Official Protocol Title:	A Phase I Study of INCB024360 (epacadostat) Alone, INCB024360 in combination with Pembrolizumab (MK-3475), and INCB024360 and Pembrolizumab in combination with Chemotherapy in Patients with Advanced Solid Tumors (KEYNOTE-434)
NCT number:	NCT02862457
Document Date:	26-Apr-2019

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Protocol-specific Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

TITLE:

A Phase I Study of INCB024360 (epacadostat) Alone, INCB024360 in combination with Pembrolizumab (MK-3475), and INCB024360 and Pembrolizumab in combination with Chemotherapy in Patients with Advanced Solid Tumors (KEYNOTE-434)

EudraCT NUMBER: Not Applicable

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
3475-434-00	10-Jun-2016	Initial protocol
3475-434-01	16-Oct-2017	To add a cohort to investigate the safety and tolerability of INCB024360 and MK-3475 in combination with chemotherapy in subjects with advanced NSCLC (Part B).
3475-434-02	26-Apr-2019	Based on results from the KEYNOTE-654 and KEYNOTE-715 NSCLC studies, INCB024360 + pembrolizumab (KEYNOTE-654) and INCB024360 + pembrolizumab + chemotherapy (KEYNOTE-715) did not meet the pre-specified primary endpoint of improvement in the confirmed ORR. KEYNOTE-434 has been updated to simplify the trial design and to stop administration of INCB044360 in Part B (NSCLC patients).

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
1.0 2.0 5.2 5.2.1.2.1 5.2.1.2.3 5.2.2 5.5.2 5.5.3 5.8 5.8.1 6.0 7.1.2 7.1.4.1 7.1.5 7.2.1 8.0 12.6	TRIAL SUMMARY TRIAL DESIGN Trial Treatment(s) Tolerability Evaluation Rules Guideline for Dose Modification Timing of Dose Administration Restricted Medications and Measures Prohibited Medications and Measures Subject Withdrawal/Discontinuation Criteria Discontinuation of Study Therapy after CR TRIAL FLOW CHART Clinical Procedures/Assessments Withdrawal/Discontinuation Visit Requirements Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor STATISTICAL ANALYSIS PLAN Description of the iRECIST Process for Assessment of Disease Progression	Revised text and added notes to stop INCB024360 in Part B and to simplify the trial design in both Parts were made as follows: · remove INCB024360 from Part B; · remove second course (except for patients already in second course before amendment 02 is approved); · remove follow-up phase and survival follow-up phase; · change imaging schedule to “per site SOC”; · no longer use irRECIST / iRECIST.	Based on results from the KEYNOTE-654 and KEYNOTE-715 NSCLC studies, INCB024360 + pembrolizumab (KEYNOTE-654) and INCB024360 + pembrolizumab + chemotherapy (KEYNOTE-715) did not meet the pre-specified primary endpoint of improvement in the confirmed ORR. KEYNOTE-434 has been updated to simplify the trial design and to stop administration of INCB044360 in Part B (NSCLC patients).

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
3.0	OBJECTIVE(S) & HYPOTHESIS(ES)	Addition of notes to clarify that the protocol will stop collecting efficacy endpoints and exploratory objectives may not be pursued.	Based on results from KEYNOTE-654/ KEYNOTE-715, the collection of efficacy data is not required in KEYNOTE-434
4.2.3.2	Efficacy Endpoints	Addition of notes to clarify that data for efficacy endpoints will no longer be collected, imaging will be performed per local standard of care and will be assessed by the investigator/site radiologist, and the use of irRECIST and iRECIST is discontinued.	Based on results from KEYNOTE-654/ KEYNOTE-715, the collection of additional efficacy data is not required in KEYNOTE-434.
4.3.3	Benefit/Risk for the Combination of MK-3475 and INCB024360	Addition of notes to clarify Benefit/Risk for the Combination of MK-3475 and INCB024360.	To update the benefit/risk assessment based on results from KEYNOTE-654/ KEYNOTE-715.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
5.2.1.2.5 5.5.3 12.4	Procedures for Subjects Exhibiting Serotonin Syndrome (SS) Prohibited Medications and Measures Prohibited Monoamine Oxidase Inhibitors and Drugs Associated with Significant Monoamine Oxidase Inhibitory Activity	Updated information regarding the risks of SS with the use of INCB024360 was provided. Texts were revised to clarify that the use of MAOIs is no longer prohibited in the study.	To align with current practices across the INCB024360 development program as supported in the current version of the INCB024360 IB.
7.3.2	Independent Pulmonary Radiographic Adviser	Revised texts that pulmonary radiographic changes by an independent pulmonary radiographic adviser will be reviewed as necessary.	Based on the current data in this study, review by an independent pulmonary radiographic adviser should be conducted as necessary.

1.0 TRIAL SUMMARY

Abbreviated Title	Phase I study of INCB024360 (epacadostat) alone/combo with MK-3475 and Chemotherapy in solid tumors
Sponsor Product Identifiers	MK-3475 (pembrolizumab), INCB024360 (epacadostat)
Trial Phase	Phase I
Clinical Indication	Advanced solid tumors
Trial Type	Interventional
Type of control	No treatment control
Route of administration	MK-3475: Intravenous, INCB024360: oral
Trial Blinding	Unblinded Open-label
Treatment Groups	**Part A (Solid tumors)** ● Cohort 1 (To assess the safety and tolerability of INCB024360 administered alone) Dose Level 1: INCB024360 25 mg BID alone, followed by INCB024360 25 mg BID + MK-3475 200 mg Q3W Dose Level 2: INCB024360 100 mg BID alone, followed by INCB024360 100 mg BID + MK-3475 200 mg Q3W ● Cohort 2 (To assess the safety and tolerability of INCB024360 administered in combination with MK-3475) Dose Level 1: INCB024360 25 mg BID + MK-3475 200 mg Q3W Dose Level 2: INCB024360 100 mg BID + MK-3475 200 mg Q3W **Part B (NSCLC)** ● Cohort 1: MK-3475 200 mg Q3W in combination with Cisplatin and Pemetrexed (Non-Squamous) ● Cohort 2: MK-3475 200 mg Q3W in combination with Carboplatin and Pemetrexed (Non-Squamous) ● Cohort 3: MK-3475 200 mg Q3W in combination with Carboplatin and Paclitaxel (Squamous and Non-Squamous) NOTE: The original study design allocate participants into 2 Parts: INCB024360 + pembrolizumab and INCB024360 + pembrolizumab + chemotherapy. As of Amendment 02, INCB024360 is stopped from Part B of original treatment cohorts. Thus, participants remaining in Part B receive pembrolizumab plus chemotherapy as per protocol, based on the cohort to which they were originally assigned, unless they choose to discontinue from the study completely and be treated with standard of care.
Number of trial subjects	Approximately 15 (Part A) and 18 (Part B) subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 2 years from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.

Duration of Participation	Each subject will participate in the trial from the time the subject signs the informed consent form (ICF) through the final protocol-specified contact. After a screening phase of 4 weeks, eligible subjects will be assigned to receive trial treatment until the subject meets the discontinuation criteria such as progressive disease (PD), unacceptable adverse event(s), or until the subject has received 35 administrations of MK-3475 (approximately 2 years) (Section 5.8). For Part A, subjects who are already in second course before Amendment 02 is approved would be eligible to continue to receive trial treatment for up to 17 additional administrations of INCB024360 + MK-3475 (approximately one year) upon experiencing PD (Section 7.1.5.5). Otherwise subjects in Part A and part B will not receive INCB024360, and also will not receive second course (additional 17 administrations of MK-3475). After the end of treatment, each subject will be followed for the occurrence of adverse events and spontaneously reported pregnancy for 90 days and 120 days (or 30 days if the subject initiates new anticancer therapy) as described under section 7.2 of the protocol. As of Amendment 02, the last study visit is the Safety Follow-up Visit.

A list of abbreviations used in this document can be found in Section 12.8.

2.0 TRIAL DESIGN

2.1 Trial Design

NOTE: As of Amendment 02, INCB024360 is removed from the treatment groups in Part B. Participants may choose to discontinue from the study and be treated as per standard of care or continue on study. All participants in Part B remaining on study receive pembrolizumab plus chemotherapy, as per protocol. For Part A only, the Second Course Phase is applied to the subjects who are already in second course as of Amendment 02. Second course is no longer available for new participants in Part A or Part B. The last study visit is the Safety Follow-up Visit, and there will be no follow-up for survival status. All imaging will be performed as per local standard of care; data will not be collected or sent for central imaging vender. This section has been updated accordingly.

This is an open-label, non-randomized, multi-center, Phase I study of MK-3475 (pembrolizumab), INCB024360 (epacadostat) , INCB024360 (epacadostat) and chemotherapy in Japanese subjects with advanced solid tumors to be conducted in conformance with Good Clinical Practices. The primary objective of the trial was to evaluate the safety and tolerability of INCB024360 administered alone and in combination with MK-3475 in subjects with advanced solid tumors and the safety and tolerability of INCB024360 and MK-3475 in combination with chemotherapy in subjects with advanced NSCLC.

In this study, we evaluated the safety and tolerability of the dose of INCB024360 alone and in combination with MK-3475 in advanced solid tumors (Part A Cohort 1 and 2, respectively) and INCB024360 and MK-3475 in combination with chemotherapy with each chemotherapy Cohort in advanced NSCLC (Part B Cohort 1, 2 and 3).

NOTE: The original study design allocated participants into 2 Parts: INCB024360 + pembrolizumab (Figure 2 and Figure 3) and INCB024360 + pembrolizumab + chemotherapy (Figure 4). As of Amendment 02, INCB024360 is stopped from Part B (Figure 5). Thus, participants remaining in Part B receive pembrolizumab plus chemotherapy as per protocol, based on the cohort to which they were originally assigned, unless they choose to discontinue from the study completely and be treated with standard of care. No second course will be available for new participants.

Part A (Advanced Solid Tumor)

- Cohort 1 (To assess the safety and tolerability of INCB024360 administered alone)

  Dose Level 1: INCB024360 25 mg BID alone, followed by INCB024360 25 mg BID + MK-3475 200 mg Q3W

  Dose Level 2†: INCB024360 100 mg BID alone, followed by INCB024360 100 mg BID + MK-3475 200 mg Q3W

  † In the Dose Level 2 (100 mg BID), we enrolled 3 patients to evaluate the safety, tolerability and pharmacokinetics (PK)of INCB024360 administered alone, and to evaluate the safety and PK of INCB024360 in combination with MK-3475.

