, approximately weekly the sponsor will conduct telephone conferences with investigators in order to review cohort-specific data, overall safety data from prior cohorts (if applicable), and to agree on dose escalation, de-escalation, and cohort expansion decisions. For Phase 2, safety and tolerability will be carefully monitored throughout the study by the sponsor in accordance with interim safety analyses planned procedures as described in Section 9.6.

8.9. Events of Clinical Interest

Selected nonserious and serious AEs of special interest are also known as ECIs and must be recorded as such in the eCRF and reported to the sponsor within 24 hours either by electronic media or paper. Sponsor contact information can be found in the Investigator Study File Binder (or equivalent). Events of Clinical Interest for this study include:

1. An overdose of sponsor's product, as defined in Section 8.6 — Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. An elevated AST or ALT laboratory value that is ≥ 3 × the ULN and an elevated total bilirubin laboratory value that is ≥ 2 × the ULN and, at the same time, an alkaline phosphatase laboratory value that is < 2 × the ULN, as determined by way of Protocol-specified laboratory testing or unscheduled laboratory testing.

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

[redacted] This syndrome has been most closely associated with use of MAOIs, meperidine (Demerol®), linezolid, or methylene blue; all of these agents are prohibited during the study. Selective serotonin reuptake inhibitors and SNRIs are permitted in the study. Procedures listed in Section 5.6.5 will be implemented if subjects exhibit the signs and symptoms of SS described in Section 7.5.4, including tremor, hyperreflexia, and spontaneous, ocular, or inducible clonus together with agitation, fever, diaphoresis, or muscle rigidity.

8.10. Product Complaints

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

All product complaints associated with material packaged, labeled, and released by the sponsor or its designee will be reported.

The investigator or his/her designee is responsible for reporting a complete description of the product complaint and any associated AEs via email or other written communication to the Incyte contact.

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

9. STATISTICS

9.1. Study Populations

Efficacy Evaluable: All subjects enrolled in the study who take at least 1 dose of study drug.

Safety Evaluable: All subjects enrolled in the study who take at least 1 dose of study drug.

[redacted]

9.2. Selection of Sample Size

9.2.1. 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 INCB024360 in combination with MK-3475. 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 4.1. 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).

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

The sample size of 18 to 42 subjects are expected to be enrolled in each of the 14 response expansion cohorts (NSCLC PD-L1 positive, NSCLC PD-L1 low/negative or indeterminate, melanoma [3 cohorts – checkpoint-naïve, primary refractory and relapsed], transitional cell carcinoma of the GU tract, TNBC, ovarian cancer, SCCHN, DLBCL, MSI high CRC, clear cell RCC, gastric cancer, and 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 21.

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 21: Sample Size Calculation for Each Cohort: Comparing to 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 0%-49% or indeterminate)	12%	32%	25
Melanoma (immune checkpoint-naïve)	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.

9.3. Level of Significance

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

9.4. Statistical Analyses

9.4.1. Primary Analyses

Primary efficacy analysis will be conducted for the Phase 2 efficacy evaluable population. The primary variable for the Phase 2 expansion portion of the study is ORR, which is defined as the proportion of subjects with best response (CR or PR) by irRECIST v1.1 for select solid tumors and modified Lugano Classification (Cheson et al 2014) for DLBCL. The 95% exact CI for the ORR will be estimated using the Clopper-Pearson method. One sample binomial test will be used to test the null hypotheses.

9.4.2. Secondary Analyses

Secondary efficacy analysis will be conducted for the efficacy evaluable population.

Progression-free survival is defined as number of days from the first day of taking study drug to the earlier of death or disease progression by irRECIST v1.1 for select solid tumors and modified Lugano Classification (Cheson et al 2014) for DLBCL. Time-to-event data will be analyzed by the Kaplan-Meier method, treating subjects with no observed death or progression as censored at

their last valid response assessment or last valid response assessment date prior to post study cancer treatment. For the OS analysis, the nonparametric Kaplan-Meier method will be used to estimate the survival time distribution and the median survival of each tumor type.

For objective responders, the duration of response is the time from the first objective response contributing to an objective response, to the first objective response of PD (by irRECIST v1.1) occurring after the first objective response contributing to the objective response. Median duration of response will be estimated using the Kaplan-Meier method. The duration of disease control is the time from the treatment start date to the first objective response of PD (by irRECIST v1.1 or Lugano Classification (Cheson et al 2014) occurring after the first objective response of CR/PR/SD. Median duration of disease control will be estimated using the Kaplan-Meier method.

The ordinal response scores are defined as the following:

- 1 = Complete response 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 per irRECIST v1.1
- 5 = Progressive disease per irRECIST v1.1

The frequency of subjects in each category will be summarized by tumor type.

For OS analysis, the Kaplan-Meier method will be used to estimate the survival time distribution and the median survival of each tumor type.

9.4.3. Safety Analyses

The principal analysis will be based on the safety evaluable population, according to treatment assignment.

Adverse events will be coded by the MedDRA, and incidences will be tabulated by preferred term and system organ class for all events, related events, events ≥ Grade 3 and adverse events of special interest. Severity of AEs will be based on the CTCAE scale as indicated in Section 8.1.1. Quantitative safety variables and their changes from baseline (laboratory, vital signs) will be summarized with descriptive statistics. Clinically significant abnormal values will be flagged and tabulated based on predefined criteria.

Exposure will be analyzed by describing dose intensity, which is defined as the dose-received divided by the dose planned over a given time interval. This will be done by cycle as well as overall cycles received for MK-3475 + INCB024360. The percentage of subjects with any delay and/or reduction will also be calculated.

The clinical laboratory data will be analyzed using summary statistics (eg, means and frequencies), and no formal statistical comparisons among the treatments are planned. In addition, these values will also be classified into CTCAE toxicity grades and tabulated. Descriptive statistics and mean change from baseline will be determined for vital signs at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities.

9.5. Data Monitoring Committee

Not applicable.

9.6. Interim Safety Analyses

An interim safety analysis is planned for Phase 2 after 20 subjects have been enrolled and treated for 9 weeks, and then approximately every 3 months thereafter. If the following is reported during these reviews, 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 agents.

Based on these rules, the probabilities of stopping a treatment group for safety is provided in Table 22.

Table 22: 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[a]
5%	0.0%
10%	0.04%
15%	0.58%
20%	3.17%
25%	10.35%
30%	24.31%
40%	85.37%

[a] 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).

No formal interim analysis for futility or efficacy is planned for this study.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Investigational Products Description

10.1.1. Packaging, Labeling, and Preparation of Study Drug

10.1.1.1. INCB024360

The study drug will be available as 25 mg and 100 mg tablets packaged in high-density polyethylene bottles. All tablet excipients comply with the requirements of the applicable compendial monographs (Ph. Eur., USP/NF) (refer to the iIB). All Incyte investigational product labels will be in the local language and will comply with the legal requirements of each country.

10.1.1.2. MK-3475

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the Protocol and any applicable laws and regulations. Clinical supplies will be provided by Merck as summarized in Table 23.

Table 23: MK-3475 Product Descriptions

Product Name and Potency	Dosage Form
MK-3475 100 mg/4 mL	Solution for Injection

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

10.1.2. Storage and Stability of Study Drugs

10.1.2.1. INCB024360

Clinical supplies must be stored as described in the iIB.

10.1.2.2. MK-3475

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Receipt and dispensing of study drug must be recorded by an authorized person at the study site. Clinical supplies may not be used for any purpose other than that stated in the Protocol.

10.2. Accountability, Handling, and Disposal of INCB024360 and MK-3475

Responsibility for drug accountability at the study site rests with the investigator; however, the investigator may assign some of the drug accountability duties to an appropriate pharmacist or other designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities.

The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug according to their institution policies. The investigator or designee must maintain records that document:

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

These records should include dates, quantities, batch or serial numbers (if available), and the unique code numbers (if available) assigned to the investigational product and study subjects.

The investigational product must be used only in accordance with the Protocol. The investigator will also maintain records adequately documenting that the subjects were provided the correct study drug specified.

Completed accountability records will be archived by the site. At the completion of the study, the investigator or designee will oversee shipment of any remaining INCB024360 back to the sponsor or its designee for destruction according to institutional standard operating procedures. If local procedures mandate site destruction of investigational supply, prior written approval must be obtained from Incyte.

Upon completion or termination of the study, all unused and/or partially used MK-3475 will be destroyed at the site per institutional policy. It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

11. STUDY ADMINISTRATION

11.1. Data Management

11.1.1. Data Collection

The investigator will be provided with an eCRF for each subject. Entries made in the eCRF must be verifiable against source documents; any discrepancies should be explained and documented. The investigator will be responsible for reviewing all data and eCRF entries and will sign and date the designated pages in each subject's eCRF, verifying that the information is true and correct. The investigator is responsible for the review and approval of all responses.

11.1.2. Data Management

Data management will be performed from eCRFs. All eCRF data will be entered into a validated database. All data entry, verification, and validation will be performed in accordance with the current standard operating procedures of the Data Management Department at the sponsor or its designee. The database will be authorized for lock once all defined procedures are completed.

11.2. Study Monitoring

Qualified representatives of the sponsor or its designee, "study monitors," will monitor the study according to a predetermined monitoring plan. Monitoring visits provide the sponsor with the opportunity to:

- Evaluate the progress of the study.
- Verify the accuracy and completeness of eCRFs.
- Assure that all Protocol requirements, applicable laws and/or regulations, and investigator's obligations are being fulfilled.
- Resolve any inconsistencies in the study records.

The investigator must allow the study monitors to periodically review, at mutually convenient times during the study and after the study has been completed, all CRFs and office, hospital, and laboratory records supporting the participation of each subject in the study. The eCRFs and other documentation supporting the study must be kept up-to-date by the investigator and the research staff at the investigative site. These study materials must be available for review by the study monitor, and/or other qualified representatives of the sponsor or its designee, at each monitoring visit.

The study monitor will review the various records of the study (eCRFs, subject medical and laboratory records, and other pertinent data). The study monitor will verify the eCRF data against original source documentation for accuracy and completeness. The study monitor will identify data discrepancies and collaborate with the investigator and research staff to resolve the discrepancies in a timely manner. Protocol deviations will also be identified and recorded on a "Protocol Deviation Log." The study monitor will follow an "Issue Escalation" plan in order to ensure that each issue identified during a monitoring visit is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements.

11.3. Protocol Adherence

The principal investigator must obtain IRB or IEC approval for the investigation. Initial IRB or IEC approval and all materials approved by the IRB or IEC for this study including the subject ICF and recruitment materials must be maintained by the investigator and made available for inspection.

Each investigator must adhere to the Protocol as described in this document and agree that changes to the Protocol, with the exception of medical emergencies, must be discussed and approved, firstly, by the sponsor or its designee and, secondly, by the IRB or IEC. Each investigator is responsible for enrolling subjects who have met the Protocol inclusion and exclusion criteria. The IRB or IEC that granted original approval, or the IRB or IEC currently responsible for overseeing the conduct of the study, must be notified of all changes in and deviations from the Protocol that may increase risk to the subject, and/or that may adversely affect the rights of the subject or validity of the investigation. The investigator must send a copy of the approval letter from the IRB or IEC to the sponsor or its designee and retain the original in the site study regulatory file.

Major eligibility deviations must be reported to the IRB or IEC in accordance with the IRB or IEC requirements. During the course of the study, the monitor must notify the sponsor or its designee of subjects found not to have met eligibility criteria. The medical monitor, in collaboration with the investigator, will determine if the subject should be withdrawn from the study.

11.4. Financial Disclosure

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

Any new investigators or subinvestigators added to the covered clinical study during its conduct must also submit a completed Clinical Investigator Financial Disclosure Request Form. During a covered clinical study, any changes to the financial information previously reported by a clinical investigator must be reported to the sponsor or its designee. At the conclusion of the covered clinical study, the clinical investigators will be reminded of their obligation to report to the sponsor or its designee any changes to the financial information previously reported. The clinical investigators will also be reminded that they must report any changes in their financial information for a period of 1 year after completion of the covered clinical study.

11.5. Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act and the Food and Drug Administration Amendments Act, the sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to the Clinical Trials Data Bank, www.clinicaltrials.gov. Information posted will allow individuals to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. Sponsor Audits

At some point during the study, individuals from the sponsor's Quality Assurance department and/or their authorized representative may visit the investigator's site to conduct an audit of the study. The purpose of this visit will be to determine the investigator's adherence to the Protocol, applicable regulations, and the sponsor's procedures, in addition to assessing the accuracy of the study data. Before initiating this audit, the investigator will be contacted by the sponsor to arrange a convenient time for this visit. The investigator and staff are expected to cooperate with the auditors and allow access to all subject records supporting the eCRFs and other study-related documents.

12.2. Inspection by Regulatory Authorities

At some point during the investigational product's development program, a regulatory authority may visit the investigator to conduct an inspection of the study and the site. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for purposes of conducting an inspection.

13. ETHICS

13.1. Ethical Conduct of the Study

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and conducted in adherence to the study Protocol, GCPs as defined in Title 21 of the US CFR Parts 50, 54 56, 312, and Part 11, as well as ICH GCP consolidated guidelines (E6) and applicable regulatory requirements.

13.2. Written Informed Consent

Informed consent documentation that includes both information about the study and the ICF will be prepared and given to the subject. This document will contain all elements required by the ICH E6 Guideline for GCP and any additional elements required by local regulations. The document must be in a language understandable to the subject and must specify who informed the subject. Where required by local law, the person who informs the subject must be a physician.

The principal investigator at each center will ensure that the subject is given full and adequate verbal and written information about the nature, purpose, and the possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue study drug and withdraw from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated ICF must be obtained before conducting any study procedures. The principal investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject. The investigator should inform the subject's primary physician about the subject's participation in the study if the subject has a primary physician and if the subject agrees to the primary physician being informed.

Preparation of the ICF is the responsibility of the investigator and must include all elements required by the ICH GCP, and applicable regulatory requirements, and must adhere to the ethical principles that have their origin in the Declaration of Helsinki. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and approve all changes to site-specific ICFs. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to subject records. Before the beginning of the study, the IRB or IEC must provide the investigator with written approval/favorable opinion of the written ICF and any other information to be provided to the subjects.

13.3. Ethics Review

It is the responsibility of the investigator to assure that all aspects of the ethics review are conducted in accordance with the Declaration of Helsinki as described in the ICH E6: Guideline for GCP, and/or local laws, whichever provides the greatest level of protection for the study participants. The Protocol and any information supplied to the subject to obtain informed consent, including written ICFs, subject recruitment procedures (eg, advertisements), and written information to be provided to subjects (information leaflets), must be reviewed and approved by a qualified IRB/IEC before enrollment of participants in the study. Before initiation of the study,

the sponsor or its designee must receive documentation of the IRB or IEC approval, which specifically identifies the study/Protocol, and a list of the committee members.

The principal investigator is responsible for informing the IRB or IEC of any amendment to the Protocol in accordance with local requirements. Protocol amendments and revisions to the ICF must be submitted to and approved by the IRB or IEC.

Investigators must submit progress reports to the IRB or IEC in accordance with the IRB or IEC requirements and local regulations. Annual re-approval of the study must be obtained. Copies of progress reports and annual re-approvals must be sent to the sponsor or its designee.

The principal investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The sponsor or its designee will provide this information to the principal investigator.

When the sponsor or its designee provides the investigator with a safety report, the investigator is responsible for ensuring that the safety report is reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by their respective IRBs.

After completion or termination of the study, the investigator must submit a final report to the IRB or IEC and to the sponsor or its designee.

The investigator, as part of the records retention requirements for the study, must maintain documentation of all submissions, correspondence, and approvals to and from the IRB or IEC.

Each clinical investigator is responsible to conduct the study in accordance with the Protocol, all applicable laws, regulations, and GCP according to ICH guidelines.

13.4. Data Privacy

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

14. DATA HANDLING AND RECORDKEEPING

14.1. Inspection of Records

The sponsor or its designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

The investigator must ensure that all records pertaining to the conduct of the clinical study (as listed above) are adequately maintained for a period of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal termination of clinical development of the investigational product.

14.2. Retention of Records

The principal investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved, 2 years following the termination of the test article for investigation. If it becomes necessary for the sponsor or the regulatory authority to review any documentation relating to the study, the investigator must permit access to such records.

The investigator must not destroy any records associated with the study without receiving approval from Incyte. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.

Whenever possible, an original recording of an observation must be retained as the source document. However, a photocopy of a record is acceptable, provided it is legible and is a verified copy of the original document.

All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

14.3. Confidentiality

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

15. PUBLICATION POLICY

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

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For Subjects Participating in the Study:

The following methods have been determined to be more than 99% effective (< 1% failure rate per year when used consistently and correctly (Trussell 2004) and are permitted under this Protocol for use by the subject and his/her partner:

- Complete abstinence from sexual intercourse
- Double barrier methods:
  - Condom with spermicide in conjunction with use of an intrauterine device
  - Condom with spermicide in conjunction with use of a diaphragm
- Birth control patch or vaginal ring
- Oral, injectable, or implanted contraceptives
- Surgical sterilization (tubal ligation or vasectomy)

APPENDIX C. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Grade	Performance Status
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Source: Oken et al 1982.

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

Monoamine Oxidase Inhibitors	Drugs Associated With Significant Monoamine Oxidase Inhibitory Activity
Hydrazines (example phenelzine)	Meperidine
Isocarboxazid	Linezolid
Tranylcypromine	Methylene blue
Brofaromine	
Rasagiline	
Selegiline	

APPENDIX E. COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS v4.0

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

APPENDIX F. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) v1.1

RECIST v1.1* will be used in this study for assessment of tumor response with some modification. While either CT or MRI may be used, as per RECIST v1.1, CT is the preferred imaging technique in this study. See modifications to RECIST criteria being utilized in Section 7.6.3.1.

* As published in the European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

APPENDIX G. RESPONSE CRITERIA FOR DIFFUSE LARGE B-CELL LYMPHOMA

The updated Cheson criteria that now incorporates the Lugano Classification will be utilized for this study to determine response in subjects with DLBCL with some modification as described in Section 7.6.3.1.

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin Lymphoma: the Lugano classification. J Clin Oncol 2014;30:3059-3068.

APPENDIX H. PUBLICATION ON SEROTONIN SYNDROME

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

CURRENT CONCEPTS

The Serotonin Syndrome

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N Engl J Med 2005;352:1112-20.

THE SEROTONIN SYNDROME IS A POTENTIALLY LIFE-THREATENING adverse drug reaction that results from therapeutic drug use, intentional self-poisoning, or inadvertent interactions between drugs. Three features of the serotonin syndrome are critical to an understanding of the disorder. First, the serotonin syndrome is not an idiopathic drug reaction; it is a predictable consequence of excess serotonergic agonism of central nervous system (CNS) receptors and peripheral serotonergic receptors.[1,2] Second, excess serotonin produces a spectrum of clinical findings.[3] Third, clinical manifestations of the serotonin syndrome range from barely perceptible to lethal. The death of an 18-year-old patient named Libby Zion in New York City more than 20 years ago, which resulted from coadministration of meperidine and phenelzine, remains the most widely recognized and dramatic example of this preventable condition.[4]

DEFINITION AND EPIDEMIOLOGY

The serotonin syndrome is often described as a clinical triad of mental-status changes, autonomic hyperactivity, and neuromuscular abnormalities, but not all of these findings are consistently present in all patients with the disorder (Fig. 1).[5,6] Signs of excess serotonin range from tremor and diarrhea in mild cases to delirium, neuromuscular rigidity, and hyperthermia in life-threatening cases. The difficulty for clinicians is that mild symptoms may be easily overlooked, and an inadvertent increase in the dose of the causative agent or the addition of a drug with proserotonergic effects may provoke a dramatic clinical deterioration.

The incidence of the serotonin syndrome is thought to mirror the increasing number of proserotonergic agents being used in clinical practice.[7] In 2002, the Toxic Exposure Surveillance System, which receives case descriptions from office-based practices, inpatient settings, and emergency departments, reported 26,733 incidences of exposure to selective serotonin-reuptake inhibitors (SSRIs) that caused significant toxic effects in 7349 persons and resulted in 93 deaths.[8,9] The assessment of the serotonin syndrome in therapeutic drug dosing has relied on post-marketing surveillance studies, one of which identified an incidence of 0.4 case per 1000 patient-months for patients who were taking nefazodone.[10] Performing a rigorous epidemiologic assessment of the serotonin syndrome, however, is difficult, since more than 85 percent of physicians are unaware of the serotonin syndrome as a clinical diagnosis.[10] The syndrome occurs in approximately 14 to 16 percent of persons who overdose on SSRIs.[8]

Although the serotonin syndrome has occurred in a broad range of clinical environments, several barriers limit the ability of clinicians to diagnose the condition. First, the syndrome may be missed because of its protean manifestations. Clinicians and patients may dismiss symptoms such as tremor with diarrhea or hypertension as inconsequential or unrelated to drug therapy; anxiety and akathisia may be misattributed to the patient's mental state.[5,10] Second, a strict application of the diagnostic criteria proposed

by Sternbach potentially rules out what are now recognized as mild, early, or subacute cases of the disorder.[1,11] Third, clinicians cannot diagnose a condition of which they are unaware, even though the serotonin syndrome is not rare and has been identified in patients of all ages, including the elderly, children, and newborn infants.[10,12-14]

A striking number of drugs and drug combinations have been associated with the serotonin syndrome (Table 1). These include monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants, SSRIs, opiate analgesics, over-the-counter cough medicines, antibiotics, weight-reduction agents, antiemetics, antimigraine agents, drugs of abuse, and herbal products; the withdrawal of medications has also been associated with the syndrome.[1,4,12,15-23] A single therapeutic dose of an SSRI has caused the serotonin syndrome.[12] Moreover, the addition of drugs that inhibit cytochrome isoforms CYP2D6 and CYP3A4 to therapeutic SSRI regimens has been associated with the condition.[16,24,25] Administration of serotonergic agents within five weeks after the discontinuation of fluoxetine therapy has produced a drug interaction culminating in the serotonin syndrome, presumably the result of the demethylation of fluoxetine to norfluoxetine, a serotonergic metabolite with a longer serum half-life than its parent compound.[13] Specific drugs, such as MAOIs that are irreversible or nonselective or that inhibit monoamine oxidase subtype A, are strongly associated with severe cases of the syndrome, especially when these agents are used in combination with meperidine, dextromethorphan, SSRIs, or methylenedioxymethamphetamine (MDMA, or "ecstasy").[4,8,15,26,27]

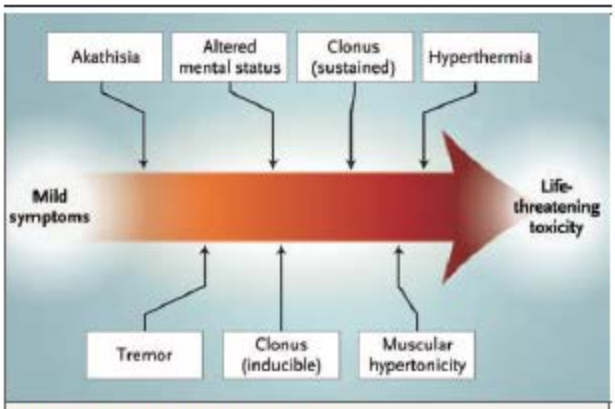

Figure 1. **Spectrum of Clinical Findings.**
Manifestations of the serotonin syndrome range from mild to life-threatening. The vertical arrows suggest the approximate point at which clinical findings initially appear in the spectrum of the disease, but all findings may not be consistently present in a single patient with the serotonin syndrome. Severe signs may mask other clinical findings. For example, muscular hypertonicity can overwhelm tremor and hyperreflexia.

MANIFESTATIONS

The serotonin syndrome encompasses a range of clinical findings. Patients with mild cases may be afebrile but have tachycardia, with a physical examination that is notable for autonomic findings such as shivering, diaphoresis, or mydriasis (Fig. 2). The neurologic examination may reveal intermittent tremor or myoclonus, as well as hyperreflexia.

A representative example of a moderate case of the serotonin syndrome involves such vital-sign abnormalities as tachycardia, hypertension, and hyperthermia. A core temperature as high as 40°C is common in moderate intoxication. Common features of the physical examination are mydriasis, hyperactive bowel sounds, diaphoresis, and normal skin color. Interestingly, the hyperreflexia and clonus seen in moderate cases may be considerably greater in the lower extremities than in the upper extremities; patellar deep-tendon reflexes often demonstrate clonus for several seconds after a single tap of the tendon, whereas the brachioradialis reflex is only slightly increased. Patients may exhibit horizontal ocular clonus. Changes in mental status include mild agitation or hypervigilance, as well as slightly pressured speech. Patients may easily startle or adopt a peculiar head-turning behavior characterized by repetitive rotation of the head with the neck held in moderate extension.

In contrast, a patient with a severe case of the serotonin syndrome may have severe hypertension and tachycardia that may abruptly deteriorate into frank shock. Such patients may have agitated delirium as well as muscular rigidity and hypertonicity. Again, the increase in muscle tone is considerably greater in the lower extremities. The muscle hyperactivity may produce a core temperature of more than 41.1°C in life-threatening cases. Laboratory abnormalities that occur in severe cases include metabolic acidosis, rhabdomyolysis, elevated levels of serum aminotransferase and creatinine, seizures, renal failure, and disseminated intravascular coagulopathy. Many of these abnormalities arise, however, as a consequence of poorly treated hyperthermia.

Table 1. Drugs and Drug Interactions Associated with the Serotonin Syndrome.

Drugs associated with the serotonin syndrome
Selective serotonin-reuptake inhibitors: sertraline, fluoxetine, fluvoxamine, paroxetine, and citalopram
Antidepressant drugs: trazodone, nefazodone, buspirone, clomipramine, and venlafaxine
Monoamine oxidase inhibitors: phenelzine, moclobemide, clorgiline, and isocarboxazid
Anticonvulsants: valproate
Analgesics: meperidine, fentanyl, tramadol, and pentazocine
Antiemetic agents: ondansetron, granisetron, and metoclopramide
Antimigraine drugs: sumatriptan
Bariatric medications: sibutramine
Antibiotics: linezolide (a monoamine oxidase inhibitor) and ritonavir (through inhibition of cytochrome P-450 enzyme isoform 3A4)
Over-the-counter cough and cold remedies: dextromethorphan
Drugs of abuse: methylenedioxymethamphetamine (MDMA, or "ecstasy"), lysergic acid diethylamide (LSD), 5-methoxydiisopropyltryptamine ("foxy methoxy"), Syrian rue (contains harmine and harmaline, both monoamine oxidase inhibitors)
Dietary supplements and herbal products: tryptophan, *Hypericum perforatum* (St. John's wort), Panax ginseng (ginseng)
Other: lithium
Drug interactions associated with severe serotonin syndrome
Zoloft, Prozac, Sarafem, Luvox, Paxil, Celexa, Desyrel, Serzone, Buspar, Anafranil, Effexor, Nardil, Manerix, Marplan, Depakote, Demerol, Duragesic, Sublimaze, Ultram, Talwin, Zofran, Kytril, Reglan, Imitrex, Meridia, Redux, Pondimin, Zyvox, Norvir, Parnate, Tofranil, Remeron
Phenelzine and meperidine
Tranylcypromine and imipramine
Phenelzine and selective serotonin-reuptake inhibitors
Paroxetine and buspirone
Linezolide and citalopram
Moclobemide and selective serotonin-reuptake inhibitors
Tramadol, venlafaxine, and mirtazapine

To better delineate the signs and symptoms that define the serotonin syndrome, the clinical findings in 2222 consecutive cases of self-poisoning with serotonergic drugs were rigorously assessed on the basis of information from a detailed toxicology registry.[2] These findings were then compared with the "gold standard," the assignment of a diagnosis of the serotonin syndrome by a medical toxicologist.[2] The clinical findings that had a statistically significant association with the diagnosis of the syndrome were primarily neuromuscular, including hyperreflexia, inducible clonus, myoclonus, ocular clonus, spontaneous clonus, peripheral hypertonicity, and shivering.[2] Autonomic derangements were tachycardia on admission, mydriasis, diaphoresis, and the presence of bowel sounds and diarrhea.[2] Abnormalities in mental status that were significantly associated with the serotonin syndrome were agitation and delirium.[2] Hyperthermia that was caused by muscular hypertonicity, defined in this study as a temperature of more than 38°C, was not as strongly associated with the diagnosis of the serotonin syndrome but occurred in severely intoxicated patients.[2]

The onset of symptoms is usually rapid, with clinical findings often occurring within minutes after a change in medication or self-poisoning.[28] Approximately 60 percent of patients with the serotonin syndrome present within six hours after initial use of medication, an overdose, or a change in dosing.[28] Patients with mild manifestations may present with subacute or chronic symptoms, whereas severe cases may progress rapidly to death. The serotonin syndrome is not believed to resolve spontaneously as long as precipitating agents continue to be administered.

PATHOPHYSIOLOGY AND MOLECULAR MECHANISMS

Serotonin is produced by the decarboxylation and hydroxylation of L-tryptophan. Its quantity and actions are tightly regulated by a combination of reuptake mechanisms, feedback loops, and metabolizing enzymes (Fig. 3). Serotonin receptors are divided into seven 5-hydroxytryptamine (5-HT) families (5-HT_1 to 5-HT_7), several of which have multiple members (e.g., 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F}). Further structural and operational diversity is achieved by allelic polymorphisms, splice variants, receptor isoforms, and the formation of receptor heterodimers.[29]

Serotonergic neurons in the CNS are found primarily in the midline raphe nuclei, located in the brain stem from the midbrain to the medulla.[30] The rostral end of this system assists in the regulation of wakefulness, affective behavior, food intake, thermoregulation, migraine, emesis, and sexual behavior.[30] The neurons of the raphe in the lower pons and medulla participate in the regulation of nociception and motor tone.[30] In the periphery, the serotonin system assists in the regulation of vascular tone and gastrointestinal motility.[30]

No single receptor appears to be responsible for the development of the serotonin syndrome, although several lines of evidence converge to suggest that agonism of 5-HT_{2A} receptors contributes substantially to the condition.[31-35] Additional subtypes of serotonin receptors, such as 5-HT_{1A}, may contribute through a pharmacodynamic interaction in which increased synaptic concentrations of serotonin agonist saturate all receptor subtypes. Nora-

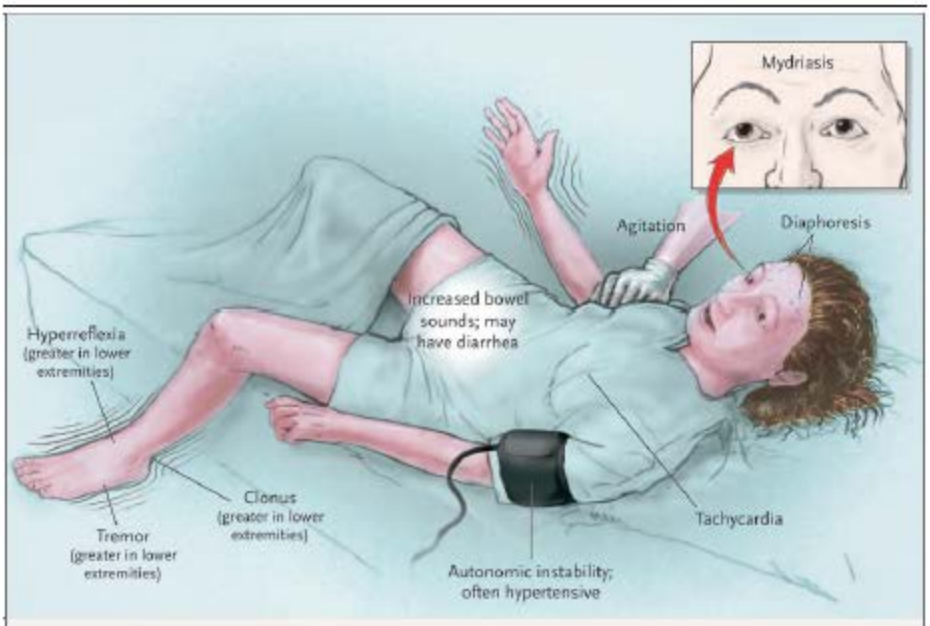

Figure 2. Findings in a Patient with Moderately Severe Serotonin Syndrome.
Hyperkinetic neuromuscular findings of tremor or clonus and hyperreflexia should lead the clinician to consider the diagnosis of the serotonin syndrome.

drenergic CNS hyperactivity may play a critical role, since the degree to which CNS norepinephrine concentrations are increased in the serotonin syndrome may correlate with the clinical outcome.[33,35,36] Other neurotransmitters, including *N*-methyl-D-aspartate (NMDA) receptor antagonists and γ-aminobutyric acid (GABA), may affect the development of the syndrome, but the role of these agents is less clear.[33,37] Dopaminergic receptors have been implicated, but this association may arise from pharmacodynamic interactions, direct interactions between serotonin and dopamine receptors, other mechanisms, or a misdiagnosis of the serotonin syndrome as the neuroleptic malignant syndrome.[26,33,38,39]

DIAGNOSIS

No laboratory tests confirm the diagnosis of the serotonin syndrome. Instead, the presence of tremor, clonus, or akathisia without additional extrapyramidal signs should lead clinicians to consider the diagnosis, which must be inferred from the patient's history and physical examination. When obtaining the patient's history, clinicians should inquire about the use of prescription and over-the-counter drugs, illicit substances, and dietary supplements, since all of these agents have been implicated in the development of the serotonin syndrome. The evolution of symptoms and their rate of change should also be reviewed. Physical examination should include a focused assessment of deep-tendon reflexes, clonus, and muscle rigidity, in addition to an evaluation of the size and reactivity of the pupils, the dryness of the oral mucosa, the intensity of bowel sounds, skin color, and the presence or absence of diaphoresis.