- Cohort 2 (To assess the safety and tolerability of INCB024360 administered in combination with MK-3475)

  Dose Level 1: INCB024360 25 mg BID + MK-3475 200 mg Q3W

  Dose Level 2: INCB024360 100 mg BID + MK-3475 200 mg Q3W

This study will utilize a modified Toxicity Probability Interval (TPI) method [1] design that will evaluate the safety and tolerability of the dose of INCB024360 alone and in combination with MK-3475 and include up to 9 subjects (up to 3 subjects for Dose Level 2 in Cohort 1) at the identified dose of INCB024360 for further evaluation. A maximum of 42 subjects will be enrolled in this trial. The final number will depend on empirical safety data and observed dose-limiting toxicities (DLTs) (Note: A total of 15 patients were enrolled in Part A). Cohorts of 3-9 patients will be hospitalized and monitored during the first 1 week of DLT evaluation period for INCB024360 alone + 21-day administered INCB024360 in combination with MK-3475 (Cycle 1 of Cohort 1) or 21-day of DLT evaluation period for INCB024360 in combination with MK-3475 (Cycle 1 of Cohort 2).

There is no data of clinical studies to evaluate the tolerability of INCB024360 administered alone in Japanese patients, so we will enroll the patients as follows (Figure 1);

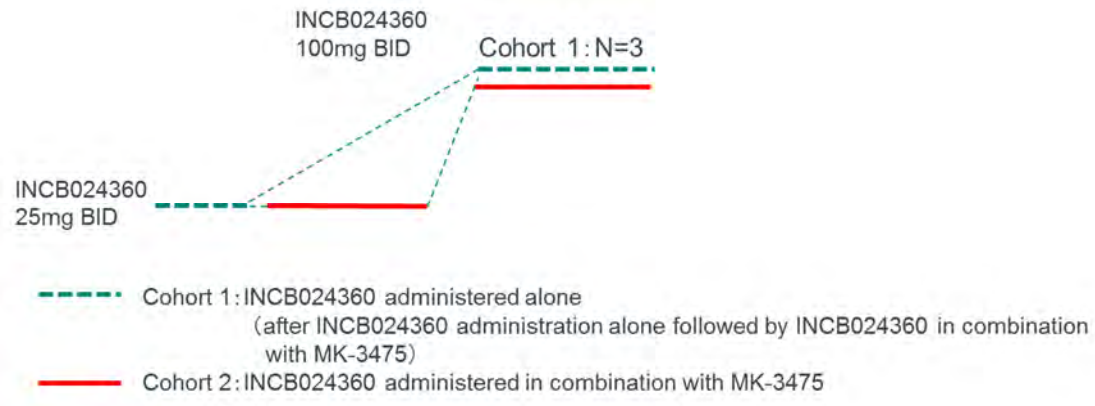

Figure 1 Flow of Patients Enrollment in This Study

1) Three patients will be initially enrolled at Dose Level 1 of Cohort 1, and following those 3 patients, dosing will proceed based on observed DLTs in cohorts of size 3 as appropriate.
2) After the assessment of tolerability of 1), three patients will be initially enrolled at Dose Level 1 of Cohort 2, and following those 3 patients, dosing will proceed based on observed DLTs in cohorts of size 3 as appropriate.
3) After the assessment of tolerability of 2), the administration of Dose Level 2 of Cohort 2 will be started and the assessment of tolerability will be evaluated by enrolling at least 6 patients. At the same timing, three patients will be enrolled at Dose Level 2 of Cohort 1 to evaluate the safety, tolerability and PK of INCB024360 administered alone, and the safety and PK on INCB024360 administered in combination with MK-3475.

In the safety assessments, if 0 of 3, ≤ 1 of 6, or ≤ 3 of 9 patients experience a DLT at the dose level, it will be considered to be tolerated. The definition of DLT specific guidelines and the dose finding rule are outlined in Sections 5.2.1.2.2 and 5.2.1.2.1.

In the first cycle (cycle 1) of cohort 1, INCB024360 will be orally administered alone for 5 days (Day 1-5) followed by 2 days rest period (Day 6-7), and then INCB024360 will be orally administered for 21 days (Day 8-28) in combination with the 200 mg dose of MK-3475 intravenously administered Q3W (Day 8). In the subsequent cycles (Cycle 2 and onwards), INCB024360 BID and MK-3475 Q3W will be administered in 21-day period. In Cohort 2, INCB024360 BID and MK-3475 Q3W will be administered in 21-day period from Cycle 1.

Part B (NSCLC)

NOTE: The DLT evaluation of INCB024360 and MK-3475 in combination with chemotherapy was conducted according to the following as of Amendment 01. As of Amendment 02, INCB024360 is removed from all original treatment cohorts.

INCB024360 and MK-3475 in combination with chemotherapy will be administered in this part.

The investigator will perform screening test after informed consent to confirm that the candidate meet all the criteria determined in the protocol. The investigators will inform the Sponsor of the chemotherapy (Cohort) that Investigators will select prior to treatment

allocation. Following the investigators confirm the eligibility of the patient based on results from the screening test, he/she will assign allocation number to each eligible patient according to order of the registration. 6 advanced NSCLC patients will be enrolled in each cohort.

If the sponsor and DMC determine that 3 more additional patients are needed to evaluate the safety and tolerability, 3 additional patients will be added in the cohorts after the amendment.

- The assessment of tolerability of INCB024360 100 mg BID and MK-3475 200 mg Q3W in combination with cisplatin 75 mg/m^2 Q3W and pemetrexed 500 mg/m^2 Q3W (Non-Squamous). As of Amendment 02, INCB024360 is removed.
- The assessment of tolerability of INCB024360 100 mg BID and MK-3475 200 mg Q3W in combination with carboplatin AUC 5 Q3W and pemetrexed 500 mg/m^2 Q3W (Non-Squamous). As of Amendment 02, INCB024360 is removed.
- The assessment of tolerability of INCB024360 100 mg BID and MK-3475 200 mg Q3W in combination with carboplatin AUC 6 Q3W and paclitaxel 200 mg/m^2 Q3W (Squamous and Non-Squamous). As of Amendment 02, INCB024360 is removed.

Subjects will be treated with INCB024360 and MK-3475 in combination with chemotherapy for 4 cycles, followed by in combination with pemetrexed in cohort 1 and 2.

Cohorts of 6 patients will be hospitalized and monitored during the first 3 week of DLT evaluation period for INCB024360 and MK-3475 in combination with chemotherapy. In the safety assessments, if 0 of 3 or ≤ 2 of 6 patients experience a DLT at the dose level, it will be considered to be tolerated.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

2.2 Trial Diagram

The trial designs as of Amendment 01 are depicted in Figure 2, Figure 3 and Figure 4. The trial designs in Part B as of Amendment 02 are depicted in Figure 5.

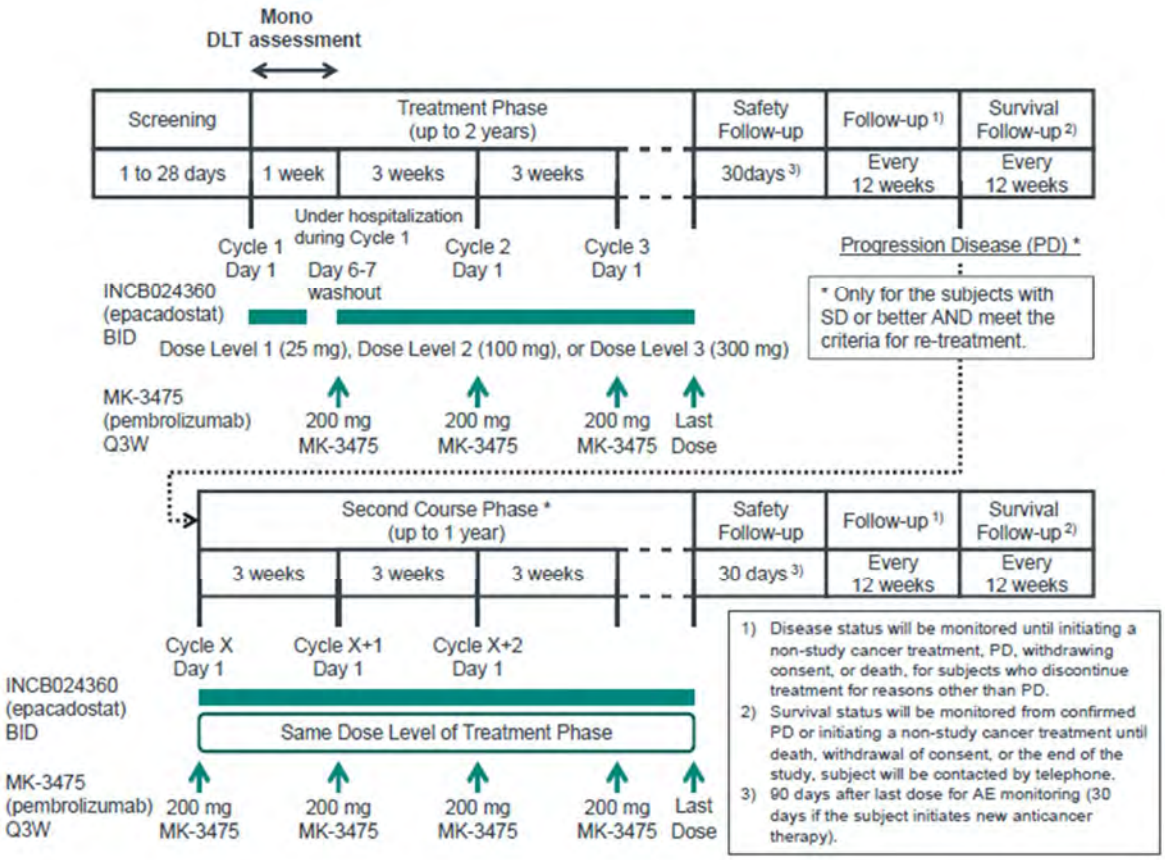

Figure 2 Study Design of the cohort to evaluate the DLT of INCB024360 administered alone (Part A cohort 1)

Retreatment is no longer available with Amendment 02 if they did not already start second course.