Although several diagnostic criteria have been developed, we prefer the decision rules described in Figure 4.[2,11,14,40] These rules, when compared with the original diagnostic criteria, are simpler, more sensitive (84 percent vs. 75 percent), and more specific (97 percent vs. 96 percent) for diagnosing the serotonin syndrome.[1,2] Clonus (inducible, spontaneous, and ocular) is the most important finding in establishing the diagnosis of the serotonin syndrome.[2,27,41] Clinicians should always be aware

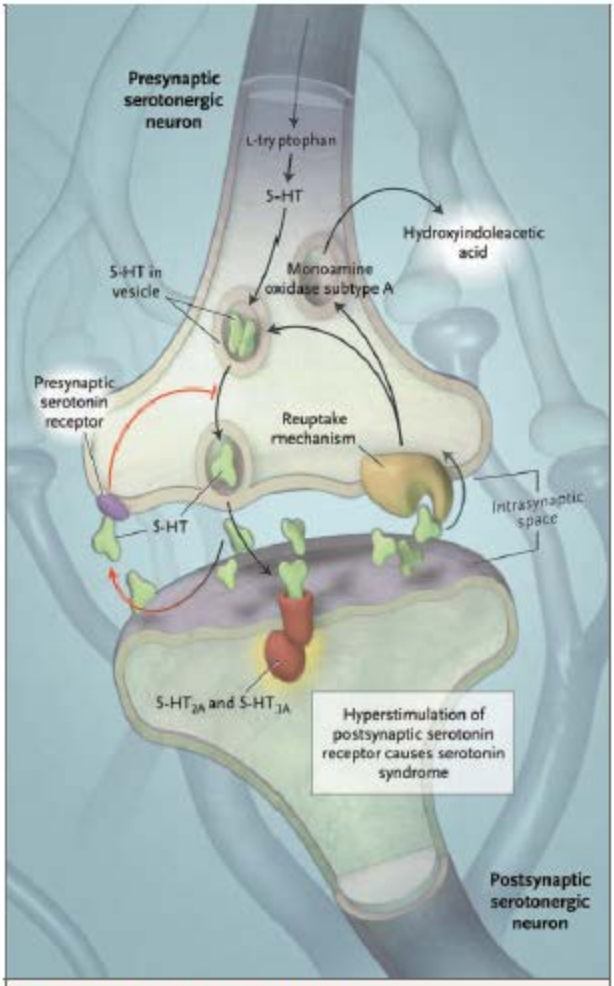

Figure 3. Serotonin Biosynthesis and Metabolism.

Serotonin is produced in presynaptic neurons by hydroxylation and decarboxylation of L-tryptophan. Serotonin is then incorporated into vesicles, where it resides until it is needed for neurotransmission. After axonal stimulation, serotonin is released into the intrasynaptic space; presynaptic serotonin receptors function as a feedback loop to inhibit exocytosis of vesicles (shown in red). Serotonin then binds to postsynaptic receptors to effect neurotransmission. A reuptake mechanism returns serotonin to the cytoplasm of the presynaptic neuron, where it is reintroduced into vesicles. Serotonin is then metabolized by monoamine oxidase subtype A to hydroxyindoleacetic acid.

that hyperthermia and hypertonicity occur in life-threatening cases, but muscle rigidity may mask the highly distinguishing findings of clonus and hyperreflexia and therefore cloud the diagnosis.[2,42]

The differential diagnosis includes anticholinergic poisoning, malignant hyperthermia, and the neuroleptic malignant syndrome, each of which can be readily distinguished from the serotonin syndrome on clinical grounds and on the basis of the medication history (Table 2). Patients with the anticholinergic syndrome have normal reflexes and show the "toxidrome" of mydriasis; agitated delirium; dry oral mucosa; hot, dry, erythematous skin; urinary retention; and an absence of bowel sounds. Hyperactive bowel sounds — along with neuromuscular abnormalities, diaphoresis, and normal skin color — distinguish the serotonin syndrome from the anticholinergic toxidrome.[2]

Malignant hyperthermia is a pharmacogenetic disorder characterized by increasing concentrations of end-tidal carbon dioxide, hypertonicity, hyperthermia, and metabolic acidosis. The disorder occurs within minutes after exposure to inhalational anesthetic agents.[43] On physical examination, the skin is often mottled, with cyanotic areas contrasting with patches of bright red flushing.[43] The rigor mortis–like rigidity of skeletal muscles and hyporeflexia that are seen in malignant hyperthermia further distinguish this condition from the serotonin syndrome.[43]

The neuroleptic malignant syndrome is an idiopathic reaction to dopamine antagonists, a condition that is defined by a slow onset, bradykinesia or akinesia, "lead pipe" muscular rigidity, hyperthermia, fluctuating consciousness, and autonomic instability.[44] Signs and symptoms of the neuroleptic malignant syndrome typically evolve during several days, in contrast to the rapid onset and hyperkinesia of the serotonin syndrome. Knowledge of the precipitating drug also helps in distinguishing between syndromes: dopamine antagonists produce bradykinesia, whereas serotonin agonists produce hyperkinesia.[45]

MANAGEMENT

Management of the serotonin syndrome involves the removal of the precipitating drugs, the provision of supportive care, the control of agitation, the administration of 5-HT_{2A} antagonists, the control of autonomic instability, and the control of hyperthermia.[45] Many cases of the serotonin syndrome typically resolve within 24 hours after the initiation of therapy and the discontinuation of serotonergic drugs, but symptoms may persist in patients taking drugs with long elimination half-lives, active metab-

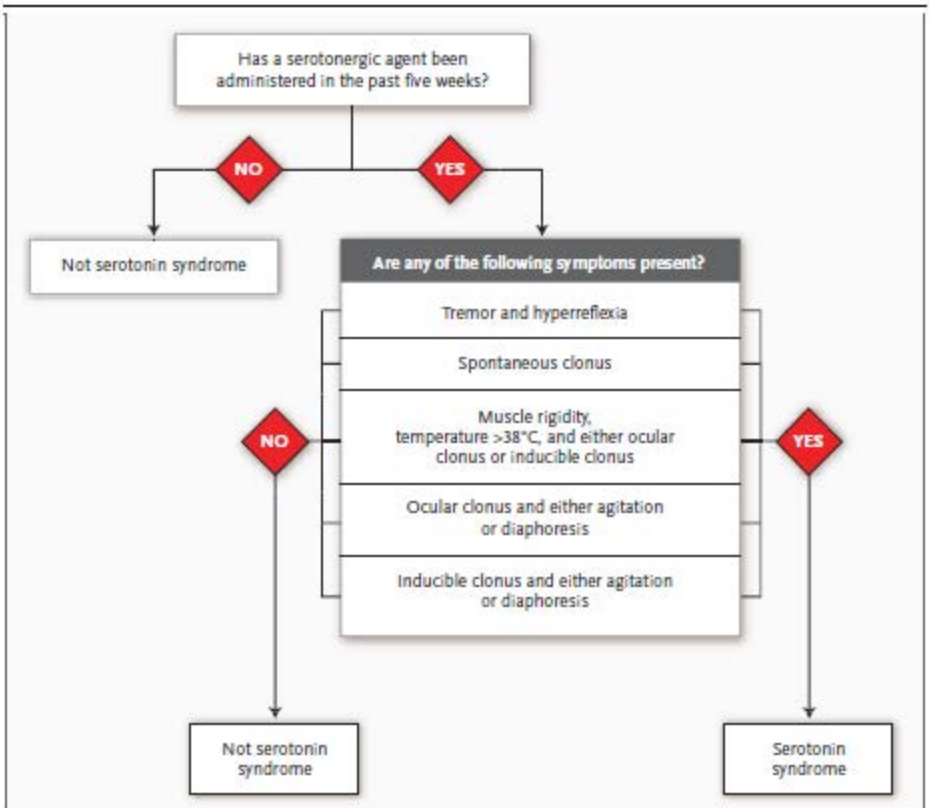

Figure 4. Algorithm for Diagnosis.

The neuromuscular features of clonus and hyperreflexia are highly diagnostic for the serotonin syndrome, and their occurrence in the setting of serotonergic drug use establishes the diagnosis. Clinicians should be aware that muscle rigidity can overwhelm other neuromuscular findings and mask the diagnosis. Criteria adapted from Dunkley.[2]

olites, or a protracted duration of action. Supportive care, comprising the administration of intravenous fluids and correction of vital signs, remains a mainstay of therapy. However, an abrupt deterioration in the condition of a patient who has been conservatively treated indicates the need for an immediate, aggressive response.[1,2,45]

The intensity of therapy depends on the severity of illness. Mild cases (e.g., with hyperreflexia and tremor but no fever) can usually be managed with supportive care, removal of the precipitating drugs, and treatment with benzodiazepines. Moderately ill patients should have all cardiorespiratory and thermal abnormalities aggressively corrected and may benefit from the administration of 5-HT_{2A} antagonists. Hyperthermic patients (those whose temperature is more than 41.1°C) are severely ill and should receive the above therapies as well as immediate sedation, neuromuscular paralysis, and orotracheal intubation.

Control of agitation with benzodiazepines is essential in the management of the serotonin syndrome, regardless of its severity. Benzodiazepines such as diazepam improve survival in animal models and blunt the hyperadrenergic component of the syndrome.[37,45] Physical restraints are ill-advised and may contribute to mortality by enforcing isometric muscle contractions that are associated with severe lactic acidosis and hyperthermia.[46] If physical restraints are used, they must be rapidly replaced with chemical sedation.

Pharmacologically directed therapy involves the

Table 2. Manifestations of Severe Serotonin Syndrome and Related Clinical Conditions.

Condition	Medication History	Time Needed for Condition to Develop	Vital Signs	Pupils	Mucosa	Skin	Bowel Sounds	Neuromuscular Tone	Reflexes	Mental Status
Serotonin syndrome	Proserotonergic drug	<12 hr	Hypertension, tachycardia, tachypnea, hyperthermia (>41.1°C)	Mydriasis	Sialorrhea	Diaphoresis	Hyperactive	Increased, predominantly in lower extremities	Hyperreflexia, clonus (unless masked by increased muscle tone)	Agitation, coma
Anticholinergic "toxidrome"	Anticholinergic agent	<12 hr	Hypertension (mild), tachycardia, tachypnea, hyperthermia (typically 38.8°C or less)	Mydriasis	Dry	Erythema, hot and dry to touch	Decreased or absent	Normal	Normal	Agitated delirium
Neuroleptic malignant syndrome	Dopamine antagonist	1–3 days	Hypertension, tachycardia, tachypnea, hyperthermia (>41.1°C)	Normal	Sialorrhea	Pallor, diaphoresis	Normal or decreased	"Lead-pipe" rigidity present in all muscle groups	Bradyreflexia	Stupor, akinetic mutism, coma
Malignant hyperthermia	Inhalational anesthesia	30 min to 24 hr after administration of inhalational anesthesia or succinylcholine	Hypertension, tachycardia, tachypnea, hyperthermia (can be as high as 46.0°C)	Normal	Normal	Mottled appearance, diaphoresis	Decreased	Rigor mortis–like rigidity	Hyporeflexia	Agitation

administration of 5-HT_{2A} antagonists.[7,45] Cyproheptadine is the recommended therapy for the serotonin syndrome, although its efficacy has not been rigorously established.[7,45] Treatment of the serotonin syndrome in adults may require 12 to 32 mg of the drug during a 24-hour period, a dose that binds 85 to 95 percent of serotonin receptors.[47] Clinicians should consider an initial dose of 12 mg of cyproheptadine and then 2 mg every two hours if symptoms continue. Maintenance dosing involves the administration of 8 mg of cyproheptadine every six hours. Cyproheptadine is available only in oral form, but tablets may be crushed and administered by nasogastric tube. Atypical antipsychotic agents with 5-HT_{2A}–antagonist activity may be beneficial in treating the serotonin syndrome. The sublingual administration of 10 mg of olanzapine has been used successfully, but its efficacy has not been rigorously determined.[48] Clinicians desiring a parenteral agent should consider the intramuscular administration of 50 to 100 mg of chlorpromazine.[45] Even though chlorpromazine is an outdated therapy that has been replaced in psychiatric practice by newer agents, its use may nonetheless be considered in severe cases.[45]

Control of autonomic instability involves stabilization of fluctuating pulse and blood pressure. Hypotension arising from MAOI interactions should be treated with low doses of direct-acting sympathomimetic amines (e.g., norepinephrine, phenylephrine, and epinephrine). Direct agonists do not require intracellular metabolism to generate a vasoactive amine, but their concentration in the synapse is regulated by catecholamine-O-methyl transferase. Indirect agents such as dopamine are metabolized to epinephrine and norepinephrine. Under normal conditions, monoamine oxidase limits the intracellular concentration of these metabolites. When inhibited, however, monoamine oxidase cannot control the amount of epinephrine and norepinephrine produced, and an exaggerated hemodynamic response may ensue. Patients in whom hypertension and tachycardia develop, either as a result of pressor therapy or from poisoning itself, should be treated with short-acting agents such as nitroprusside and esmolol.

Control of hyperthermia involves eliminating excessive muscle activity. Although benzodiazepines have a beneficial effect in moderate cases, in severely ill patients with hyperthermia (a temperature of more than 41.1°C) immediate paralysis should be induced with nondepolarizing agents such as ve-

curonium, followed by orotracheal intubation and ventilation. Clinicians should avoid succinylcholine because of the risk of arrhythmia from hyperkalemia associated with rhabdomyolysis. Recent case reports have shown that premature termination of neuromuscular paralysis was associated with a recrudescence of hyperthermia.[49] There is no role for antipyretic agents in the management of the serotonin syndrome; the increase in body temperature is due to muscular activity, not an alteration in the hypothalamic temperature set point.