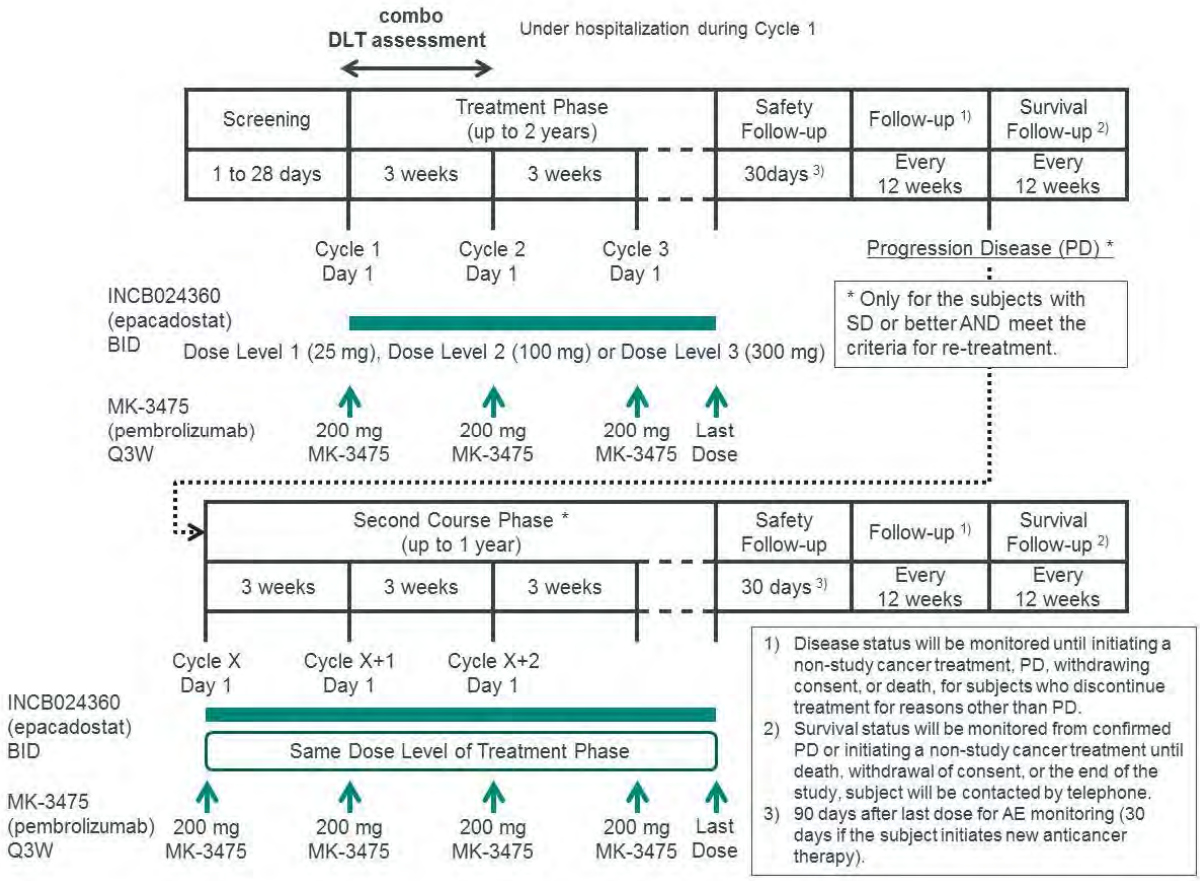

Figure 3 Study Design of the cohort to evaluate the DLT of INCB024360 administered in combination with MK-3475 (Part A cohort 2)

Retreatment is no longer available with Amendment 02 if they did not already start second course.

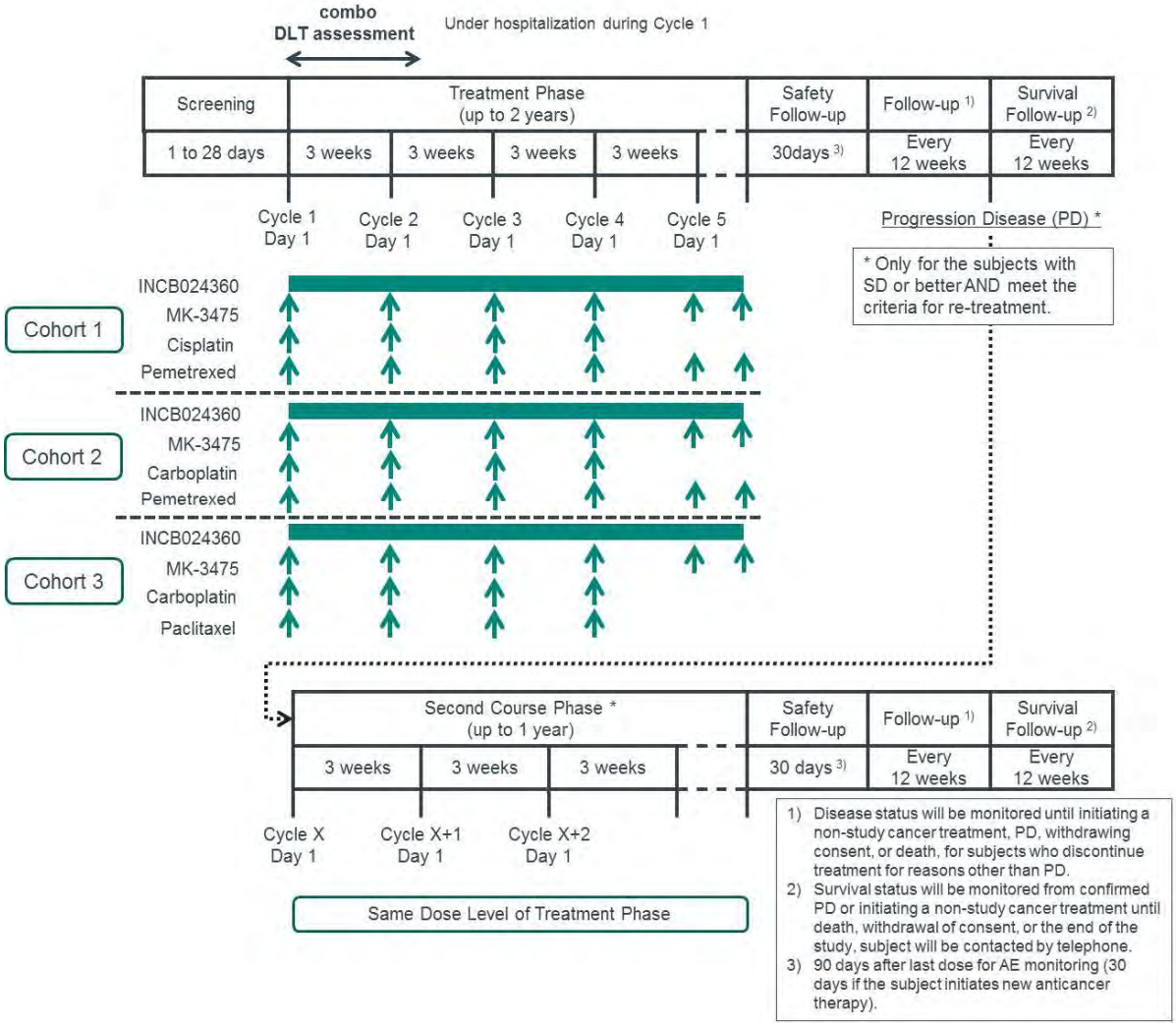

Figure 4 Study Design of the cohort to evaluate the DLT of INCB024360 and MK-3475 administered in combination with chemotherapy (Part B) as of Amendment 01

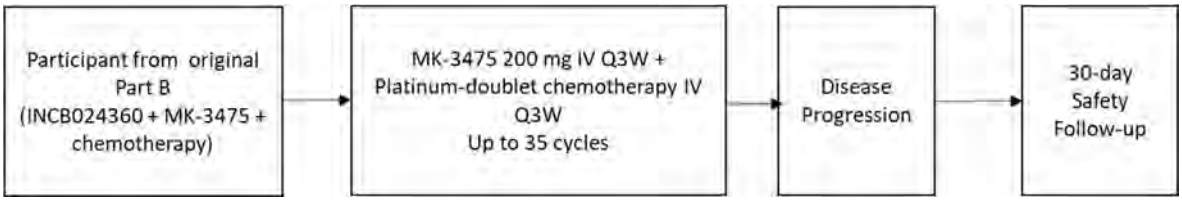

Figure 5 Study Design as of Amendment 02 in Part B

No retreatment will be available.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

Objective: To evaluate the Cohort specific safety and tolerability of INCB024360 administered alone and in combination with MK-3475 (Part A Cohort 1 and 2, respectively), and INCB024360 and MK-3475 in combination with chemotherapy (Part B Chemotherapy Cohort 1, 2 and 3).

3.2 Secondary Objective(s) & Hypothesis(es)

1) **Objective**: To evaluate the pharmacokinetic/pharmacodynamics profiles of INCB024360 alone and in combination with MK-3475 (Part A Cohort 1 and 2, respectively), and INCB024360 and MK-3475 in combination with chemotherapy (Part B Chemotherapy Cohort 1, 2 and 3).

3.3 Exploratory Objectives

1) **Objective**: To evaluate the presence of anti-MK-3475 antibodies when administered concomitantly.
2) **Objective**: To evaluate the anti-tumor activity (ORR, DOR and PFS by RECIST 1.1 and irRECIST/iRECIST as assessed by local site, and OS) of INCB024360 in combination with MK-3475 and INCB024360 and MK-3475 in combination with chemotherapy.
3) **Objective**: To evaluate the correlation between PD-L1 expression levels, indoleamine 2,3-dioxygenase-1 (IDO1) expression, and tumor response when administered concomitantly.
4) **Objective**: To identify molecular (genomic, metabolic and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of MK-3475 and INCB024360.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the respective Investigator's Brochure (IB) for detailed background information on MK-3475 and INCB024360. Refer to the individual package inserts for each component of chemotherapy.

4.1.1 Pharmaceutical and Therapeutic Background

INCB024360 (epacadostat) represents a novel, potent, and selective inhibitor of the enzyme indoleamine 2,3-dioxygenase-1 (IDO1) in both human tumor cells and human dendritic cells (DCs). MK-3475 (pembrolizumab) is a potent and highly selective humanized monoclonal antibody (mAb) of the immunoglobulin IgG4/kappa isotype designed to directly block the interaction between PD-1 (programmed cell death-1) and its ligands PD-L1 and PD-L2. This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression

and ultimately immune rejection. For a thorough discussion of the pharmacology of MK-3475 and INCB024360, refer to the IBs.

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [2]. 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 [3], [4]. Histologic evaluation of many human cancers shows extensive infiltration by inflammatory and immune cells [5], 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 exposes 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.

4.1.1.1 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) [6], [7]. 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 [8], [9]. 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 [10], [11].

Expression has also been shown during thymic development on CD4-CD8- (double negative) T cells as well as subsets of macrophages and dendritic cells [12]. 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 [13], [14], [15], [9]. 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 [9]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant

levels of this T-cell inhibitor. High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types, including renal cell carcinoma [16], pancreatic carcinoma [17], hepatocellular carcinoma [18], and ovarian carcinoma [19]. Furthermore, PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma [20]. 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.

4.1.1.2 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 [21]. 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 (e.g., gut, respiratory tract, placenta, spleen), consistent with a role for regulating tryptophan metabolism in a local microenvironment [22]. Within the immune system, IDO1 activity is specifically induced in cells such as DCs and macrophages at localized sites of inflammation [23].

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 [24]. Both the reduction in local tryptophan levels and the production of tryptophan catabolites that are inhibitory to cell proliferation contribute to the immunosuppressive effects [25]. IDO1 activity also promotes the differentiation of naive T cells to cells with a regulatory phenotype (Treg) [26]. 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 [27], 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 [28]. A critical role for IDO1 in immunomodulation has been confirmed in numerous animal models, including models of allograft tolerance, inflammation, and cancer [22]. While IDO1 inhibition can exacerbate disease in models of autoimmune disorders [22], IDO1 null mice show no evidence of susceptibility to developing spontaneous autoimmunity or alterations in immune system development [24], 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 [29], [30]. In addition, studies with 1-methyl-tryptophan, demonstrate that IDO1 inhibition dramatically increases the efficacy of various chemotherapeutic agents (e.g., platinum compounds, taxane derivatives, cyclophosphamide) without increased toxicity [30]. 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 [31], [32]. 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 [29]. 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 [33], [34], [35], [36], [37]. 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.

4.1.1.3 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 [10], [38]. Nivolumab/MK-3475, a fully human IgG4 antibody blocking PD-1, produced durable overall responses in patients with melanoma, renal cell cancer, and non-small cell lung cancer (NSCLC) [39], [40], [41]. 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 [42].

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 [43], [44]. 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 Phase I/II study of INCB024360 in combination with MK-3475 (INCB24360-202), 60 subjects were enrolled as of the data cutoff (29-October-2015) and were treated with INCB024360 25 mg BID (n=4), 50 mg BID (n=20), 100 mg BID (n=18), and 300 mg BID (n=18) in combination with MK-3475 2 mg/kg or 200 mg IV Q3W. Based on the preliminary, unaudited data as of the data cutoff (29-October-2015), no Grade 4 treatment-related AEs were reported. Three subjects (5%) discontinued for a treatment-related AE:

Grade 3 arthralgia, Grade 3 AST increased, and Grade 2 nervous system disorder. No treatment-related deaths occurred. Treatment-emergent AEs were reported in 44 subjects (73.0%). The most frequently reported AEs (≥10%) were rash (27%) followed by fatigue (23%).

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 various cancers. Refer to Section 4.2.1.1 for the safety and efficacy data from Phase I/II study (INCB 24360-202).

4.1.2 Pre-clinical and Clinical Trials

Refer to the IBs for MK-3475 and INCB024360 for preclinical and clinical study data.

4.1.3 Ongoing Clinical Trials

Refer to the IBs for MK-3475 and INCB024360 for ongoing clinical study data.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Non-clinical data and clinical data obtained with non-Japanese subjects so far supports the clinical development of MK-3475 in Japanese. If the safety profile is acceptable in Japanese subjects, this study will support the regulatory approval of this combination and further development in Japan. The patients with advanced solid tumors and NSCLC will be enrolled into Part A and B respectively.

In an ongoing dose-escalation and expansion Phase 1/2 study of MK-3475 in combination with INCB024360 subjects with Stage IIIB, IV, or recurrent NSCLC, melanoma, transitional cell carcinoma (TCC), renal cell carcinoma (RCC), triple negative breast cancer (TNBC), endometrial adenocarcinoma (EA), or squamous cell carcinoma of the head and neck (SCCHN) are being enrolled in ex-Japan (INCB 24360-202). Subjects previously treated with PD-1 or CTLA-4 targeted therapies were excluded. Safety, tolerability, and investigator-assessed tumor response (RECIST 1.1) were evaluated.

As of 27-Feb-2017, among the 40 evaluable previously-treated participants with NSCLC, the ORR was 35% and DCR was 60%, which includes 2 participants with a CR. PD-L1 TPS test results were available in 28/40 efficacy-evaluable participants. Among the participants treated with the recommended dose of epacadostat 100 mg BID, ORR and DCR for participants with TPS ≥50% and ≤2 prior treatments were 43% (3/7; all PR) and 57% (4/7; 1 SD), respectively; for participants with TPS <50% and ≤2 prior treatments, ORR and DCR were 33% (6/18; 1 CR) and 56% (10/18; 4 SD), respectively. For participants with ≤2 prior treatments whose PD-L1 status was unknown, the ORR and DCR were 45% (5/11, 1 CR) and 73% (3 SD), respectively [45].

In the Phase 2 study KEYNOTE-021 Cohort G, pembrolizumab plus pemetrexed and carboplatin showed statistically significant increases in objective response rate (ORR) and

PFS compared to pemetrexed and carboplatin alone in participants with non-squamous advanced NSCLC, regardless of PD-L1 status. These results established pembrolizumab plus chemotherapy as an efficacious option for first-line (1L) therapy in patients with NSCLC. The data from KEYNOTE-021 Cohort G led to US FDA approval; these findings are being further evaluated in the ongoing Phase 3 studies KEYNOTE-189 (non-squamous) and KEYNOTE-407 (squamous).

KEYNOTE-024 was a multicenter, international, randomized, open-label, controlled study of IV pembrolizumab monotherapy versus the choice of multiple SOC platinum based chemotherapies in participants previously untreated for their Stage IV 1L NSCLC (squamous and non-squamous), whose tumors expressed PD-L1 at TPS ≥50%, and in whom EGFR or ALK-directed therapy is not indicated. During screening, 1653 participants provided evaluable tissue for PD-L1 evaluation with 500 participants yielding a TPS ≥50% (30.2%). First-line treatment with pembrolizumab (n=154) significantly prolonged PFS (HR 0.50; 95% confidence interval (CI): 0.37, 0.68; p<0.001) and OS (HR 0.60; 95% CI: 0.41, 0.89; p = 0.005) compared with SOC chemotherapy (n=151), inclusive of pemetrexed maintenance for participants with non-squamous tumors. In addition, pembrolizumab was associated with a higher ORR, including a higher complete response (CR) rate, as well as a longer DOR as compared to SOC. Pembrolizumab was better tolerated than chemotherapy and AEs were easily managed. The observed safety profile of the pembrolizumab arm was consistent with the safety profile for pembrolizumab established to date. Based on the mechanism of action of pembrolizumab, immune-related AEs (irAEs), including pneumonitis, occurred at a greater frequency with pembrolizumab compared to chemotherapy. Most irAEs were of Grade 1 or 2 severity and none led to death. These data underscore the substantial benefit of pembrolizumab as initial therapy for participants with previously untreated, advanced NSCLC whose tumors express high levels of PD-L1 (TPS ≥50%), in whom EGFR or ALK-directed therapy is not indicated.

4.2.2 Rationale for Dose Selection/Regimen/Modification

4.2.2.1 Justification for Treatment Regimen

The dose selected for the current study was formed on the basis of having a well-tolerated safety profile as monotherapy and in combination with MK-3475, a robust objective response rate, durable disease control rates, as well as providing optimal target inhibition of IDO1 based on nonclinical models. Doses of INCB024360 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 MK-3475, nivolumab, durvalumab and atezolizumab are currently being evaluated in several ongoing Phase II studies. Doses of MK-3475 2 mg/kg and 200 mg Q3W flat dose have been studied in the ongoing Phase I/II study of MK-3475 in combination with INCB024360. Reductions in tumor burden were seen in 15 of 19 evaluable subjects across doses of 25 mg BID to 100 mg BID in combination with MK-3475 2 mg/kg and 200 mg Q3W flat dosing. Objective responses were observed across all dose levels tested and this combination has been well tolerated. The starting dose of INCB024360 when evaluating the tolerability of INCB024360 in combination with MK-3475 is 25 mg BID in which no DLT was observed when administered in combination with MK-3475 in global phase 1/2 study (INCB24360-202 study). Before the evaluation of tolerability of INCB024360 in combination with

MK-3475, the tolerability of INCB024360 administered alone will be evaluated in the same dose (25 mg BID).

Based on a PK-pharmacodynamic model for epacadostat, the Cavg for nearly all participants exceeded the IC50, the range of active drug exposure seen in nonclinical models in the first-in-human study, INCB 24360-101, a detailed review of the effect of dose and exposure on the pharmacodynamics effect of epacadostat on the tryptophan pathway was performed. Using an ex vivo assay optimized for determining the inhibition of the metabolism of tryptophan to kynurenine by IDO1, epacadostat treatment produced significant dose-dependent reductions in plasma kynurenine levels and in the plasma kynurenine/tryptophan ratio at all doses and in all patients. Near maximal changes were observed at doses of ≥100 mg BID with >80% to 90% inhibition of IDO1 achieved throughout the dosing period [46].

This study is a first clinical trial for INCB024360 in Japan, so PK and preliminary safety will be assessed as monotherapy during the first week of Cycle 1. INCB024360 will be administered alone in the initial 5 days (Day 1-5 of Cycle 1), in order to reach the steady-state of INCB024360 to assess PK parameters. This will be followed by a 2 days washout period (Day 6-7 of Cycle 1) (calculated based on 5-times the longest $t_{1/2}$ of 6 hours of INCB024360 at a dose of 300 mg BID) so that trough levels will not be detectable for the PK assessments of combination part with MK-3475 starting from Day 8 of Cycle 1. The 7-day duration of INCB024360 monotherapy would be appropriate to evaluate safety and pharmacokinetics, considering the benefit for subjects as INCB024360 monotherapy was likely to be less efficacious from the available clinical data.