Potential pitfalls for clinicians include misdiagnosis of the serotonin syndrome, a failure to comprehend its rapidity of progression, and adverse effects of pharmacologically directed therapy. The diagnosis may be clouded by the presence of severe muscle rigidity that obscures myoclonus and hyperreflexia. If the correct diagnosis is not obvious, a prudent course is to withhold antagonist therapy and provide aggressive supportive care, sedation with benzodiazepines, and, if necessary, intubation and paralysis.[7] Because of the speed with which the condition of patients declines, physicians should anticipate the need for aggressive therapy before clinical indications are reached.

Therapies such as propranolol, bromocriptine, and dantrolene are not recommended.[7,45] Propranolol, a 5-HT_{1A} antagonist with a long duration of action, may cause hypotension and shock in patients with autonomic instability. Furthermore, propranolol can abolish tachycardia that can be used to determine the duration and effectiveness of therapy.[2] Bromocriptine, a dopamine agonist, and dantrolene are not useful therapies; case reports citing their use probably involved a misdiagnosis of another condition as the serotonin syndrome.[7,35,45] Bromocriptine has been implicated in the development of the serotonin syndrome, and its use in patients in whom the neuroleptic malignant syndrome is misdiagnosed may worsen serotonergic signs.[27,50] According to one report, the administration of bromocriptine and dantrolene to a patient with the serotonin syndrome caused an abrupt increase in temperature, culminating in death.[39] This finding is supported by the observation that dantrolene has no effect on survival in animal models.[34,35]

Antagonist therapy with the use of cyproheptadine and chlorpromazine may have unintended effects. The dosage of cyproheptadine used to treat the serotonin syndrome may cause sedation, but this effect is a goal of therapy and should not deter clinicians from using the drug. Chlorpromazine is an outmoded drug that has been associated with severe orthostatic hypotension and has been thought to aggravate hyperthermia. Patients who require acute parenteral therapy for the serotonin syndrome are often hypertensive and are not ambulatory, so that the risk of orthostatic hypotension is minimized. Hyperthermia in response to neuroleptic administration is an idiopathic response; the normal outcome is hypothermia. Nonetheless, chlorpromazine should not be administered to a patient with hypotension or the neuroleptic malignant syndrome, since the drug could potentially exacerbate clinical findings.

PREVENTION

The serotonin syndrome can be avoided by a combination of pharmacogenomic research, the education of physicians, modifications in prescribing practices, and the use of technological advances. The application of pharmacogenomic principles can potentially protect patients at risk for the syndrome before the administration of serotonergic agents. Once toxicity occurs, consultation with a medical toxicologist, a clinical pharmacology service, or a poison-control center can identify proserotonergic agents and drug interactions, assist clinicians in anticipating adverse effects, and provide valuable clinical decision-making experience. The avoidance of multidrug regimens is critical to the prevention of the serotonin syndrome. If multiple agents are required, however, computer-based ordering systems and the use of personal digital assistants can detect drug interactions and decrease reliance on memory in drug ordering. Post-marketing surveillance linked to physician education has been proposed to improve awareness of the serotonin syndrome.[10]

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APPENDIX I. CHILD-PUGH SCORE

Child-Pugh Score

Measure	1 Point	2 Points	3 Points
Total bilirubin, µmol/L (mg/dL)	< 34 (< 2)	34-50 (2-3)	> 50 (> 3)
Serum albumin, g/dL	> 3.5	2.8 – 3.5	< 2.8
Prothrombin time, prolongation(s)	< 4.0	4.0 – 6.0	> 6.0
Ascites	None	Mild (or suppressed with medication)	Moderate to Severe (or refractory)
Hepatic encephalopathy	None	Grade I-II	Grade III-IV

Interpretation

Points	Class	1-Year Survival	2-Year Survival
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%

Sources: Cholongitas et al 2005, Child and Turcotte 1964, Pugh et al 1973.

APPENDIX J. GUIDANCE FOR DIAGNOSIS AND MANAGEMENT OF HEPATIC EVENTS IN SUBJECTS WITH HCC

All of the events listed below will require holding study treatment, notification of the sponsor within 24 hours, and a hepatology consultation. All cases should be entered into EDC and recorded as events of clinical interest/immune AEs. All cases of re-treatment and permanent discontinuation must be reported to the sponsor and recorded in the database.

a. ALT:
   i. Among subjects with baseline ALT < 2 × ULN: ALT ≥ 5 × ULN
   ii. Among subjects with baseline ALT ≥ 2 × ULN: ALT > 3 × the baseline level
   iii. ALT > 500 U/L regardless of baseline level
b. AST:
   i. Among subjects with baseline AST < 2 × ULN: AST ≥ 5 × ULN
   ii. Among subjects with baseline AST ≥ 2 × ULN: AST > 3 × the baseline level
   iii. AST >500 U/L regardless of baseline level
c. Total bilirubin:
   i. Among subjects with baseline levels < 1.5 mg/dL: a value of > 2 mg/dL
   ii. Among subjects with baseline levels that are ≥ 1.5 mg/dL: a value ≥ 2 × the baseline level
   iii. Total bilirubin >3.0 mg/dL regardless of baseline level
d. Regardless of laboratory values, hepatic decompensation diagnosed clinically, including:
   i. New onset clinically detectable ascites
   ii. Gastrointestinal bleeding suggestive of portal hypertension (e.g., esophageal or gastric varices)
   iii. Hepatic encephalopathy

Immediate assessment

- All subjects
- All subjects should be evaluated according to directions below within 72 hours
- Procedures:
  - Obtain a consultation with a hepatologist
  - Obtain a work-up for hepatitis if there is no underlying hepatitis, including hepatitis A, B,C, D, E, Epstein-Barr virus, and cytomegalovirus
  - Assess for ingestion of drugs/supplements with hepatotoxic potential
  - Assess for alcohol ingestion

- Assess for potential bacterial infection, biliary obstruction, or occult gastrointestinal bleeding
- Repeat ALT, AST, total bilirubin (Tbil), direct bilirubin (Dbil), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (GGT), INR, and complete blood count (CBC) with differential
- Other laboratories or imaging studies as clinically indicated
- Consider liver biopsy if indicated by hepatologist

Hepatitis C-infected subjects (including subjects who previously achieved SVR 12)

- In addition to the above, measure HCV RNA viral load

Hepatitis B-infected subjects

- HBV DNA, HbsAg, HbeAg, anti-HBc (total), anti-Hbe, and anti-HBs
- Subjects should be questioned about compliance with the use of anti-viral agents.

Permanent Discontinuation Criteria for Subjects with Hepatic Adverse Events

Therapy should also be **permanently discontinued** for any of the following:

- ALT > 20 × ULN
- CP score of ≥ 9 points
- Gastrointestinal bleeding suggestive of portal hypertension (eg, esophageal or gastric varices)
- New onset of clinically detectable ascites
- Hepatic encephalopathy
- Recurrence of a severe or life-threatening event, or of any of the laboratory abnormalities listed above, that are presumed to be immune-related

Diagnosis and Management of Hepatic Adverse Events

Subjects with HCC are at risk for a range of complications that can cause hepatic laboratory abnormalities with or without clinical decompensation. Those with a history of chronic HCV or HBV infection also have the potential to experience virologic flares. Immune-related hepatitis has been observed in ~1% of subjects who received pembrolizumab alone. The following section provides further guidance on the diagnosis and management of potential hepatic complications among HCC subjects in this study.

a. Hepatitis B Flare

Hepatitis B flares are characterized by rapid elevations of ALT and AST to > 5 × ULN and/or > 3 × baseline. ALT elevation to ≥ 10 × ULN is common. In the absence of hepatic decompensation, ALT/AST elevations are typically isolated (ie, limited/no elevations of bilirubin/ALP). Subjects who are compliant with antiviral therapy should have continued suppression of HBV DNA at the time of flare; thus, detection of HBV DNA should prompt

questioning of subjects for compliance. Laboratory abnormalities secondary to flare are typically observed for 3 to 5 weeks.

Among subjects with HBV, a flare should be considered if this pattern is observed and there is no evidence of an alternative etiology. Guidelines for subjects with a diagnosis of HBV flare are as follows:

- Care should be instituted in consultation with a hepatologist.
- For subjects who have detectable HBV DNA, reinstitute antiviral therapy.
- If the subject is clinically stable, study drug administration may be interrupted for up to 12 weeks. Subjects should undergo weekly laboratory tests, including AST, ALT, ALP, Tbil, Dbil, INR, HbsAg, HBV DNA (if detected at the onset of the flare). Obtain anti-Hbe, anti-HBs, and HBV DNA levels (if not detected at the onset of the flare) every 2 to 3 weeks.
- If ALT returns to normal or Grade 1 (if normal at baseline), or to baseline grade (if Grade 2 at baseline) within 12 weeks, and subjects are clinically stable, subjects may restart study treatment. If these conditions are not met, then study treatment should be permanently discontinued.

b. Hepatitis C Recurrence or Flare

Subjects who achieved SVR 12 and subjects with ongoing HCV infection are eligible for enrollment. In rare circumstances, HCV subjects who achieve SVR 12 may relapse at later time points. Relapse is characterized by detection of HCV RNA, often accompanied by ALT elevations to > 5 ×ULN. In the absence of hepatic decompensation, ALT/AST elevations are typically isolated (ie, limited/no elevations of bilirubin/ALP).

Among subjects with uncontrolled hepatitis C, virologic flares are possible. Hepatitis C flares are characterized by rapid elevations of ALT and AST to > 5 ×ULN and/or > 3 × baseline along with an increase in HCV RNA. ALT elevation to ≥ 10 × ULN and a 1 log elevation in HCV RNA level are common. In the absence of hepatic decompensation, ALT/AST elevations are typically isolated (ie, limited/no elevations of bilirubin/ALP). Laboratory abnormalities secondary to flare or recurrence are typically observed for 3 to 5 weeks.

Guidelines for subjects with recurrent HCV infection or an HCV flare are described below:

i. Recurrent HCV infection:

If the subject entered the study with an HCV RNA test of "Target not Detected" and has confirmed detectable HCV RNA (2 specimens, 1 week apart), then the subject has experienced a late HCV relapse or a recurrent infection.

- Question the subject about use of injection or inhalation drugs.
- At the time of first detection of HCV RNA, send a specimen for HCV genotyping.
- Measure AST, ALT, ALP, Tbil, Dbil, and INR weekly.
- Measure HCV RNA levels every 2 weeks.
- Therapy with HCV antiviral treatments should be strongly considered.

ii. HCV Flare:

- At the time of first detection of HCV RNA, send a specimen for HCV genotyping.
- Measure AST, ALT, ALP, Tbil, Dbil, INR weekly.
- Measure HCV RNA levels every 2 weeks.
- Therapy with HCV anti-viral treatments should be strongly considered.

iii. For both recurrent infection and HCV flare: if ALT returns to normal or Grade 1 (if normal at baseline), or to baseline grade (if Grade 2 at baseline) within 12 weeks, and the subjects are clinically stable, subjects may restart study treatment. If these conditions are not met, then study treatment should be permanently discontinued.

c. Immune-Related Hepatitis

i. Description: Immune-related hepatitis due to study treatment should be suspected if any of the following is seen:

- AST or ALT baseline values are less than 2 × ULN, and AST or ALT laboratory values increase to ≥ 5 × ULN.
- Among subjects with baseline ALT or AST ≥ 2 × ULN, levels increase to > 3 × the baseline level.
- AST/ALT > 500 U/L regardless of baseline level.
- Among subjects with baseline Tbil levels < 1.5 mg/dL: a value of > 2.0 mg/dL.
- Among subjects with baseline Tbil levels that are ≥ 1.5 mg/dL: a value of ≥ 2 × the baseline level.
- Total bilirubin > 3.0 mg/dL regardless of baseline level.

Immune-related hepatitis is a diagnosis made after excluding other possible etiologies for the change. Viral flare (if applicable), biliary or vascular obstruction, infection, medications, and alcohol use must be ruled out (see below).

ii. Management

- Interrupt study treatment and alert the sponsor as per ECI criteria above for ALT, AST, bilirubin, and hepatic decompensation.
- Start IV corticosteroid (methylprednisolone 125 mg or equivalent) followed by oral corticosteroid.
- Monitor with biweekly laboratory tests including AST, ALT, Tbil, Dbil, ALP, and INR.
- If symptoms and laboratory tests resolve to Grade ≤1 or baseline (if abnormal at baseline), taper steroids over 28 days. Study treatment may be restarted after steroid treatment has been tapered to prednisone ≤ 10 mg/day (or equivalent dose of another agent). Treatment and laboratory results must be reported on a case report form (CRF).

- If laboratory abnormalities do not resolve within 3 weeks, or steroids cannot be lowered to ≤10 mg/day (or prednisone equivalent) within 12 weeks, or subjects show evidence of decompensation to CP C status or have esophageal or variceal bleeding at any point, treatment must be permanently discontinued. This must be reported on a CRF.

d. Other Hepatic Adverse Events

- Infection needs to be ruled out with cultures of blood, urine, and ascites (if possible), as well as chest x-ray and abdominal imaging if relevant. If an infection is found, antibiotics should be started.
- If Tbil is elevated above baseline, magnetic resonance cholangiopan-creatography or ultrasound with Doppler should be obtained to rule out vascular compromise, biliary obstruction, and/or tumor progression. If biliary obstruction is present, consultation with a gastroenterologist and/or an interventional radiologist should be obtained to see if the obstruction may be relieved.
- A careful review of drugs, including herbal and alternative medications, should be obtained, and alcohol use should be ruled out.
- For all of these cases, subjects may resume study treatment if they are clinically stable after appropriate therapy or discontinue the causative agent, as long as laboratory values have returned to Grade 1 or baseline (if normal or Grade 1 at start) or to baseline grade within 3 weeks.
- Treatment must be permanently discontinued if the subject is off study treatment therapy for infection, obstruction, or drug/alcohol-related toxicity for more than 3 weeks, or if they have esophageal bleeding, or become CP C at any point.

APPENDIX K. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment (Version) 1:	03 APR 2014
Amendment (Version) 2:	09 DEC 2014
Amendment (Version) 3:	19 FEB 2015
Amendment (Version) 4:	20 MAY 2015
Amendment (Version) 5:	11 JAN 2016
Amendment (Version) 6:	12 JUL 2016
Amendment (Version) 7:	15 FEB 2017
Amendment (Version) 8:	30 AUG 2017
Amendment (Version) 9:	24 JAN 2018
Amendment (Version) 10:	02 JUL 2018

Amendment 10 (02 JUL 2018)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to close the study to future enrollment and provide guidance for handling subjects still on study, specifically with respect to options for monotherapy and re-treatment options and to reduce study procedures overall.

1. **Synopsis; Section 1.1.4, Combined Immune Checkpoint Inhibition; Section 1.2.1, Rationale for Combining PD-1 Inhibitor and IDO1 Inhibitor in Advanced or Metastatic Cancers; Section 1.3.3, Risks for the Combination of INCB024360 and MK-3475; Section 4, Investigational Plan; Section 7.6.6.1, Tumor Biopsy in the Phase 2 Melanoma Primary Refractory and Relapsed Cohorts**

   Description of change: Phase 2 cohorts of primary refractory and relapsed melanoma, HCC, and MSI-high CRC will be closed to further enrollment.

   Rationale for change: Based on emerging data, from the Phase 3 KEYNOTE-252/ ECHO-301 study in advanced or metastatic melanoma, the sponsor has decided to limit the scope of testing for this combination of INCB024360 + MK-3475 to those already tested.

2. **Synopsis; Section 5.1.1, INCB024360; Section 5.4, Duration of Treatment and Subject Participation; Section 6.2 Treatment Phase**

   Description of change: INCB024360 monotherapy (including re-treatment monotherapy) has been removed as an option for subjects who have not already initiated such treatment. Subjects already on INCB024360 monotherapy can continue for up to

12 months. Monotherapy treatment beyond 12 months will require medical monitor approval.