4.2.2.2 Rationale for a Fixed Dose of MK-3475

The planned dose of pembrolizumab for this trial is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from eight randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every two weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically based pharmacokinetic [PBPK] analysis) at 200 mg Q3W

Among the eight randomized dose-comparison studies, a total of 2262 subjects were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W vs. 10 mg/kg Q2W (KN001 B2, KN001 D, KN002, KN010 and KN021), and three studies compared 10 mg/kg Q3W vs. 10 mg/kg Q2W (KN001 B3, KN001 F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5 to 7.5 fold difference in exposure.

The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-/exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Secondly, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other subject covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizmab protocols.

Furthermore, PK of MK-3475 in Japanese patients are similar to that in non-Japanese patients. Thus the 200 mg Q3W fixed dose regimen is considered an appropriate fixed dose for other solid tumor indications as well.

4.2.2.3 Rationale for Chemotherapy Dosing Regimens

The dosing regimens of chemotherapy represent the SOC per the approved product labels. Chemotherapy may be reduced, interrupted, or discontinued at the Investigator’s discretion using the approved product labels and local regulations.

4.2.3 Rationale for Endpoints

4.2.3.1 Safety Endpoints

NOTE: As of Amendment 02, INCB024360 is stopped from Part B.

The primary safety objective of this study is to characterize the safety and tolerability of INCB024360 alone and in combination with MK-3475 in subjects with advanced solid tumors. In addition to general laboratory tests, immune laboratory test will be evaluated considering the mode of action of MK-3475. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received INCB024360 alone and in combination with MK-3475, including serious adverse events (SAEs).

Safety will be assessed by reported adverse experiences using CTCAE, Version 4.0. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. Since pneumonitis has been previously

reported in clinical studies of anti-PD-1 antibodies including MK-3475, pulmonary radiographic changes and its features will be evaluated by investigators and an independent radiologist from a potential risk of pneumonitis.

4.2.3.2 Efficacy Endpoints

NOTE: As of Amendment 02, data for efficacy endpoints, including disease assessments based on imaging, are no longer being collected. Imaging will be performed per local standard of care and will be assessed by the investigator/site radiologist. Also, the use of irRECIST and iRECIST is discontinued. The following irRECIST and iRECIST language is no longer applicable. Participants with radiographic disease progression as determined by RECIST 1.1 by investigator assessment will discontinue from study treatment; no confirmatory scans are required. However, if the participant is achieving a clinically meaningful benefit, an exception to continue with study treatment without epacadostat may be considered following consultation with the MSD.

Efficacy will be evaluated as an exploratory objective for ORR, DOR, PFS, and OS per RECIST 1.1 by the local site. RECIST 1.1 will also be used by the local site to determine eligibility and irRECIST/iRECIST will be used to make treatment decisions.

Modified RECIST for Immune related RECIST (irRECIST)

RECIST 1.1 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 [47]. Standard RECIST may not provide an accurate response assessment of immunotherapeutic agents such as MK-3475. Therefore, RECIST 1.1 will be used with the adaptations, in which a confirmation assessment of disease progression must be obtained at least 4 weeks after the initial disease assessment indicating progressive disease.

Modified RECIST for Immune-based Therapeutics (iRECIST)

RECIST 1.1 will be adapted to account for the unique tumor response seen following treatment with pembrolizumab. Immunotherapeutic agents such as pembrolizumab may produce antitumorveffects 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 participants treated with pembrolizumab may manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

Thus, standard RECIST 1.1 may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Based on an analysis of participants with melanoma enrolled in KEYNOTE-001, 7% of evaluable participants experienced delayed or early tumor pseudo-progression. Of note, participants who had PD by RECIST 1.1 but not by the immune-related response criteria [48] had longer OS than participants with PD by both criteria [49]. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of participants. These findings support the need to

apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical responses in immunotherapy and enables treatment beyond initial radiographic progression, if the participant is clinically stable.

iRECIST assessment has been developed and published by the RECIST Working Group, with input from leading experts from industry and academia, along with participation from the US Food and Drug Administration and the European Medicines Agency [50]. The unidimensional measurement of target lesions, qualitative assessment of non-target lesions, and response categories are identical to RECIST 1.1, until progression is seen by RECIST 1.1. However, if a participant is clinically stable, additional imaging may be performed to confirm radiographic progression. iRECIST will be used by site investigators to assess tumor response and progression, and make treatment decisions, as well as for exploratory efficacy analyses where specified.

4.2.3.3 Pharmacokinetic/Pharmacodynamic/Immunogenicity Endpoints

Blood samples will be obtained to measure pharmacokinetics of MK-3475 and INCB024360. Plasma will be collected to assess the effects on kynurenine and tryptopohan. The pharmacokinetic parameters of INCB024360 will be calculated by non-compartmental analysis. Subsequently, the concentration-time data to be obtained from MK-3475 serum assays will be used for a population PK analysis if needed. In addition, an exploratory investigation on the formation of anti-MK-3475 antibody (ADA) and its effect on the pharmacokinetics of MK-3475 will also be evaluated for interpretation of immunogenicity results considering MK-3475 is a humanized monoclonal anti-PD-1 antibody. Pharmacokinetics of INCB024360 will be compared between INCB024360 plus MK-3475 dosing and INCB024360 alone dosing, and the impact of MK-3475 dosing on the pharmacokinetics of INCB024360 will be assessed. The sampling time points for MK-3475 PK, PD, and ADA have been determined taking the long half-life (two to three weeks) of MK-3475 into account.

4.2.3.4 Planned Exploratory Biomarker Research

Tumor biopsy analyses to evaluate IDO1 expression (+/-), PD-L1 expression (positive versus negative/indeterminate) in tumor tissue and immune cell infiltrate at baseline and correlate expression with response, PFS and/or OS. The expression of exploratory histological biomarkers will also be assessed.

Cancer immunotherapies represent an important and novel class of antitumor agents. However, the mechanism of action of these exciting new therapies is not completely understood and much remains to be learned regarding how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer immunotherapy, as well as determinants of AEs in the course of our clinical studies. These efforts will attempt to identify predictive biomarkers and generate information that will better guide single-agent and combination therapy with immuno-oncology drugs.

To identify biomarkers, biospecimens (ie, blood components, tumor material) will be collected to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules. Whole blood, serum, and tumor tissue will be collected for

assessments as outlined in section 6.0 and correlated with clinical outcomes as appropriate. Details regarding sample processing, handling, and shipping will be provided in the Laboratory Manual. Investigations may include but are not limited to:

Germline genetic analyses from blood

This research will evaluate whether genetic variation within a clinical study population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome in order to interpret tumor-specific DNA mutations. DNA in blood may also be used to examine the T-cell receptor profile in blood to compare with the profile in the tumor. Microsatellite instability (MSI) may also be evaluated, as this is an important biomarker for some cancers.

Genetic (DNA) analyses from tumor and blood

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (ie, mutations, methylation status, microsatellite instability). Key molecular changes of interest to immune-oncology drug development include the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Increased mutational burden (sometimes referred to as a 'hyper-mutated' state) may generate neo-antigen presentation in the tumor microenvironment. To conduct the first type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome-wide approaches may be used for this effort. Note that in order to understand tumor-specific mutations, it is necessary to compare the tumor genome with the germline genome. Microsatellite instability may also be evaluated as this is an important biomarker for some cancers. If sufficient sample quantity is available, to conduct an assessment of T-cell clonality in tumor and in circulating T lymphocytes, a DNA sequencing approach may be undertaken with a specific focus on the analysis of diversity versus the clonality of the T-cell receptor repertoire.

Tumor RNA analyses

Both genome-wide and targeted messenger RNA (mRNA) expression profiling and sequencing in tumor tissue may be performed to define gene expression signatures that correlate to clinical response to treatment with pembrolizumab or the combination of pembrolizumab and epacadostat. Pembrolizumab induces a response in tumors that is characterized by an inflamed/immune phenotype. Specific immune-related gene sets (ie, those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes related to the immune system may also be evaluated (eg, IL-10). MicroRNA profiling may also be pursued.

Proteomics and immunohistochemistry (IHC) using blood or tumor

Tumor and blood samples from this study may undergo proteomic analyses (eg, PD-L1 IHC). PD-L1 protein level in tumor sections, assessed by IHC, has been shown to correlate with response to pembrolizumab in patients with NSCLC, and an in vitro diagnostic device has been developed for use with pembrolizumab in NSCLC. Preliminary data indicates that this association may also be true in additional cancer types (ie, triple negative breast cancer, head and neck, and gastric).

Additional tumor or blood-derived proteins may also correlate with response to the combination of pembrolizumab and epacadostat. Therefore, tumor tissue may be subjected to proteomic analyses using a variety of platforms that could include but are not limited to immunoassays and liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for the study treatments. Similar to PD-L1 expression, tumor biopsy materials may be used to assess tumor IDO1 protein or mRNA expression. Tumor samples may be assessed for the extent and location of immune infiltrate, which may include an analysis of the number and the location of CD8+ and FOXP3+ T-lymphocytes, macrophages, and neutrophils.

Other blood-derived biomarkers

In addition to expression on the tumor tissue, PD-L1 and other tumor and immune response derived proteins can be shed from tumor and released into the blood. Correlation of expression with response to pembrolizumab or the combination of pembrolizumab and epacadostat may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor biomarkers. Serum analytes may include cytokines and other markers of inflammation and immune status, tumor markers, and markers of metabolism and nutritional status. If serum samples are depleted, then additional markers may be evaluated at the discretion of the Sponsor or MSD using remaining PK plasma samples. This research would serve to develop such assays for future clinical use.