Rationale for change: Based on emerging data from the Phase 3 KEYNOTE-252/ECHO-301 study in advanced or metastatic melanoma, use of INCB024360 is no longer being investigated in melanoma nor as a single agent.

3. **Synopsis; Section 5.1.1, INCB024360; Section 5.4, Duration of Treatment and Subject Participation; Section 5.8.1, Discontinuation of MK-3475 Treatment After Complete Response; Section 6.2 Treatment Phase**

   Description of change: Melanoma subjects will be instructed to stop taking INCB024360 and continue MK-3475 monotherapy. If subjects wish to continue on combination therapy that includes INCB024360, medical monitor approval is needed. Subjects who complete of 24 months (35 administrations of MK-3475) and previously met Protocol criteria for re-treatment will no longer be offered the option of re-treatment (second course treatment). Subjects who initiated the re-treatment phase before Amendment 10 will be allowed to continue for up to 12 months.

   Rationale for change: Given the finding of the KEYNOTE-252/ECHO-301 Phase 3 study, the second course of treatment will not be offered, and future data collection will be limited.

4. **Section 5.6.3, Procedures for Subjects Exhibiting Immune-Related Adverse Events (Table 8, Dose Modifications and Toxicity Management Guidelines for Immune-Related Adverse Events)**

   Description of change: Added that after recurrent Grade 3 colitis, participants will be permanently discontinued from the study.

   Rationale for change: To align with KEYTRUDA® Summary of Product Characteristics (SmPC) and Company Core Data Sheet (CCDS).

5. **Synopsis; Section 6, Study Assessments (Table 12, Schedule of Assessments); Section 7.6, Efficacy Assessments; Section 7.6.5 Tumor Markers**

   Description of change: Imaging assessments and tumor markers have been revised to every 9 weeks for the first 2 timepoints (Weeks 9 and 18) and then will be performed every 12 weeks thereafter.

   Rationale for change: Because primary study objectives have been met, timing of imaging assessments has been reset to align more closely with standard of care.

6. **Synopsis; Section 4.1, Overall Study Design; Section 5.4, Duration of Treatment and Subject Participation; Section 5.8, Criteria for Permanent Discontinuation of Drug; Section 6, Study Assessments (Table 12, Schedule of Assessments); Section 6.4.2, Follow-Up; Section 6.4.3, Survival Follow-Up; Section 7.4.6, Poststudy Anticancer Therapy Status; Section 7.10.6, Withdrawal or Discontinuation**

   Description of change: Follow-up visit for disease progression and survival have been removed. Subjects will be followed for safety for up to 90 days after the subject has stopped study treatment or 30 days after cessation of study treatment if the subject initiates new anticancer therapy.

   Rationale for change: Because study objectives for efficacy have been met, assessment of disease status after study treatment have been removed.

7. **Synopsis; Section 6, Study Assessments (Table 13, Laboratory Assessments); Section 6.4.1, Safety Follow-Up; [redacted]; [redacted] Section 7.10.3, Administration of INCB024360 and Compliance; Section 7.10.5, Distribution of Subject Reminder Cards and Diaries**

   [redacted]

   Rationale for change: A sufficient number of samples have been collected to date.

8. [redacted] **Section 6, Study Assessments (Table 12, Schedule of Assessments); Section 7.5.4, Assessment of Serotonin Syndrome Symptoms**

   Description of change: Assessment of serotonin syndrome has been removed from study procedures. Subjects are informed of this theoretical risk during informed consent and are provided with a serotonin syndrome information sheet.

   Rationale for change: Removal of serotonin syndrome assessment is consistent with IB v10.

9. **Section 6, Study Assessments (Table 12, Schedule of Assessments); Section 7.5.6, Twelve-Lead Electrocardiograms**

   Description of change: Serial ECG testing on C1D1 and C2D1 has been removed. Single ECGs will be performed per the Protocol at screening and EOT only.

   Rationale for change: A thorough QTc study has been completed and [redacted] agreement has been received to be able to remove serial ECG monitoring from ongoing and new studies with epacadostat.

10. **Section 6, Study Assessments (Table 13, Laboratory Assessments; Table 14, Laboratory Tests: Required Analytes); Section 7.5.7, Laboratory Assessments**

    Description of change: Lipids will no longer be included in laboratory testing, and all laboratory tests have been changed to local testing.

    Rationale for change: A sufficient number of samples have been collected and analyzed to date in the event that a future analyses is needed. Local laboratory testing will simplify procedures for sites and subjects.

11. **Section 8.1.1 Definitions and Reporting of Adverse Events**

    Description of change: Adverse Event/SAE reporting of progression of disease under study will no longer be required.

    Rationale for change: This change is made to align this Protocol with Incyte's current policy for reporting disease progression as AE/SAE, which aligned with FDA guidance.

12. **Section 5.13, Prohibited Medications**

    Description of change: Mefenamic acid has been removed from the list of prohibited UGT1A9 medications.

    Rationale for change: To be consistent with current epacadostat IB v10.

13. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment, including the addition of all summary of changes to the last appendix.

Amendment 9 (24 JAN 2018)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to update dose modification guidelines and toxicity management guidelines for immune-related adverse events (irAEs) for MK-3475 and INCB024360.

1. **Section 5.6.2, Criteria and Procedures for Interruption (Table 7: Dose Modifications for INCB024360 [Epacadostat] and Table 8: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events)**

   Description of change: Text has been added to clarify that only 2 dose reductions of INCB024360 are permitted.

   Rationale for change: There was no specific text addressing the number of dose reductions permitted.

2. **Section 5.6.3, Procedures for Subjects Exhibiting Immune-Related Adverse Events (Table 8: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events); Section 5.6.5, Procedures for Subjects Exhibiting Serotonin Syndrome**

   Description of change: Section 5.6.3 was organized into 1 table for dose modification and toxicity management guidelines for irAEs, Table 8. Merck updated guidance related to irAEs, and Incyte updated the guidance related to serotonin syndrome. Specifically, myocarditis has been added to Table 8, and the category "other immune AEs" has been split to provide separate guidance on each Grade. In Section 5.6.5 for serotonin syndrome, guidance has been added to hold MK-3475 until immune toxicity can be ruled out.

   Rationale for change: These changes were made based on continuous monitoring of safety across the MK-3475 and INCB024360 programs.

3. **Section 5.8.1, Discontinuation of MK-3475 Treatment After Complete Response; Section 6.2.1, Second Course Phase (Re-treatment Period)**

   Description of change: Text has been added to allow subjects treated in Phase 1 with the 2 mg/kg dose of MK-3475 and/or an INCB024360 dose below the recommended Phase 2 dose to begin second course therapy, if eligible. The 200 mg flat dose of MK-3475 and the recommended Phase 2 dose of INCB024360 dose of 100 mg BID may be used if subjects did not require a dose reduction during their initial combination treatment.

   Rationale for change: INCB024360 100 mg BID was selected as the recommended dose for the Phase 2 portion of this study and the Phase 3 studies for INCB024360 in combination with MK-3475, because this regimen had better tolerability, as demonstrated by the Phase 1 safety data that included fewer dose modifications (ie, suspension and reductions) while maintaining consistent inhibition of IDO1. Near maximal pharmacodynamic changes were observed at doses ≥ 100 mg BID with > 80% to 90% inhibition of IDO1 achieved throughout the dosing period.

For MK-3475, the selection of the 200 mg Q3W dosing is now included in the label. The data supported 200 mg Q3W as an appropriate dose for multiple indications. The data demonstrated that exposures that are within the flat therapeutic range of 2 mg/kg Q3W to 10 mg/kg Q2W are associated with near maximal efficacy for pembrolizumab and are close to the exposure achieved at 2 mg/kg Q3W. There were no meaningful differences observed in [redacted] among tumor types. On this basis, both dosing schedules, 2 mg/kg Q3W and 200 mg Q3W, are available for multiple indications for pembrolizumab and are appropriate for use in this study.

4. **Section 5.9, Study Completion**

   Description of change: The definition of study completion has been updated to include the completion of primary and secondary objectives.

   Rationale for change: The definition has been updated to allow for data to be analyzed and for clinical study reports to be completed in a reasonable timeframe relative to cohort completion.

5. **Section 5.13, Prohibited Medications and Measures**

   Description of change: Incyte has updated the list of prohibited UGT1A9 inhibitors to remove estradiol (17 beta) and propofol and removed melatonin as a prohibited medication.

   Rationale for change: The list of prohibited UGT1A9 inhibitors was updated to align with a combination of limited in vitro data and anecdotal reports in recent published literature. Melatonin has been removed because of a lack of specific, strong in vitro or clinical data supporting that it could precipitate serotonin syndrome.

6. **Section 6, Study Assessments (Table 12: Schedule of Assessments)**

   Description of change: Pathology review of tumor tissue has been added as a required procedure for the 2 new biopsy-driven melanoma cohorts recently added in Protocol Amendment 8.

   Rationale for change: Incyte requires confirmation of tumor tissue in specimen samples before submitting biopsy samples for central testing.

7. **Section 6, Study Assessments (Table 16: Laboratory Tests: Required Analytes)**

   Description of change: Plasma testing has been added as an option for evaluation of lipase.

   Rationale for change: The option for serum or plasma analysis has been added to allow flexibility for sites whose laboratory standards are to test based on plasma.

8. **Section 9.1, Study Populations; Section 9.4.3 Safety Analyses**

   Description of change: The per protocol analysis has been removed from the statistical analysis plan. The exposure analyses related to dose modifications and the hematology laboratory analyses related to plots over time have been updated.

   Rationale for change: All subjects will be included in both the safety and efficacy analyses. The exposure and laboratory analyses have been updated to align with the statistical analysis plan.

9. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment, including the addition of all summary of changes to the last appendix.

Amendment 8 (30 AUG 2017)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to add 2 additional melanoma-specific cohorts to the Phase 2 expansion portion of the study.

1. **Synopsis; Section 3, Subject Eligibility; Section 4.1, Overall Study Design; Section 4.4, Number of Subjects; Section 6, Study Assessments; Section 7, Conduct of Study Assessments and Procedures; Section 9.2.2, Sample Size for the Phase 2 Expansion Portion of the Study**

   Description of change: The Phase 2 expansion portion of the study has been revised to include 14 cohorts instead of 12. The new cohorts will include subjects with primary refractory and relapsed metastatic melanoma after prior treatment with an anti–PD-1 or anti–PD-L1 therapy. The relevant study design, number of subjects, inclusion/exclusion criteria, study assessments, and statistics sections have been updated accordingly.

   Rationale for change: Based on emerging clinical data, subjects with primary refractory or relapsed melanoma after anti–PD-1 or anti–PD-L1 therapy would be of interest to include in the study and represents an unmet need for patients.

2. **Synopsis; Section 3.2, Subject Inclusion Criteria (criteria 8e, 8f, 10a, and 10j)**

   Description of change: Requirements for AST, ALT, and bilirubin values have been clarified and terminology has been updated for the prior therapy requirements for subjects with driver mutations in NSCLC.

   Rationale for change: Inclusion criteria have been updated to address AST, ALT, and bilirubin limits in subjects with or without liver metastases, to clarify that not only tyrosine kinase inhibitors specifically but therapy targeted for the specific mutation present should be given if the subject is positive for EGFR, KRAS, or EMLA4-ALK, and to clarify that refusal of therapy includes HER2-directed therapy in addition to chemotherapy.

3. **Synopsis, Section 3.3, Subject Exclusion Criteria (criteria 13, 20, and 25); Section 5.12, Restricted Medications and Measures**

   Description of change: The duplication of hepatitis requirements specific for subjects with HCC have been removed from criterion 13 and reference to HCC-specific inclusion and exclusion criteria has been added. Details have been added to criterion 20 and Section 5.12 to address exceptions for use of systemic corticosteroids and to criterion 25 to clarify that allergic reactions include severe hypersensitivity reactions to pembrolizumab and/or any of its excipients.

   Rationale for change: The addition of the exceptions for subjects with HCC in exclusion criterion 13 has created confusion for non-HCC subjects; therefore, it has been removed from this criterion and the requirements for subjects with HCC are now only in the HCC-specific inclusion/exclusion. Clarifications were also added to exclusion criteria 20 and 25 to address exceptions for subjects who need brief steroid use for prophylaxis for imaging procedures and for exclusion of subjects with prior

pembrolizumab therapy now that prior treatment with anti–PD-1 agents are permitted in the new cohorts.

4. **Section 1.1.1, Inhibition of PD-1 as a Target for Cancer; Section 1.1.4, Combined Immune Checkpoint Inhibition; Section 1.3.3, Risks for the Combination of INCB024360 and MK-3475; Section 1.4, Justification for Treatment Regimen**

   Description of change: Information was added regarding the recent additional approvals of pembrolizumab and updated safety data from the current study (INCB 24360-202) as of 27 FEB 2017. Data were included on 294 subjects treated at the recommended Phase 2 dose of 100 mg BID.

   Rationale for change: To provide updated background information and additional safety data supporting the Phase 2 dose selected.

5. [redacted] **Section 5.6.5, Procedures for Subjects Exhibiting Serotonin Syndrome; Section 8.9, Events of Clinical Interest**

   Description of change: The risks related to serotonin syndrome have been updated to reflect current status.

   Rationale for change: As of 27 FEB 2017, 2 subjects across the epacadostat program (958 subjects treated) have reported serotonin syndrome or symptoms of serotonin syndrome; both were mild in their severity and resolved.

6. **Section 5.6.3, Procedures for Subjects Exhibiting Immune-Related Adverse Events**

   Description of change: Additional general instructions/recommendations for management of immune-related adverse events have been added.

   Rationale for change: Merck has updated their general instructions/recommendations for management of immune-related adverse events across their program and those have been incorporated in this Protocol.

7. [redacted]

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

Amendment 7 (15 FEB 2017)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to add 2 additional cohorts for gastric cancer and hepatocellular carcinoma.to the Phase 2 expansion portion of the study.

1. **Synopsis; Section 1, Introduction; Section 3, Subject Eligibility; Section 4.1, Overall Study Design; Section 4.4, Number of Subjects; Section 5.6, Does Adjustment of Study Drugs; Section 6, Study Assessments; Section 7, Conduct of Study Assessments; Section 9.2.2, Sample Size for the Phase 2 Expansion Portion of the Study; Appendix J, Guidance for Diagnosis and Management of Hepatic Events in Subjects With HCC**

   Description of change: The Phase 2 expansion portion of the study has been revised to include 12 cohorts instead of 10. The new cohorts added will include subjects with gastric cancer and those with hepatocellular carcinoma. The relevant study design, number of subjects, inclusion/exclusion criteria, study assessments, and statistics sections have been updated accordingly.

   Rationale for change: Based on emerging clinical data subjects with gastric cancer and hepatocellular carcinoma would be of interest to include in the study.

3. **Synopsis, Section 4.1, Overall Study Design; Section 4.1.2, Phase 2 Cohort Expansions; Section 9.2.2 Statistics related to the NSCLC cohorts**

   Description of change: The terminology used to describe the PD-L1 low/negative cohort has been clarified across all sections of the Protocol to be consistent and to provide a clear definition for PD-L1 low/negative as TPS score of 0% to 49% for this cohort.

   Rationale for change: The statistics for the PD-L1 high and low/negative cohorts have been amended to reflect most current data available.

4. **Section 1.1.3, Rationale for Studying Immunotherapy in Advanced or Metastatic Cancers**

   Description of change: Updated to include information regarding new indications approved for pembrolizumab in 2016, and data on the use of pembrolizumab in subjects with adenocarcinoma of the stomach or gastro-oesophageal junction and nivolumab in subjects with hepatocellular carcinoma.

   Rationale for change: To provide current information.

5. **Section 3, Subject Eligibility**

   Description of change: Inclusion criterion 8 was revised to allow local laboratory results to be used if the central results are not available at the time of enrollment or within the 7-day window of Cycle 1 Day 1. Laboratory range requirements (8a-8h) were updated for specific tumor types, including the requirement for documentation of mutation status for NSCLC subjects (criterion 10a). The RCC and MSI high CRC inclusion criteria (10h and 10i) have been updated to address the approval of PD-1 therapy in RCC and the limited the number of prior therapies permitted for MSI high CRC (no more than 2 prior therapies). In exclusion criterion 13, hepatitis B/C testing requirements have been clarified.

   Rationale for change: To clarify inclusion/exclusion criteria.

6. **Synopsis; Section 5.1.1, INCB024360; Section 5.4, Duration of Treatment and Subject Participation; Section 5.8.1, Discontinuation of MK-3475 Treatment After Complete Response; Section 6.2, Treatment Phase**

   Description of change: Text has been added to clarify that subjects discontinuing MK-3475 after 35 infusions may continue on INCB024360 or stop both therapies.

   Rationale for change: There is no requirement to continue on monotherapy INCB024360 at the time of discontinuation of MK-3475.

7. **Section 5.6.3, Procedures for Subject Exhibiting Immune-Related Adverse Events; Section 5.6.3.1, Procedures and Guidelines for Rash; Section 5.6.3.2, Procedures and Guidelines for Lipase or Amylase Elevations; Section 5.6.3.3, Procedures and Guidelines for Pneumonitis; Section 5.6.3.5, Procedures and Guidance for Hepatitis**

   Description of change: Subsections have been added to Section 5.6.3 outlining guidelines for the management and treatment of rash (Section 5.6.3.1) and lipase or amylase elevations (Section 5.6.3.2). Guidance for recurrent Grade 2 pneumonitis has been added to Section 5.6.3.3, and supportive care guidance for hepatitis has been updated in Section 5.6.3.5.

   Rationale for change: Clarification has been provided for dose holds/adjustments and supportive care for drug-related rash that provide specific guidance for Grade 3 rashes. Additional guidance has been provided for subjects who experience asymptomatic elevations of amylase and/or lipase without clinical signs or symptoms of pancreatitis. Asymptomatic elevations in amylase and lipase have been noted in patients treated with PD-1/PD-L1 targeted therapy. This guidance allows for subjects to continue therapy, with appropriate monitoring, after clinically responsive conditions have been diagnosed and properly treated.

   Additional guidance for subjects experiencing pneumonitis has been added, recommending discontinuation of study drugs when Grade 3 or 4 pneumonitis occurs or when Grade 2 pneumonitis recurs after appropriate therapy. This is consistent with current guidelines provided for pembrolizumab single-agent therapy. Guidelines for treating drug-related hepatitis have been updated with steroid recommendations for Grade 2 events and the recommendation for study drug discontinuation at Grade 3 or Grade 4 events.

8. **Section 5.11.1.1, Antiviral Therapies**

   Description of change: Section added to include a list of antivirals with no known drug-drug interactions with pembrolizumab and epacadostat.

   Rationale for change: Antiviral therapies for subjects with HCC with a history of HBV are permitted; therefore a list of therapies with no known drug-drug interaction was provided.

9. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the protocol and are noted in the attached red-line/strike-out version of the amendment.

Amendment 6 (12 JUL 2016)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to add an additional cohort of microsatellite-instability high colorectal cancer to the Phase 2 expansion portion of the study and additional updates based on emerging data.

1. **Synopsis; Section 1, Introduction; Section 3, Subject Eligibility; Section 4.1, Overall Study Design; Section 4.4, Number of Subjects; Section 9.2.2, Sample Size for the Phase 2 Expansion Portion of the Study**

   Description of change: The Phase 2 expansion portion of the study was revised to include 10 cohorts instead of 9. The new cohort added includes subjects with microsatellite-instability high colorectal cancer. The relevant study design, number of subjects, inclusion/exclusion criteria, and statistics sections have been updated accordingly.

   Rationale for change: Based on emerging clinical data subjects with microsatellite-instability high colorectal cancer would be of interest to include in the study.

2. **Synopsis; Section 3.2, Subject Inclusion Criteria; Section 6, Study Assessments (Table 19: Laboratory Assessments); Section 7.4.3, PD-L1 Testing**

   Description of change: PD-L1 testing to determine cohort assignment for the Phase 2 NSCLC cohort may be tested locally or centrally using only the FDA-approved assay (PD-L1 IHC 22C3 pharmDX).

   Rationale for change: The purpose of this change is to allow for quicker turnaround of results for subjects to be treated sooner.

3. **Section 1.1.1, Inhibition of PD-1 as a Target in Cancer; Section 1.1.4, Combined Immune Checkpoint Inhibition; Section 1.3, Potential Risks and Benefits of the Treatment Regimen; Section 1.4, Justification of Regimen**

   Description of change: Information was added regarding the recent additional approvals of pembrolizumab and updated safety data from the current study (INCB 24360-202) as of 28 MAR 2016. Data were included on more than 100 subjects treated at the recommended Phase 2 dose of 100 mg BID.

   Rationale for change: To provide updated background information and additional safety data supporting the Phase 2 dose selected.

4. **Section 3.2, Subject Inclusion Criteria; Section 3.3, Subject Exclusion Criteria**

   Description of change: An exception for the use of prior anti–CTLA-4 therapy was included in inclusion criterion #10b for subjects with melanoma and in exclusion criterion #6. Inclusion criterion #10h for renal cell carcinoma has been updated to reflect current standard of care.

   Rationale for change: Due to changing standard of care in melanoma, the inclusion criterion has been updated. The inclusion criteria for renal cell carcinoma have been updated to clarify that standard-of-care regimens are required before potential inclusion in the current study.

5. **Synopsis; Section 3.2, Subject Inclusion Criteria; Section 6, Study Assessments (Table 18: Schedule of Assessments)**

   Description of change: Inclusion criterion 11 (baseline tumor biopsies) was updated to indicate that fresh formalin-fixed or formalin-fixed paraffin-embedded tumor tissue blocks are preferred, and if a block is not available, a minimum 20 unstained freshly cut slides may be submitted to the testing laboratory per the specifications in the laboratory manual. Table 18 was updated to reflect that archived tissue samples may be acceptable and should be submitted during screening before study drug administration on Cycle 1 Day 1.

   Rationale for change: Additional details related to tumor tissue collection have been added to clarify what meets the inclusion criteria.

6. **Section 3.3, Subject Exclusion Criteria**

   Description of change: Exclusion criteria #10 (history of pneumonitis), #11 (prior radiotherapy), #17 (monoamine oxidase inhibitors), and #20 (systemic corticosteroids) were edited to provide further clarification and consistency for noted criteria.

   Rationale for change: Details have been added to further clarify intent of the exclusion criteria.

7. **Section 5.12, Restricted Medications and Measures; Section 5.13, Prohibited Medications**

   Description of change: The permitted dose of systemic steroids has been revised from ≤ 7.5 mg/day to ≤ 10 mg/day of prednisone or equivalents. Clarity added around the use of propofol for on-study biopsy procedures has been added.

   Rationale for change: The dose restriction has been updated to be consistent with emerging data from the pembrolizumab and epacadostat programs. Because of the common use of propofol for short procedures, details regarding use for such procedures have been included in Section 5.13.

8. **Section 6, Study Assessments (Table 18: Schedule of Assessments; Table 19: Laboratory Assessments); Section 7.4.2, Tumor-Specific History**

   Description of change: A section was added to capture the detailed tumor-specific medical history being requested, such as HPV status for subjects with SCCHN, EGFR status for subjects with NSCLC, MSKCC score for subjects with RCC, and BRAF status for subjects with melanoma. Footnotes to Table 19 have also been added.

   Rationale for change: These data are relevant for understanding prognostic factors that may be present and relevant for evaluating response. Additional footnotes to the Laboratory Assessments table have been added to provide additional detail that may be noted in other sections of the Protocol for quick reference here.

10. **Section 8.6, Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor**

    Description of change: Overdose definition of > 1000 mg was added for epacadostat.

    Rationale for change: The amount of epacadostat taken that would constitute an overdose had not previously been defined.

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

Amendment 5 (11 JAN 2016)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to add additional cohorts to the Phase 2 expansion portion of the study and additional updates based on emerging data.

1. **Synopsis; Section 3, Subject Eligibility; Section 4.1, Overall Study Design; Section 4.4, Number of Subjects; Section 9.2.2, Sample Size for the Phase 2 Expansion Portion of the Study; Section 9.6, Interim Safety Analysis**

   Description of change: The Phase 2 expansion portion of the study was revised to include 9 cohorts instead of 8. The new cohort added will include subjects with clear cell renal cell carcinoma. The relevant study design, number of subjects, inclusion/exclusion criteria, and statistics sections have been updated accordingly. The recommended Phase 2 dose (RP2D) that was determined in Phase 1 was added (100 mg BID).

   Rationale for change: Based on emerging data, including data from the Phase 1 portion of this study, renal cell carcinoma and recommended Phase 2 dose has been added.

3. **Synopsis; Section 3.3, Subject Exclusion Criteria**

   Description of change: Exclusion criterion #8 was revised to specify that subjects with evidence of cerebral edema will be excluded from participation. In addition, subjects will be excluded from participation in the study if it has been < 8 weeks since radiation therapy was delivered to the CNS.

   Rationale for change: Additional language has been added to address subjects with cerebral edema present during screening and window from prior radiation therapy to the brain has been increased from 2 weeks for prior radiation to 8 weeks for radiation therapy to the brain.

4. **Section 1.1.3, Rationale for Studying Immunotherapy in Advanced or Metastatic Cancer; Section 1.1.4, Combined Immune Checkpoint Inhibition; Section 1.4.2, Rationale for Phase 2 Dose Selection of INCB024360**

   Description of change: Information was added regarding the approval of pembrolizumab for metastatic non–small cell lung cancer (NSCLC) in patients whose tumors express PD-L1 as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy; on the approval of nivolumab for metastatic NSCLC in patients with progression on or after platinum-based chemotherapy; and on the approval of nivolumab in combination with ipilimumab for the treatment of patients with BRAF V600 wild-type, unresectable or metastatic melanoma. Safety data on the current study (INCB 24360-202) as of 02 SEP 2015 [redacted] were also added.

   Rationale for change: To provide updated background information.

5. **Synopsis; Section 1.5.1, Efficacy Endpoints; [redacted]; Section 5.6.4, Treatment After Initial Evidence of Radiologic Evidence of Disease Progression; Section 6, Study Assessments; Section 7.6, Efficacy Assessments; Appendix F, Response Evaluation Criteria in Solid Tumors (RECIST) v1.1**

   Description of change: The option for independent central review of radiographic tumor assessments and references to the Site Imaging Manual have been deleted.

   Rationale for change: The Phase 2 portion of this study is no longer a randomized, blinded study; therefore, central review has been removed.

6. **Section 3.2, Subject Inclusion Criteria; Section 6, Study Assessments**

   Description of change: References to subject participation in and sample collection for future biomedical research have been deleted.

   Rationale for change: Merck has removed sample collections for future biomedical research across early phase development of pembrolizumab.

7. **Section 3.3, Subject Exclusion Criteria**

   Description of change: Subjects screening QTc interval has been modified from > 470 ms to > 480 ms.

   Rationale for change: This change was made to reflect consistency across epacadostat program.

8. **Section 5.1.2, MK-3475**

   Description of change: In Table 4 (Dosage and Mode of Administration for MK-3475), the footnote indicating that the MK-3475 dosing interval may be increased to 2 mg/kg IV every 4 weeks for AEs that require dose modifications due to toxicity has been deleted.

   Rationale for change: Merck has updated their guidance for dose modification across the pembrolizumab program to no longer allow an increase in the interval between cycles when resuming therapy after dose holds for adverse events. If a subject cannot resume therapy at the current dose and schedule, they would be removed from study treatment.

9. **Section 5.5.3, Procedures for Safety Review for Phase 2 Expansion Cohorts; Section 9.6, Interim Safety Analysis**

   Description of change: The interim safety analysis timing was updated to after 20 subjects have been enrolled and treated for 9 weeks, and then approximately every 3 months (instead of every 4 months) thereafter.

   Rationale for change: This has been updated to align with Incyte's Pharmacovigilance reviews across the epacadostat program.

10. **Section 5.6.2, Criteria and Procedures for Interruption; Section 5.8, Criteria for Permanent Discontinuation of Study Drug**

    Description of change: A footnote was added to Table 6 (Dose Modification Guidelines for Drug-Related Adverse Events) and a bullet was added to Section 5.8 to indicate that for toxicities such as recurrent or intolerant rash with the combination, subjects may have the opportunity to resume treatment with MK-3475 alone with medical monitor approval. A new table (Table 7) was added providing dose modifications for epacadostat.

    Rationale for change: To allow subjects to receive pembrolizumab alone if deriving clinical benefit from the treatment but unable to tolerate the combination therapy of pembrolizumab and epacadostat. Pembrolizumab is an approved therapy for several indications including melanoma and NSCLC, and subjects who derive clinical benefit from treatment would have the opportunity to continue treatment.

11. **Section 5.6.3, Procedures for Subjects Exhibiting Immune-Related Adverse Events; Section 5.13.1, Supportive Care Guidelines, Section 7.5.1, Adverse Events; Section 8.9, Adverse Events of Special Interest**

    Description of change: References to the Event of Clinical Interest and Immune-Related Adverse Event Guidance Document have been deleted.

    Rationale for change: Merck has incorporated relevant guidance related to events of clinical interest into the Protocol; therefore, a separate document is no longer required.

12. **Section 5.12, Restricted Medications and Measures**

    Description of change: Guidelines for coumarin-based anticoagulants were updated and a table with warfarin dose adjustment recommendations was added.

    Rationale for change: Based on the observed magnitude of epacadostat/warfarin PK interaction and PK/PD modeling results from a completed drug-drug interaction study, for an epacadostat dose of 300 mg BID, the dose of warfarin should be reduced by approximately one-third after initiation of epacadostat administration based on approximately 30% to 40% reduction in S- and R-warfarin oral clearance values. Close INR monitoring is recommended for subjects on a stable dose of warfarin who are starting treatment with epacadostat. Based on PK/PD modeling, recommendations for warfarin dose modifications for subjects have been added to the Protocol.

13. Section 5.13, Prohibited Medications and Measures

Description of change: In addition to radiation therapy, surgery has been added as prohibited with the following exception that is relevant to surgery or radiation. Treatment (radiation therapy or surgery) to a symptomatic solitary lesion or to the brain is allowed in the presence of a mixed response (some lesions improving or stable and other lesions progressing) would be permitted. Guidelines for interrupting/resuming study treatment during these procedures are included.

Rationale for change: Surgery to remove or debulk tumors or the need for additional treatment such as radiation therapy would constitute progression of disease and would indicate treatment failure. In the cases of mixed response, the opportunity to treat these solitary symptomatic lesions and resume therapy after such treatment may allow subjects the opportunity for benefit with immunotherapy.

14. Section 6, Study Assessments; Section 7.5.7.4, Pulmonary Function Tests

Description of change: Pulmonary function testing was deleted from Table 18 (Schedule of Assessments) and Table 22 (Laboratory Tests: Required Analytes), and the corresponding Section 7.5.7.4 was deleted.

Rationale for change: Based on emerging data of low incidence for pneumonitis across the pembrolizumab program and the ability to assess pneumonitis methods already included in this Protocol (CT scans), the requirement for baseline pulmonary function testing has been removed.

15. Section 6, Study Assessments; Section 7, Conduct of Study Assessments

Description of change: Assessments and laboratory assessments were revised as follows. Additional administrative changes are shown in the redline.

- Table 18 (Schedule of Assessments) and Section 7.5.4 (Assessment of Serotonin Syndrome): Serotonin syndrome assessment should be performed approximately 6 hours postdose on Cycle 1 Day 1 and then may be assessed anytime on Day 1 of all subsequent cycles and EOT (ie, it does not need to be 6 hours postdose for Day 1 assessments after Cycle 1 Day 1).
- [redacted]
- Table 19 (Laboratory Assessments): New column was added indicating laboratory assessments for Cycle 12 Day 1 and Cycle 16 Day 1.
- Weekly monitoring of liver function testing for the first 6 weeks of study treatment has been removed for Phase 2.