4.3 Benefit/Risk

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

4.3.1 Benefit/Risk from MK-3475

The safety of MK-3475 was investigated in three controlled, randomized studies (KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010) for the treatment of unresectable or metastatic melanoma or metastatic NSCLC and in an uncontrolled, open-label study (KEYNOTE-001) for the treatment of unresectable or metastatic melanoma or metastatic NSCLC. Overall, 1567 patients with melanoma (699 previously treated with ipilimumab and 868 naïve to ipilimumab) and 1232 patients with NSCLC were treated. Safety is described for the pooled population of 2799 patients (studied across three doses; 2 mg/kg every 3 weeks and 10 mg/kg every 2 or 3 weeks). The median treatment duration was 4.2 months (range 1 day to 30.4 months) including 1153 patients treated for greater than or equal to six months and 600 patients treated for greater than or equal to one year. MK-3475 was discontinued for treatment-related adverse reactions in 5% of patients. Treatment-related serious adverse events (SAEs) reported up to 90 days after the last dose occurred in 10% of patients receiving MK-3475. Of these treatment-related SAEs, the most common were pneumonitis, colitis, diarrhea, and pyrexia. Immune-mediated adverse reactions are presented based on 2799 patients with melanoma and NSCLC. The safety profile was generally similar for patients with melanoma and NSCLC. The following events were recognized as important identified risks for MK-3475: immune-mediated pneumonitis, colitis, hepatitis, nephritis, hypophysitis (including hypopituitarism and secondary adrenal insufficiency), thyroid disorders (hypothyroidism, hyperthyroidism), Type I diabetes mellitus,

uveitis, myositis, Guillain-Barré syndrome, pancreatitis, severe skin reactions, and infusion-related reactions, and myasthenic syndrome as a potential important risk.

4.3.2 Benefit/Risk from INCB024360

In 28-day toxicology studies, Cmax values have exceeded the IC50 for the IDO1 enzyme in cells (7 nM) by up to 370-fold, and the IC50 for the vasopressin 1a receptor by up to 40-fold (130-fold in single dose studies) in the absence of any toxicity, so the risk of unintended pharmacological activity is expected to be low. In the Phase I clinical study in subjects with refractory solid tumors (INCB 24360-101) doses up to 700 mg BID were given without an MTD determined. Two DLTs occurred; 1 DLT of radiation pneumonitis at the 300 mg BID dose level and 1 DLT of fatigue at the 400 mg BID dose level. INCB024360 was well tolerated.

Despite the substantial improvement in PFS and OS observed with pembrolizumab as compared to SOC platinum doublet chemotherapy in KEYNOTE-024, and the significant increases in ORR and PFS showed with pembrolizumab plus pemetrexed and carboplatin as compared to pemetrexed and carboplatin alone in KEYNOTE-021 Cohort G, there remains a need to investigate new treatments which offer the prospect of added benefit for this patient population. Details regarding specific benefits and risks of pembrolizumab treatment for participants in this clinical study may be found in the Investigator's Brochure [IB Edition 13 2017] and Informed Consent Form (ICF).

Given initial data observed in KEYNOTE-037 suggesting improved efficacy of pembrolizumab in combination with epacadostat and an overall safety profile comparable to anti-PD-1 monotherapy, this combination represents a rational and promising first-line therapeutic option in patients with metastatic NSCLC.

Epacadostat, as a single therapy, has a predictable PK profile and acceptable safety profile, but limited single-agent efficacy in participants with solid tumors in the Phase 1 study of 52 participants (INCB 24360-101). The data showing the limited efficacy in solid tumors support that an epacadostat monotherapy arm is not warranted.

An uncommon risk of IDO1 inhibition is an increase in serotonin levels that could precipitate a cluster of AEs termed serotonin syndrome (SS) when administered alone or in combination with other serotonergic agents. This rare syndrome has been associated with some monoamine oxidase inhibitors (MAOIs) and combinations of serotonergic drugs [51]. The clinical manifestations of SS range from barely perceptible to lethal; onset is rapid (within 12 hours of drug[s] administration). Preclinical data suggest that SS is unlikely following treatment with either epacadostat alone or in combination with MAOIs such as linezolid [52]. As of 27-Feb-2017, 2 of 958 participants treated across the epacadostat program have reported SS or symptoms of SS; both episodes were mild in severity and resolved.

Although the incidence of SS or symptoms of SS is uncommon, use of MAOIs are prohibited during the study, and all participants will be assessed for SS symptoms at appropriate time points after dosing as of amendment 01. Participants will be provided with an informative leaflet describing the signs and symptoms of SS along with instructions to seek immediate medical care if any of these signs or symptoms are observed.

Additional details regarding specific benefits and risks of epacadostat for participants in this clinical study may be found in the accompanying Investigator's Brochure [EPACADOSTAT (INCB024360) – Investigators Brochure. 2017] and ICF.

4.3.3 Benefit/Risk for the Combination of MK-3475 and INCB024360

NOTE: MK-3475-654 is Phase 2 Study of Pembrolizumab ± Epacadostat in PD-L1 High Metastatic NSCLC. MK-3475-715 is Phase 2 Study of Pembrolizumab/Epacadostat/Chemotherapy in Metastatic NSCLC. The recent results of the final efficacy analysis of these studies indicated the below;
In KEYNOTE-654/ECHO-305 phase II study, the combination of epacadostat and pembrolizumab did not meet the pre-specified primary endpoint of improvement in the confirmed ORR compared with pembrolizumab alone based on blinded independent central assessment.
In KEYNOTE-715/ECHO-306 phase II study, epacadostat in combination with pembrolizumab and platinum-based chemotherapy also did not meet the pre-specified primary endpoint of improvement in the confirmed ORR compared with pembrolizumab combined with chemotherapy based on blinded independent central assessment
Subsequently, the participants' treatment was unblinded, epacadostat was stopped, and the protocols were amended accordingly in those studies.
Thus, as of Amendment 02 in KN434, epacadostat/ INCB024360 has beenstopped from Part B.

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

In the ongoing Phase I/II study (INCB 24360-202/KEYNOTE-037), combining MK-3475 and INCB024360, the safety, efficacy, and tolerability of the combinations of epacadostat 25 mg BID, 50 mg BID, and 100 mg BID in combination with intravenous (IV) pembrolizumab 2 mg/kg or 200 mg Q3W were evaluated in participants including, but not limited to, Stage 3B, IV or recurrent NSCLC, melanoma, urothelial carcinoma (UC), renal cell carcinoma (RCC), ovarian cancer, triple negative breast cancer (TNBC), squamous cell carcinoma of the head and neck (SCCHN), microsatellite-instability (MSI), colorectal cancer (CRC) and diffuse large B -cell lymphoma (DLBCL). In the Phase 1 dose-escalation part, oral epacadostat 25 mg BID, 50 mg BID and 100 mg BID with Pembrolizumab 2 mg/kg IV Q3W, and epacadostat 300 mg BID with pembrolizumab 200 mg IV Q3W was evaluated. Based on the risk for early progression during dose interruptions and dose reductions associated with INCB024360 300 mg BID in combination with MK-3475 200 mg IV Q3 weeks, and a PK-pharmacodynamic model for epacadostat (Refer to section 4.2.2.1, Justification of Treatment Regimen), epacadostat 100 mg BID in combination with pembrolizumab 200 mg IV Q3W was selected as the dose for use in the Phase 2 portion of INCB 24360-202/KEYNOTE-037 and planned phase 3 studies.

As of 27-Feb-2017, a total of 294 participants were enrolled in Phase 2 (pembrolizumab 200 mg IV Q3W plus epacadostat 100 mg BID oral) and received ≥ 1 dose of epacadostat and pembrolizumab. Preliminary data show that the most common (≥10%) all-grade treatment-

related adverse events were fatigue, rash, nausea, and pruritus. Treatment-related AEs ≥Grade 3 were observed in 18% (most common: lipase increased [4%] and rash [3%]). There was one treatment- related death due to respiratory failure which was secondary to aspiration pneumonia [53].

As of 27-Feb-2017, among the 40 evaluable previously-treated participants with NSCLC, the ORR was 35% and DCR was 63%, which includes 2 participants with a CR. For the 36 participants evaluable and with 0–2 prior lines of treatment, ORR was 39% (2 CR, 12 PR) and DCR was 64% (9 SD). Among these 36 participants treated with the recommended dose of epacadostat 100 mg BID, ORR and DCR for participants with TPS ≥50% and ≤2 prior treatments were 43% (3/7; all PR) and 57% (4/7; 1 SD), respectively; for participants with TPS <50% and ≤2 prior treatments, ORR and DCR were 33% (6/18; 1 CR) and 56% (10/18; 4 SD), respectively. The remaining 1 CR and 4 PRs were observed among 11/36 patients with unknown TPS [54].

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying IB and Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with advanced solid tumor at least 20 years of age will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Be willing and able to provide written informed consent for the trial.
2. Be ≥ 20 years of age on day of signing informed consent.
3. Meet the following corresponding requirements for the part of the study they will enroll into;

   Part A

   Have a histologically-confirmed metastatic or locally advanced solid tumor that has failed to respond to standard therapy, progressed despite standard therapy, or for which standard therapy does not exist.

   Part B

   Subjects must have a histologically-confirmed or cytologically confirmed diagnosis of NSCLC, for stage IIIB/IV.

   - In cohort 1 and 2, has a histological or cytological diagnosis of non-squamous cancer.
   - Subject must be naïve to systemic therapy.

- Have confirmation that EGFR or ALK-directed therapy is not indicated (documentation of absence of tumor activating EGFR mutations AND absence of ALK and ROS1 gene rearrangements).

  a. If participant's tumor is known to have a predominantly squamous histology, molecular testing for EGFR mutation and ALK and ROS1 translocations will not be required, as this is not part of current diagnostic guidelines.

- Subject who had disease progression >6 months after completing adjuvant therapy for stage I-IIIA disease are eligible, as long as no systemic therapy was given for the recurrent disease.

4. Have the presence of at least one measurable lesion by CT or MRI per RECIST 1.1 criteria as determined by the local site investigator/radiology assessment.

   Note: Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

5. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Status (Section 12.2).

6. Have an anticipated life expectancy of at least 3 months.

7. Have laboratory and medical history parameters within Protocol-defined range. The screening laboratory tests below must be ≤ 10 days before treatment initiation.

   a. Absolute neutrophil count ≥ 1,500/mcL (without supportive care)

   b. Platelets ≥ 100,000/mcL

   c. Hemoglobin ≥9 g/dL or ≥5.6 mmol/L (without transfusions)

   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. ≤1.5 ×ULN **OR** direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN. If there is no institutional ULN, then direct bilirubin must be <40% of total bilirubin to be eligible. Note: In no case can the total bilirubin exceed 3 x ULN.

   f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN.

   g. International normalized ratio (INR) or prothrombin time (PT) and Activated partial thromboplastin time (aPTT) ≤1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants.

8. In Part A, Have provided tissue for PD-L1/IDO1 expression evaluation from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated.

Note: Subjects will be eligible to participate regardless of the level of PD-L1/IDO1 expression.

Note: Submit an evaluable sample for analysis. If submitting unstained cut slides, freshly cut slides should be submitted to the testing laboratory within 14 days from when the slides are cut. See Section 7.1.2.9 in protocol for an explanation.

Note: In Part B, the submission of tissue for PD-L1/IDO1 expression evaluation is optional.

9. Female subjects of childbearing potential* must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required

   *Subjects of child bearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

10. Female subjects of childbearing potential* must be willing to take appropriate precautions to avoid becoming pregnant as outlined in Section 5.7.2 – Contraception, for the course of the study through 120 days after the last dose of study medication.

11. Male subjects of childbearing potential must agree to take appropriate precautions to avoid fathering a child as outlined in Section 5.7.2 Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) agents (including ipilimumab or any other antibody/drug specifically targeting T-cell co-stimulation or checkpoint pathways), or IDO1 inhibitor.

2. Is currently participating or has participated in a study with an investigational compound or device within 4 weeks, or 5X half-life of the investigational compound, whichever is longer, of initial dosing on this study.

3. In Part A, Has had chemotherapy, targeted small molecule therapy, radiotherapy, major surgery, or biological cancer therapy (including monoclonal antibodies) within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to the first dose of trial treatment, or who has not recovered (≤ Grade 1 or baseline) from adverse events due to a previously administered.

   Note: Subjects with ≤ Grade 2 neuropathy or alopecia are an exception to this criterion and may qualify for the study.

   Note: If subject received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention prior to starting therapy.

   Note: Subject who received denosumab can be included at the discretion of the Investigator.

4. In Part B, Has received radiotherapy within 7 days of the first dose of trial treatment or radiation therapy to the lung that is > 30 Gy within 6 months of the first dose of trial treatment.
5. Is expected to require any other form of systemic or localized anti-neoplastic therapy while in study.
6. Has known active central nervous system (CNS) mets and/or carcinomatous meningitis.

   Note: Subjects with previously treated brain metastases and clinically stable CNS mets are allowed to participate (clinically stabile is defined as a period (at least 4 weeks prior to the first dose of trial treatment) in which (1) there is no evidence of new or enlarging CNS mets by MRI, (2) the subject is off steroids for CNS mets at least two weeks prior to the first dose of trial treatment, and (3) any neurologic symptoms have returned to baseline).
7. Patient has symptomatic ascites or pleural effusion.
   Note: A patient who is clinically stable following treatment for these conditions is eligible.
8. Has an active autoimmune disease that has required systemic treatment (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Note: Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
9. Is receiving systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 1 week prior to the first dose of trial treatment.
10. Has an active infection requiring systemic therapy.
11. Has history of (non-infectious) pneumonitis that required systemic steroids or current pneumonitis/interstitial lung disease.
12. Has received a live vaccine within 4 weeks prior to the first dose of trial treatment (refer to Section 5.5.3 for further details).
13. Has a known hypersensitivity to the components of the trial treatment or another monoclonal antibody.
14. In Part B, has a known sensitivity to any component of cisplatin, carboplatin, paclitaxel or pemetrexed.
15. In Part B, is on chronic systemic steroids. Patients with asthma that require intermittent use of bronchodilators, inhaled steroids, or local steroid injections would not be excluded from the study.
16. In Part B cohort 1 and 2, is unable to interrupt aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs), other than an aspirin dose ≤ 1.3 g per day, for a 5-day period (8-day period for long-acting agents, such as piroxicam).

17. In Part B cohort 1 and 2, is unable or unwilling to take folic acid or vitamin B_{12} supplementation.
18. Is known to be Human Immunodeficiency Virus (HIV)-positive (HIV 1/2 antibodies).
19. Has known history of or is positive for active Hepatitis B (HBsAg reactive) or has active Hepatitis C (HCV RNA). Note: Testing must be performed to determine eligibility.
    a. HBV DNA must be undetectable and HBsAg negative at screening visit.
    b. Hepatitis C antibody testing is allowed for screening purposes in countries where HCV RNA is not part of SOC. In these cases, HCV antibody positive participants will be excluded.
    c. Participants who have had definitive treatment for HCV are permitted if HCV RNA is undetectable at screening.
20. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
21. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit (Visit 1) through 120 days after the last dose of trial treatment.

    Subjects who stop breast-feeding prior to initiation of trial treatment and not expecting to resume of breast-feeding will not be excluded from the study.
22. Has received monoamine oxidase inhibitors (MAOIs) within the 3 weeks before the first dose of trial treatment.
23. Anticipates receiving any melatonin supplement, any UGT1A9 inhibitor, or any of the prohibited medications during the current trial (refer to Section 5.5.3 for further details).
24. Has any history of Serotonin Syndrome after receiving serotonergic drugs.
25. Has presence of a gastrointestinal condition that may affect drug absorption.
26. Has a history or presence of an abnormal electrocardiogram (ECG) that, in the investigator's opinion, is clinically meaningful.

    Note: Screening QTc interval ≥ 480 msec is excluded (corrected by Fredericia or Bazett formula). In the event that a single QTc is ≥ 480 milliseconds, the subject may enroll if the average QTc for the 3 ECGs is < 480 milliseconds.
27. Has a history or current evidence of any condition, therapy, or lab 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.

5.2 Trial Treatment(s)

The treatments to be used in this trial are outlined below in Table 1.

Table 1 Trial Treatments

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Part A					
INCB024360	100 mg	BID	Oral	Daily of each cycle‡ for up to 35 times of administered MK-3475 (approximately 2 years)	Experimental
MK-3475	200 mg	Every 3 weeks (Q3W)	IV infusion	Cohort 1: Day 8 of Cycle 1 and Day 1 of each subsequent cycle Cohort 2: Day 1 of each cycle for up to 35 infusions (approximately 2 years)	Experimental
Part B*					
MK-3475	200 mg	Q3W	IV infusion	Day 1 of each cycle ‡ for up to 35 infusions (approximately 2 years)	Experimental
Cisplatin	75 mg/m^2	Q3W	IV infusion†	Day 1 of each cycle Up to 4 cycle	combination therapy
Pemetrexed	500 mg/m^2	Q3W	IV infusion†	Day 1 of each cycle	combination therapy
Carboplatin	(Cohort 2) AUC 5 (Cohort 3) AUC 6	Q3W	IV infusion†	Day 1 of each cycle Up to 4 cycle	combination therapy
Paclitaxel	200 mg/m^2	Q3W	IV infusion†	Day 1 of each cycle Up to 4 cycle	combination therapy

Note: please see the allowed dose modification in Table 5.
* In Part B, chemotherapy will be administered for 4 cycles. Pemetrexed may continue as maintenance therapy after these 4 cycles until disease progression.
† Infusion of combination regimens and pre-medications will follow local institutional practice.
‡ Pembrolizumab to be administered prior to chemotherapy.

Trial treatment should begin on the day of allocation or as close as possible to the date on the day of allocation.

MK-3475 and INCB024360 indicated in Table 1 will be provided by the Sponsor.

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 trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each subject.

5.2.1.2 Dose Modification (Escalation/Titration/Other)

5.2.1.2.1 Tolerability Evaluation Rules

NOTE: The DLT evaluation of INCB024360 in combination with MK-3475 (Part A) and INCB024360 and MK-3475 in combination with chemotherapy (Part B) were conducted according to the following as of Amendment 01. As of Amendment 02, INCB024360 is stopped from Part B.

Part A

DLTs observed during the DLT evaluation period [the initial 7-day (cohort 1) or 21-day (cohort 2) of Cycle 1] will be used to determine escalation to the next dose level and the tolerability of the dose level using a modified Toxicity Probability Interval (TPI) method [1] design (Target Toxicity Rate = approximately 16.7%). The dose escalation/tolerability evaluation rules are as follows:

mTPI method:

- An initial cohort of 3 subjects is enrolled.
    - If 0/3 subjects develops a DLT, the dose level will be considered to be lower than tolerated dose, and escalation to the next dose will occur (do not escalate from Dose Level 2).
    - If 1/3 subjects develops a DLT, another 3 subjects will be enrolled at this dose level.
        - If 0 of the 3 new subjects develops a DLT (for a total of 1/6 subjects with a DLT at this dose level), the dose level will be considered to be tolerated dose.
        - If 1 of the 3 new subjects develops a DLT (for a total of 2/6 subjects with a DLT at this dose level), another 3 subjects will be enrolled at this dose level.
            - If ≤1 of the 3 new subjects develops a DLT (for a total of ≤3/9 subjects with a DLT at this dose level), the dose level will be considered to be tolerated dose.
            - If ≥2 of the 3 new subjects develop DLTs (for a total of ≥4/9 subjects with a DLT at this dose level), the dose level will be determined as not-tolerated, and de-escalate to the next lower dose unless the next lower dose level treated 9 subjects (do not de-escalate from Dose Level 1).
        - If ≥2 of the 3 new subjects develop DLTs (for a total of ≥3/6 subjects with a DLT at this dose level), the dose level will be determined as not-tolerated, and de-escalate to the next lower dose unless the next lower dose level treated 9 subjects (do not de-escalate from Dose Level 1).

- If ≥2/3 subjects develop DLTs, the dose level will be determined as not-tolerated, and de-escalate to the next lower dose unless the next lower dose level treated 9 subjects (do not de-escalate from Dose Level 1).

Table 2 Dose Evaluation Rules in Part A

		Number of subjects treated at current dose		
		3	6	9
Number of toxicities	0	E	E	E
	1	S	S	S
	2	DU	S	S
	3	DU	DU	S
	4		DU	DU
	5		DU	DU
	6		DU	DU
E = Evaluable S= Stay at the same dose DU = The current dose is unacceptably toxic, no more patients to be treated at this dose				

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 non-evaluable for DLTs. When the tolerability of INCB024360 25 mg BID and/or 100 mg BID in combination with MK-3475 200 mg Q3W has been identified, additional subjects will be enrolled unless the number of tolerability identified Dose Level is less than 6 subjects. Subjects will continue on the initial dose provided during Cycle 1 through all subsequent cycles even if it is lower than the tolerated dose. The Sponsor will decide dose escalation considering all the safety information including adverse events occurred in a subject being non-evaluable for DLTs.