Rationale for change: Due to the low incidence of liver function abnormalities noted in the Phase 1 portion of this study and across the epacadostat program, testing will be at the beginning of each cycle.

[redacted]

[redacted]

18. Section 7.5.7.1, Hematology, Lipid Panel, Coagulation Panel, Serology, and Endocrine Function Testing

Description of change: Sentence added noting that serology can be performed by a local laboratory.

Rationale for change: Due to issues with obtaining results in a timely manner for subjects to start treatment, it has been agreed to allow for local analysis for serology results when appropriate.

19. Section 7.6.1, Initial Tumor Imaging

Description of change: Instructions added to indicate that baseline brain MRI should be performed for all subjects with previously treated brain metastases; otherwise, it is only indicated if there are symptoms consistent with CNS disease based on investigator assessment.

Rationale for change: For subjects with previously treated brain metastases, obtaining a baseline image will prevent subjects with potential ongoing active CNS involvement from being enrolled in the study before receiving appropriate therapy. .

20. Section 8.1.1, Definitions and Reporting

Description of change: Adverse event severity grading scale was added for events not classified by CTCAE. Guidance was added on how to report adverse events associated with disease progression.

Rationale for change: Additional guidance has been added to assist sites in grading adverse events that may not be captured in the CTCAE criteria.

21. Incorporation of administrative changes. Other minor, administrative changes have been incorporated throughout the protocol and are noted in the attached red-line/strike-out version of the amendment.

Amendment 4 (20 MAY 2015)

Overall Rationale for the Amendment:

The purpose of this amendment is 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, triple negative breast cancer, ovarian cancer, squamous cell carcinoma of the head and neck, diffuse large B-cell lymphoma, and 2 cohorts of subjects with NSCLC based on PD-L1 expression.

1. **Title Page; Synopsis; Section 1, Introduction; Section 2, Study Objectives and Purpose; Section 3, Subject Eligibility; Section 4, Investigational Plan; Section 5, Treatment of Subjects, Section 7.6, Efficacy Assessments; Section 7.11.3, Administration of INCB024360 and Compliance; Section 8.4, Emergency Unblinding of Treatment Assignment; Section 9, Statistics; Section 10, Study Drug Materials and Management; Appendix G, Response Criteria for Diffuse Large B-Cell Lymphoma**

   Description of change: Phase 2 of the study design was changed from a randomized, double-blind, placebo-controlled study in subjects with advanced non–small cell lung cancer (NSCLC) to an open-label expansion in subjects with select cancers (NSCLC, melanoma, triple negative breast cancer, squamous cell carcinoma of the head and neck, ovarian cancer, transitional cell carcinoma of the genitourinary tract and diffuse large B-cell lymphoma [DLBCL]). Accordingly, revisions have been made to the study title; introduction and background sections related to rationale for the study, the combination with a PD-1 inhibitor (pembrolizumab) and IDO1 inhibitor (epacadostat) in these selected advanced or metastatic cancers, a fixed dose of MK-3475 (pembrolizumab); and Protocol sections related to study objectives and endpoints, study population and inclusion/exclusion criteria, overall study design, number of subjects, treatment of subjects, tumor imaging (addition of Lugano Classification for DLBCL), study drug materials (deletion of placebo), and statistical methods and analyses.

   Rationale for change: Based on emerging science and clinical data, the potential for the combination of pembrolizumab and epacadostat activity in several tumor types is now more relevant. Therefore, additional tumor types have been added to this ongoing study and will enroll after the recommended dose for Phase 2 has been determined. Additionally, new data based on PD-L1 expression suggests a predictive value in NSCLC, further supporting the evaluation of 2 cohorts of NSCLC using the new PD-L1 expression cutoff as proposed without the need for a randomized design to detect efficacy.

2. **Synopsis; Section 4, Overall Study Design (including Figure 1, Study Design)**

   Description of change: Phase 1 now includes up to 3 safety expansion cohorts of up to 9 subjects each. The first safety expansion will enroll melanoma subjects only at 50 mg BID once the preliminary safety of the 50 mg BID cohort has been established. A second safety expansion cohort will open at 100 mg BID after preliminary safety at 100 mg BID is established. A third safety expansion cohort may open at 300 mg BID if this dose is tolerated. The recommended Phase 2 dose (RP2D) will be selected from the evaluated safety expansion cohort data.

   Rationale for change: These additional safety cohort expansions have been added to obtain further safety and efficacy data prior to determining the recommended dose for Phase 2 expansion. Restricting one or more of these expansion cohorts to specific tumor types may be employed to obtain preliminary efficacy data for program-wide decision-making and planning.

3. **Synopsis; Section 3.2, Subject Inclusion Criteria**

   Description of change: In inclusion criterion 8e (laboratory parameters), the level for AST, ALT, bilirubin, and alkaline phosphatase has changed to $< 2.5 \times$ ULN; subjects with bone metastases with or without hepatic parenchymal metastases may be enrolled if alkaline phosphatase is $< 5 \times$ ULN (only with medical monitor approval if there is hepatic parenchymal metastases). The level for conjugated bilirubin has changed to $< 2.0 \times$ ULN. Inclusion criterion #10 (fresh baseline tumor biopsies) is updated to allow archived tumor tissue with medical monitor approval for subjects with inaccessible lesions (eg, ovarian cancer).

   Rationale for change: No clinically significant liver toxicity has been seen thus far in the completed dose-escalation cohorts that have included epacadostat 100 mg BID. Therefore, the highly restrictive liver chemistry testing adopted based on the experience of epacadostat and ipilimumab has been updated to provide flexibility consistent with more typical inclusion rules for liver chemistry testing.

4. **Synopsis; Section 3.3, Subject Exclusion Criteria**

   Description of change: Exclusion criterion #3 (no prior monoclonal antibody within 4 weeks before study Day 1) was updated to allow denosumab as an exception. In exclusion criterion #9 (active autoimmune disease), the exceptions were deleted. In exclusion criterion #21, the criteria for abnormal ECG were updated.

   Rationale for change: The noted revisions to the exclusion criteria have been added to provide additional guidance and clarification.

5. **Section 1.1.1, Inhibition of PD-1 as a Target for Cancer**

   Description of change: The description of MK-3475 (pembrolizumab) was updated to include its US approval information.

   Rationale for change: Pembrolizumab received US regulatory approval for use in subjects with metastatic melanoma. These data provide additional support and rationale for testing the combination in this population.

6. **Section 1.1.4, Combined Immune Checkpoint Inhibition**

   Description of change: Section has been revised to include updated data for the ongoing Phase 1 study of INCB024360 with ipilimumab (INCB 24360-201) and updated enrollment and preliminary data for the current study (INCB 24360-202).

   Rationale for change: To provide current data to support the rationale for testing the combination in these patient populations.

7. **Section 5.6.2, Criteria and Procedures for Interruption**

   Description of change: Updated to allow dosing interruptions for medical/surgical events or logistical reasons not related to study therapy (eg, elective surgery, unrelated medical events, patient vacation, and/or holidays).

   Rationale for change: Updated guidance has been provided by Merck based on current guidelines for pembrolizumab.

8. **Section 5.6.3, Procedures for Subjects Exhibiting Immune-Related Adverse Events; Section 5.13.1, Supportive Care Guidelines**

   Description of change: Recommended approaches to handling general and specific immune-related adverse events (pneumonitis, enterocolitis/diarrhea, hepatitis, hypophysitis, hypothyroidism, hyperthyroidism, renal failure, and nephritis) have been updated. Guidance for Type 1 diabetes mellitus and infusion reactions have been added/updated. Cross-references and the separate subsection on the Events of Special Interest Guidance document have been deleted.

   Rationale for change: Updated guidance has been provided by Merck based on current guidelines for pembrolizumab.

9. **Section 6, Study Assessments; Section 7.6.4.1, Bone Marrow Examination; Section 7.6.5, CA 125 Monitoring**

   Description of change: In Section 6, bone marrow examination and PET imaging (for subjects with DLBCL) were added to Table 16 (Schedule of Assessments), and CA 125 testing for subjects with ovarian cancer was added to Table 17 (Laboratory Assessments) and Table 20 (Laboratory Analytes). Sections 7.6.4.1 and 7.6.5 were added to describe these assessments.

   Rationale for change: Inclusion of additional cancer types for the Phase 2 expansion requires additional tumor-specific monitoring, which has been included in the assessments section as noted above.

10. **Section 7.6, Efficacy Assessments**

    Description of change: Additional guidance has been included for required baseline imaging requirements and for selection of target lesions.

    Rationale for change: Updated for clarity.

11. Section 8.1.1, Adverse Events, Definitions and Reporting

Description of change: Updated to indicate that disease progression and events related to disease progression (based on the investigator's judgment), including death due to disease progression, should not be recorded as AEs (or SAEs if appropriate).

Rationale for change: Clarification of Incyte guidance on the reporting of disease progression including deaths due to disease progression.

12. Section 8.6, Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

Description of change: The definition of an overdose definition for MK-3475 was revised to ≥ 1000 mg (5 times the dose), and overdose information for INCB024360 was deleted.

Rationale for change: Merck has an updated definition of overdose, which is consistent for pembrolizumab.

13. Section 8.8, Data Monitoring Committee; Section 5.5.3, Procedures for Safety Review for Phase 2 Expansion Cohorts; Section 9.5, Data Monitoring Committee; Section 9.6 Interim Safety Analyses

Description of change: These sections were revised to indicate there will not be a formal Data Monitoring Committee and the sponsor will include regularly scheduled interim safety analyses.

Rationale for change: Incyte and Merck will monitor the safety of the Phase 2 portion of the study as defined in Section 9.6, where interim safety reviews will begin in Phase 2 after 20 subjects have been enrolled and treated for 9 weeks, and then every 4 months thereafter.

14. Section 8.9, Adverse Events of Special Interest

Description of change: Information regarding immune-related events appeared twice in this section. The first instance was reformatted as an "Additional adverse events" numbered item and the second instance was deleted.

Rationale for change: Revised for clarity and to remove redundant information.

15. Incorporation of administrative changes. Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the red-line/strike-out version of the amendment.

Amendment 3 (19 FEB 2015)

Overall Rationale for the Amendment:

The primary purpose of Amendment 3 is to include an additional safety expansion cohort at 50 mg BID in subjects with metastatic melanoma.

1. **Synopsis, Overall Study Design, Statistical Methods; Section 4.1, Overall Study Design; Figure 1, Study Design; Section 9.2.1, Cohort Size in Phase 1; Section 9.4.1, Phase 1 Statistical Analysis**

   Description: An additional safety expansion cohort has been added for up to 9 subjects with metastatic melanoma at the 50 mg BID dose level once preliminary safety of the 50 mg BID cohort has been established. This is in addition to the already-planned safety expansion at the recommended Phase 2 dose (RP2D) of INCB024360 prior to initiation of Phase 2. In addition, an additional 34 subjects with melanoma may be enrolled at either the 50 mg BID dose or at the RP2D.

   Rationale: This cohort has been added to obtain further safety and efficacy data, particularly in the subset of subjects with metastatic melanoma.

2. **Synopsis, Planned Number of Subjects; Section 4.4, Number of Subjects**

   Description: The planned number of subjects has been updated to reflect the addition of safety expansion cohorts in Phase 1.

   Rationale: Additional safety cohorts have been added to further explore the safety and efficacy of this combination in subjects with metastatic melanoma.

3. **Section 1.1.1, Inhibition of PD-1 as a Target for Cancer**

   Description: Information regarding the approval of MK-3475 (pembrolizumab) by the FDA has been added to the background and rationale.

   Rationale: MK-3475 has been approved for treatment of subjects with metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

4. **Section 5.5.1, Definition of Dose-Limiting Toxicities (Table 4, Criteria for Defining Dose-Limiting Toxicities); Section 5.6.2, Criteria and Procedures Interruption (Table 5, Dose Modification Guidelines for Drug-Related Adverse Events)**

   Description: Clarification has been added to the DLT criteria for the Grade 3 rash to specify steroid use means systemic steroids.

   Rationale: Use of topical steroids only would not warrant an event to be considered a DLT.

5. **Section 5.12, Restricted Medications and Measures; Section 5.13, Prohibited Medications and Measures**

   Description: Updated guidance was added for use of coumarin-based anticoagulants.

   Rationale: A study was conduction (Study INCB 24360-102) that investigated the potential drug-drug interaction between INCB024360 and warfarin. Results from the preliminary PK and PD analyses concluded that multiple dosing of INCB024360 300 mg BID increased S-warfarin and R-warfarin geomean plasma AUCs by 43% and 68%, respectively, accompanied by mild but statistically significant INR and PT increases. Modeling showed that, with the same degree of warfarin PK interaction, the magnitude of INR increase may be significantly greater in patients on stable warfarin regimen targeting a typical INR range of 2 to 3 (which is higher than the INR observed in this study following a single warfarin dose). Therefore, we recommend an approximate one-third reduction of warfarin dose for subjects who also receive INCB024360, along with close INR monitoring. No clinically relevant interaction was observed on INCB024360 PK with concomitant warfarin.

6. **Section 5.13, Prohibited Medications and Measures**

   Description: The following has been added or clarified in the prohibited medications section: administration of an injectable flu vaccine is prohibited during the DLT observation period, clarification has been added that live attenuated vaccines are prohibited, and the list of prohibited UGT1A9 inhibitors has been updated.

   Rationale: Updates have been made to address questions related to vaccine use and UGT1A9 inhibitors.

7. **Section 6.0, Study Assessments (Table 16, Schedule of Assessments); Section 7.5.7.4, Pulmonary Function Tests**

   Description: Pulmonary function testing may be omitted for subjects with stomas due to laryngectomies.

   Rationale: Subjects with stomas are unable to perform pulmonary function testing and are therefore permitted to omit this testing at screening.

8. **Section 6.0, Study Assessments (Table 16, Schedule of Assessments; Table 17, Laboratory Assessments; Tables 18, Re-treatment Schedule of Assessments; Table 19, Re-treatment Laboratory Assessments)**

   Description: The window for follow-up (imaging post-treatment) and survival follow-up has been updated to ± 7 days.

   Rationale: The window for follow-up and survival follow-up has been updated to allow for more flexibility for subject scheduling.

9. **Section 6.0, Study Assessments (Table 17, Laboratory Assessments; Table 19, Re-treatment Laboratory Assessments); Section 7.5.7.1, Hematology, Lipid Panel, Coagulation Panel, Serology, and Endocrine Function Testing**

   Description: The footnote for coagulation panel testing in Tables 17 and 19 has been updated to reflect the use of local testing instead of central testing for subjects receiving anticoagulant therapy and require weekly monitoring. This was also updated in Section 7.5.7.1.

   Rationale: For those additional 4 weeks of monitoring, sites should perform INR testing locally in order to receive results in real time.

10. **Section 7.5.7.3, Serum Chemistry and Liver Function Tests**

    Description: Text has been added to clarify LFT monitoring requirements for subjects with persistent low-grade abnormalities.

    Rationale: Liver function test monitoring for persistent low-grade abnormalities does not need to be monitored twice a week indefinitely. Appropriate LFT monitoring intervals should be discussed with the medical monitors for these circumstances.

11. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the red-line/strike-out version of the amendment.

Amendment 2 (09 DEC 2014)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to remove the restriction for subjects currently receiving potent CYP3A4 inducers or inhibitors, revise final escalation dose for MK-3475 for the Phase 1 portion of the study, and clarify inclusion/exclusion criteria and required laboratory assessments.

1. **Synopsis, Overall Study Design and Combination Therapy, Dosage, and Mode of Administration; Section 1.4, Justification for Treatment Regimen; Section 4.1, Overall Study Design; Section 9.2.1, Cohort Size in Phase 1**

   Description of change: Phase 1 dose-escalation design was updated to a 3 + 3 + 3 design.

   Rationale for change: The design was updated to further explore the safety of the combination beyond 3 + 3.

2. **Section 3.2, Subject Inclusion Criteria**

   Description of change: Text was added inclusion criterion #2 to clarify that subjects may provide consent for future biomedical research; however, this is optional.

   Rationale for change: Previous text was not clear that consent for future biomedical research is optional.

3. **Synopsis, Study Population; Section 1, Introduction; Section 1.2, Study Rationale; Section 3.1, Study Population; Section 3.2, Subject Inclusion Criteria (criterion #3); Section 4.1, Overall Study Design**

   Description of change: Inclusion of subjects with transitional cell carcinoma of the bladder was expanded to transitional cell carcinoma of the GU tract.

   Rationale for change: The intention is to include subjects with transitional cell carcinoma (TCC) originating in the GU tract. Although bladder origin is the most common for TCC, other sites such as ureteral and renal pelvis TCC are managed similarly to TCC of the urinary bladder and may be enrolled into the study.

4. **Synopsis, Phase 1 Dose Escalation; Section 1.4.1, Rationale for Fixed Dose of MK-3475; Section 4.1.1, Phase 1 Dose-Escalation Design; Section 5.1.2, MK-3475 (Table 3: Dosage and Mode of Administration for MK-3475)**

   Description of change: The final escalation has been revised from testing 5 mg/kg and 10 mg/kg of MK-3475 with the MTD of INCB024360 to one final safety expansion at 200 mg of MK-3475 with the MTD of INCB024360. The final cohort for the Phase 1 portion of the study has been updated to a safety expansion of 9 subjects with a 2 mg/kg dose of MK-3475 and/or the equivalent dose of 200 mg instead a dose escalation of MK-3475 to 5 mg/kg and 10 mg/kg. Additional cohorts testing an every-2-week schedule of MK-3475 have been removed from the above-mentioned sections, and references to the every-2-week schedule have been deleted throughout the Protocol.

   Rationale for change: Merck & Co.'s current plan with MK-3475 includes testing a flat dose of 200 mg and no longer testing an every 2-week schedule of MK-3475 in this setting.

5. **Synopsis, Study Population; Section 3.2, Subject Inclusion Criteria (criterion #10a)**

   Description of change: For archived tumor tissue, the minimum preferred number of unstained slides has been revised from 10-15 slides to 20 slides.

   [redacted]

6. **Section 3.2, Subject Inclusion Criteria (criterion #11); Section 6, Study Assessments (Table 17: Laboratory Assessments; Table 19: Re-treatment Laboratory Assessments; Table 20: Laboratory Tests: Required Analytes); Section 7.5.7.5, Pregnancy Testing**

   Description of change: Incyte's inclusion criterion for women of childbearing potential has been revised and is currently being incorporated into all Incyte Protocols. These updates include combining the male and female criteria into one and removing the requirement for FSH testing for postmenopausal women.

   Rationale for change: Revised due to an update within Incyte standards across all programs.

7. **Synopsis, Key Exclusion Criteria; Section 3.3, Subject Exclusion Criteria**

   Description of change to exclusion criterion #4: Reference to Phase 2 was added to the description for exclusion criterion #4.

   Rationale for change: Exclusion criterion #4 is specific for the Phase 2 part of the study only.

   Description of change to exclusion criterion #5: Radiation therapy was removed from exclusion criterion #5.

   Rationale for change: Radiation therapy was removed from exclusion criterion #5 because it was redundant with exclusion criterion #11.

   Description of change to exclusion criterion #9: Additional clarification has been included for the current and prior treatment restrictions for subjects with an active or a history of an autoimmune disease.

   Rationale for change: This criterion has been updated to provide additional guidance around autoimmune disease that requires treatment and exceptions that would be considered for replacement therapy.

   Description of change to criterion #26: An exclusion criterion has been added for any known allergy or reaction to any component of either study drug formulation.

   Rationale for change: This exclusion has been added to exclude subjects that may be at risk for a reaction to the study treatment or any component of the study treatment.

8. **Section 3.3, Subject Exclusion Criteria (criterion #22); Section 5.13, Prohibited Medications; Appendix E, Prohibited Inhibitors and Inducers of Cytochrome P450 3A4**

   Description of change: Exclusion of subjects currently receiving therapy with potent CYP3A4 inducers or inhibitors was removed.

   Rationale for change: Analysis of human plasma samples indicated that INCB024360 is metabolized by 2 major pathways: O-glucuronidation and reduction. The O-glucuronide (M9) was formed by UGT1A9 and the reduced metabolite (M11) appears to be catalyzed by intestinal microflora. Metabolite M11 is also further metabolized to M12, a product formed by oxidative cleavage catalyzed by CYPs. Quantitation of all 3 metabolites in human, mice, and dog plasma are currently underway to establish safety margins. The identification of the 2 major pathways and the enzymes responsible for those pathways has enabled the refinement of the inclusion/exclusion criteria around concomitant medications. Since CYP3A4 is not involved in the 2 primary metabolic pathways, restrictions for CYP inducers and inhibitors is no longer necessary or justified. These data has been filed to this study's IND (121,704) on July 14, 2014, Serial Number SN 0004.

9. **Synopsis, Treatment; Section 5.1.1, INCB024360 or Matching Placebo; Section 5.4, Duration of Treatment and Subject Participation; Section 6.2, Treatment Phase**

   Description of change: The information regarding re-treatment of subjects who continue on INCB024360 that is detailed in Section 6.2.1, Second Course Phase (Re-treatment Period), has been added to the above-noted sections.

   Rationale for change: This was an administrative update to make the text consistent across all relevant sections of the Protocol related to the treatment phase of the study and the duration of treatment for subjects.

10. **Section 5.5.1, Definition of Dose-Limiting Toxicities (Table 4: Criteria for Defining Dose-Limiting Toxicities)**

    Description of change: Additional criteria for Grade 3 rash have been added to the nonhematologic toxicities section of Table 4.

    Rationale for change: Grade 3 rashes in the absence of desquamation, no mucosal involvement that does not require steroids and resolves to Grade 1 will not be considered at DLT since these are manageable and quickly reversible.

11. **Section 5.6, Dose Adjustments for Study Drugs (Table 5: Dose Modification Guidelines for Drug-Related Adverse Events); Section 5.6.3, Procedures for Subjects Exhibiting Immune-Related Adverse Events**

    Description of change: Updates to the dose modification guidelines have been made.

    Rationale for change: Merck and Co. recently updated their dose modification guidelines for several adverse events across their MK-3475 program; therefore, those updates have been incorporated in this Protocol.

12. **Synopsis, Study Schedule/Procedures; Section 6, Study Assessments (Table 16: Study Assessments and Table 18: Re-treatment Study Assessments); Section 7.6.4, Tumor Biopsy**

    Description of change: Timing of optional tumor biopsy has been opened to allow for optional biopsy to occur any time after Cycle 1 Day 14.

    Rationale for change: A tumor tissue sample for correlative research would be useful any time after steady state is achieved and to allow for flexibility for the subjects and sites.

13. **Section 6, Study Assessments (Table 18: Re-treatment Schedule of Assessments and Table 19: Re-treatment Laboratory Assessments)**

    Description of change: Tables have been added for subjects entered into the re-treatment phase of the study.

    Rationale for change: The re-treatment assessment schedules were previously part of main schedules of assessments; however, several differences were hard to tease out and new tables were therefore created for ease of reference for sites.

14. **Section 6, Study Assessments (Table 20: Laboratory Tests: Required Analytes)**

    Description of change: HBV-DNA serology testing has been added to the Serology list of required analytes. The HS-CRP test has been revised to analyze CRP by standard method instead of the highly sensitive (HS-CRP) assay, and the erythrocyte sedimentation rate (ESR) has been removed.

    Rationale for change: Exclusion criterion #13 requires testing for HBV DNA for inclusion in the study; however, the analyte table did not include this test. The HBV-DNA test is a requirement and should be performed as part of subject screening and was therefore added to Table 20. HS-CRP is a more sensitive test in the lower range that is used more often to assess risk of developing myocardial infarction in patients presenting with acute coronary syndromes or assessment of risk of developing cardiovascular disease or ischemic events in individuals who do not manifest disease at present. The measurement of CRP has been used historically to assess activity of inflammatory disease and to monitor inflammatory processes. In this study, the interest is in the role of inflammation in cancer; therefore, the CRP test is the more appropriate test to be performed. The ESR testing was originally implemented to look for autoimmune inflammation in the INCB024360 program, but it does not appear to be sensitive enough to changes (or dramatic changes in inflammation have not occurred) so that it no longer seems necessary to run this in these studies.

15. **Section 6.4.1, Safety Follow-Up**

    Description of change: Guidance has been added to the Protocol to complete safety follow-up visits prior to initiation of any new anticancer therapy.

    Rationale for change: Guidance to complete safety follow-up visits prior to initiation of any new anticancer therapy has been added to prevent assessments for toxicity after additional treatments have been given.

16. Section 7.5.1, Adverse Events; Section 8.9, Adverse Events of Special Interest

Description of change: Additional language has been included in these sections of the Protocol to provide consistent reporting guidance for events of clinical interest.

Rationale for change: Additional language for reporting of AEs of special interest across the MK-3475 program has been updated and is now included in these sections of the Protocol to provide consistent guidance for reporting events of clinical interest.

18. Section 9.5, Data Monitoring Committee

Description of change: Investigators were removed from membership in DMC text.

Rationale for change: This study will utilize an internal DMC made up of individuals from the co-sponsor of this study (Merck) who is not directly involved in the study to oversee the safety and conduct of this study.

19. Section 9.6, Interim Analysis (Table 27: Probability of Early Termination for Various Safety Event Rates)

Description of change: The heading for the first 2 columns in Table 27 were corrected and the last 2 columns were deleted and a footnote added.

Rationale for change: The interim analysis text is correct as written for Phase 2. The headings of the first 2 columns in Table 27 should reflect the rule in the text above the table and read "Proportion of subjects having an AE ≥ Grade 3 that was attributable to the investigational agent." Columns 3 and 4 were inadvertently left in from a previous discussion to focus on immune-related toxicity, but it was decided to consider ALL Grade 3 or greater AEs for the interim safety analyses.

20. Section 15, Publication Policy

Description of change: The following sentence was added to the publication policy section of the Protocol: Study results will be published in accordance with applicable local and national regulations.

Rationale for change: Incyte Protocol template language was updated to comply with local and national regulations.

21. Incorporation of administrative changes. Other minor, administrative changes have been incorporated throughout the protocol and are noted in the attached red-line/strike-out version of the amendment.

Amendment 1 (03 APR 2014)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to address [redacted] queries for the justification of combining MK-3475 10 mg/kg with INCB024360 at the recommended Phase 2 dose (RP2D) in Cohort 5 and to incorporate [redacted] Clinical Pharmacology comments.

1. **Section 1.4, Justification for Treatment Regimen**

   Description of change: Text has been revised to clarify that MK-3475 regimens currently being studied in Phase 2 and Phase 3 include 2 mg/kg and 10 mg/kg every 2 weeks or every 3 weeks, and that the optimal dose and schedule for MK-3475 has not yet been established.

   Rationale for change: [redacted] to include in the Protocol to acknowledge that optimal dose and schedule has not yet been established in the MK-3475 program.

2. **Synopsis, Overall Study Design for Phase 1 Dose Escalation; Section 4.1.1, Phase 1 Dose-Escalation Design, and Figure 1, Study Design**

   Description of change: The final dose escalation cohort has been updated to include an intermediate dose of 5 mg/kg MK-3475 to be tested in combination with the RP2D of INCB024360 prior to a final escalation with 10 mg/kg of MK-3475.

   Rationale for change: Emerging monotherapy data from MK-3475 Protocol 001 indicate that the safety profile of MK-3475 at 10 mg/kg is comparable to that of MK-3475 at 2 mg/kg. Safety data from the 2 dose levels have been compared in MK-3475 P001 in both ipilimumab-refractory melanoma patients and ipilimumab-naïve patients. In each instance, lower frequencies of drug-related Grade 3-5 adverse events and drug-related serious adverse events were seen in the 10 mg/kg cohort as compared to the 2 mg/kg cohort. Therefore, it is anticipated that the MTD of INCB024360 in conjunction with MK-3475 at 10 mg/kg will be safe and well tolerated, but an interim dose of MK-3475 of 5 mg/kg will be tested before a final escalation to 10 mg/kg MK-3475 with the RP2D of INCB024360.

3. **Section 6, Study Assessments, Tables 13 and Table 15, Serum Chemistry Testing and Fertility Testing; Section 7.5.7.3, Serum Chemistry and Liver Function Tests; Section 7.5.7.5, Pregnancy and Fertility Testing**

   Description of change: All serum chemistry testing and fertility testing will be performed by the site's local laboratory instead of being sent for central analysis.

   Rationale for change: For patient and site convenience, serum chemistry testing will be performed locally.

4. **Section 6, Study Assessments, Table 13 and Table 15, Lipid Panel**

   Description of change: Administrative correction has been made to add lipid testing in the schedule of laboratory assessments per the laboratory analytes table.

   Rationale for change: Lipid testing was inadvertently excluded in the schedule for laboratory assessments; however, it was included in the table of required analytes.

5. Section 7.5.6, Twelve-Lead Electrocardiograms

Description of change: Text has been corrected to instruct sites that any clinically significant abnormal findings after signing informed consent should be recorded as an adverse event.

Rationale for change: Incyte requires any event that occurs from time of consent (not time of first dose of study drug) be recorded as an adverse event and not medical history.

[redacted]

8. Section 7.11.3, Administration of INCB024360 and Compliance

Description of change: Text has been added to clarify that dosing of INCB024360 should occur in the clinic on all [redacted] sample collection days.

Rationale for change: Clarification was needed. As currently written, it was not clear when INCB024360 should be dosed in clinic or self-administered at home.

9. Synopsis, Combination Therapy, Dosage, and Mode of Administration; Section 5.1.1, INCB024360 or Matching Placebo; Section 7.11.3, Administration of INCB024360 and Compliance

Description of change: How INCB024360 will be administered with regard to food was added to the Protocol.

Rationale for change: INCB024360 may be administered without regard to food; however, this was not specified in the Protocol.

10. Section 3.3, Subject Exclusion Criteria

Description of change: Subjects with QTc interval of > 470 msec at study entry and subjects with congenital long QT syndrome has been added as exclusion criterion #21.

Rationale for change: Change requested [redacted]

11. Section 3.3, Subject Exclusion Criteria; Section 5.13, Prohibited Medications and Measures; Appendix E, Prohibited Inhibitors and Inducers of Cytochrome P450 3A4.

Description of change: Exclusion criterion #22 has been added for subjects taking drugs that are known to be strong inhibitors and/or inducers of CYP3A4 from 2 weeks before Day 1 of study drug administration and throughout the study, and Appendix E has been added to include a list of prohibited inducers and inhibitors of cytochrome P450 3A4.

Rationale for change: Change requested [redacted].

12. Section 6, Study Assessments (Tables 12 and 14, Schedules of Assessments); Section 7.5.6, Twelve-Lead Electrocardiograms

Description of change: Additional ECG monitoring was added to Cycle 1 Day 1, and monitoring on Cycle 2 Day 1 was revised to be performed around the maximal and steady-state plasma concentrations (C_{max} and $C_{max,ss}$) of INCB024360, and as clinically indicated.

Rationale for change: Change requested [redacted].

13. Section 9.4.3, Secondary Analyses

Description of change: Analysis details for the secondary endpoint of time to progression have been included.

Rationale for change: Time to progression analysis for the secondary objective evaluating time to disease progression had been omitted from the Protocol.

14. Incorporation of administrative changes. Other minor, administrative changes have been incorporated throughout the protocol and are noted in the attached red-line/strike-out version of the amendment.

Signature Manifest

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24360-202 Protocol Am 10

Approval and Release

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