During the study, dose interruptions and/or dose decreases may be implemented based on toxicity as described in Section 5.2.1.2.3. However, dose adjustments should not be made during the DLT observation period without discussion with the Sponsor. Intra-subject dose escalation is not permitted.

Part B

DLTs observed during the DLT evaluation period (21-day of Cycle 1) will be used to determine the tolerability of the dose level using Toxicity Profile Interval (TPI) [1] design (Target Toxicity Rate = approximately 30.0%). The tolerability evaluation rules are as follows:

- 6 subjects are enrolled into each cohort based on TPI design in the combination regimen; (respectively parallel enrollment is allowed).
  - If 0/3 ≤2/6 subjects develop a DLT at the combination regimen, then it is considered to be tolerated.
  - If ≥3/6 subjects develop a DLT, the regimen will be considered to be not tolerated.

Table 3 Dose Evaluation Rules in Part B

		Number of subjects treated at current dose	
		3	6
Number of toxicities	0	E	E
	1	S	E
	2	D	S
	3	DU	D
	4		DU
	5		DU
	6		DU
E = Evaluable S= Stay at the same dose D=De-escalate to the previous lower dose DU = The current dose is unacceptably toxic, no more patients to be treated at this dose			

The subject that cannot be treated with more than 90% of prescribed dosage for MK-3475 and/or chemotherapy by reason of other than DLT toxicity will be removed from the subjects of DLT evaluation and then add the additional subjects in this cohort.

5.2.1.2.2 Definition of Dose Limiting Toxicity (DLT)

Observed DLTs for treatment period in Cycle 1 will be used for dose finding. Subjects will be hospitalized and monitored for the development of DLTs during Cycle 1. Toxicities will be graded in severity according to the guidelines outlined in the NCI-CTCAE version 4.0.

A DLT will be defined as the occurrence of any treatment-emergent AE in Table 4 occurring up to and including Study Day 7 (1-week observation period: Part A cohort 1) or Day 21 (3-week observation period: Part A cohort 2 and Part B). 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 4 Criteria for Defining Dose-Limiting Toxicities (DLTs)

Hematologic Toxicities: **Part A** • Any Grade 4 thrombocytopenia • Any Grade 4 neutropenia lasting > 1 week • Febrile neutropenia (irrespective of the duration) **Part B** • Any Grade 4 thrombocytopenia • Any Grade 4 neutropenia lasting > 7 days using appropriate supportive treatment • Febrile neutropenia (irrespective of the duration) if the event is considered as clinically significant for the patient deemed by investigator and sponsor.
Non-Hematologic Toxicities: • Any Grade 4 toxicity • Any Grade 3 laboratory abnormality lasting > 1 week • Any other Grade 3 toxicity EXCLUDING: – Nausea or vomiting controlled by medical intervention within 72 hours – 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, or not resulting in missing a MK-3475 dose or INCB024360 doses for 7 days • Episcleritis, uveitis, or iritis of Grade 2 or higher
General : • If subjects are unable to receive 75% of INCB024360 during the DLT observation period because of toxicity, even if the toxicity does not meet DLT criteria defined above (Part A cohort 1). • If subjects are unable to receive 75% of INCB024360 or 1 dose of MK-3475 during the DLT observation period because of toxicity, even if the toxicity does not meet DLT criteria defined above (Part A cohort 2 and Part B). • Greater than 2 week delay in initiating cycle 2 due to toxicity

The SPONSOR and the principal investigator will decide the appropriateness of the DLT, and enrollment of additional patients in consultation with the Data and Safety Monitoring Committee as needed.

5.2.1.2.3 Guideline for Dose Modification

NOTE: As of Amendment 02, INCB024360 is stopped from Part B.

Dose modification and toxicity management for immune-related AEs (irAEs) associated with pembrolizumab and/or epacadostat should be managed as follows.

Adverse events (both non-serious and serious) associated with MK-3475 and INCB024360 exposure may represent an immunologic etiology. These irAEs may occur shortly after the first dose or several months after the last dose of treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were

reversible and could be managed with interruptions of MK-3475, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue MK-3475 and INCB024360 and administer corticosteroids.

Table 5 summarizes the irAE dose modification actions for MK-3475 and INCB024360. Of note, participants who require dose reduction of INCB024360 due to AEs will remain at the lower dose, summarized in Table 6. Re-escalation of INCB024360 is not permitted.

In cases where MK-3475 dosing is held, dosing for INCB024360 must also be held until MK-3475 may resume. Participants are allowed, however, to receive MK-3475 monotherapy at the Investigator's discretion upon improvement of the irAE to Grade 0 or 1 (eg, if the toxicity was considered related to the combination therapy and not MK-3475 monotherapy), unless discontinuation of both study treatments is specified in Table 5.

Except in cases of emergency, it is recommended that the Investigator consult with the medical monitor (or other representative of MSD) before temporarily interrupting therapy for reasons other than protocol-mandated medication hold.

Table 5 Dose Modification Guidelines for Drug-Related Adverse Events for MK-3475 and INCB024360

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Study Medication	Action Taken with Study Medication	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
Pneumonitis	Grade 2	Pembrolizumab	Withhold until Grade 0-1	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
		Epacadostat	Withhold until Grade 0-1 Related: Reduce by 1 dose level. Not Related: Same dose level.		
	Grade 3 or 4, or recurrent grade 2	Pembrolizumab	Permanently discontinue		
		Epacadostat	Permanently discontinue		
Diarrhea / colitis	Grade 2 or 3	Pembrolizumab	Withhold until Grade 0-1	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with 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.
		Epacadostat	Withhold until Grade 0-1 Related: Reduce by 1 dose level. Not Related: Same dose level.		
	Grade 4	Pembrolizumab	Permanently discontinue		
		Epacadostat	Permanently discontinue		

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Study Medication	Action Taken with Study Medication	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
AST / ALT Elevation or Increased Bilirubin	Grade 2	Pembrolizumab	Withhold until 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 value returns to baseline or is stable
		Epacadostat	Withhold until Grade 0-1 Related: Reduce by 1 dose level. Not Related: Same dose level.		
	Grade 3 or 4	Pembrolizumab	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
		Epacadostat	Permanently discontinue		
Type 1 diabetes mellitus (T1DM) or Hyperglycemia[a]	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Pembrolizumab	Withhold until Grade 0-1	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
		Epacadostat	Withhold until Grade 0-1 Related: Reduce by 1 dose level. Not Related: Same dose level.		

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Study Medication	Action Taken with Study Medication	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
Hypophysitis	Grade 2	Pembrolizumab	Withhold until Grade 0-1	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
		Epacadostat	Withhold until Grade 0-1 Related: Reduce by 1 dose level. Not Related: Same dose level.		
	Grade 3 or 4	Pembrolizumab	Withhold until Grade 0- 1 or permanently discontinue[b]		
		Epacadostat	Withhold until Grade 0- 1 or permanently discontinue[b] Related: Reduce by 1 dose level. Not Related: Same dose level.		
Hyperthyroidism[a]	Grade 2	Pembrolizumab	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
		Epacadostat	Continue		
	Grade 3 or 4	Pembrolizumab	Withhold until Grade 0- 1 or permanently discontinue[b]		
		Epacadostat	Withhold until Grade 0- 1 or permanently discontinue[b] Related: Reduce by 1 dose level. Not Related: Same dose level.		

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Study Medication	Action Taken with Study Medication	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
Hypothyroidism[a]	Grade 2-4	Pembrolizumab	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
		Epacadostat	Continue		
Nephritis and Renal Dysfunction	Grade 2	Pembrolizumab	Withhold until Grade 0- 1	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
		Epacadostat	Withhold until Grade 0-1 Related: Reduce by 1 dose level. Not Related: Same dose level.		
	Grade 3 or 4	Pembrolizumab	Permanently discontinue		
		Epacadostat	Permanently discontinue		
Myocarditis	Grade 1 or 2	Pembrolizumab	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
		Epacadostat	Withhold until Grade 0 Once resolved to Grade 0, may restart: Related: Reduce by 1 dose level. Not Related: Same dose level.		
	Grade 3 or 4	Pembrolizumab	Permanently discontinue		
		Epacadostat	Permanently discontinue		

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Study Medication	Action Taken with Study Medication	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
Rash	1 or 2	Pembrolizumab	Continue	• Manage with topical steroids with or without drug interruption.	
		Epacadostat	Continue		
	3 [c]	Pembrolizumab	Withhold until 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 epacadostat 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.
		Epacadostat	Withhold until Grade 0-1 Related: Reduce by 1 dose level. Not Related: Same dose level.		
	4	Pembrolizumab	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	
		Epacadostat	Permanently discontinue		

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Study Medication	Action Taken with Study Medication	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
Asymptomatic [d] Amylase or Lipase Increased	3	Pembrolizumab	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.
		Epacadostat	May continue treatment with medical monitor approval		
	4	Pembrolizumab	Withhold until toxicity resolves to Grade 0-1		
		Epacadostat	Withhold until toxicity resolves to Grade 0-1 Related: Reduce by 1 dose level. Not Related: Same dose level.		

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Study Medication	Action Taken with Study Medication	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
All Other Immune-related AEs	Intolerable/ persistent Grade 2	Pembrolizumab	Withhold until Grade 0- 1	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
		Epacadostat	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,	Pembrolizumab	Withhold until Grade 0-1, or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
		Epacadostat	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: Guillain-Barre Syndrome encephalitis		
	Grade 4 or recurrent Grade 3	Pembrolizumab	Permanently discontinue		
		Epacadostat	Permanently discontinue		

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Study Medication	Action Taken with Study Medication	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up

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 pembrolizumab and epacadostat have been withheld, pembrolizumab and epacadostat can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab and epacadostat 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 epacadostat dose reductions to dose level -2 re-occurs, regardless of the causality to epacadostat, epacadostat should be discontinued. If a participant who is being treated at dose level -2 has a different AE that is considered unrelated to epacadostat by the Investigator, the participant may resume study treatment at dose level -2 after discussion with MSD Clinical Director.

NOTES:

a. For participants with Grade 3 or 4 immune-related endocrinopathy where withholding of pembrolizumab and epacadostat is required, pembrolizumab and epacadostat 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 pembrolizumab + epacadostat 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 medication
d. If Grade 4 lipase/amylase elevation is asymptomatic and abdominal imaging suggests no pathology, study drug administration dosing may continue (with or without dose reduction) with medical monitor approval.

AE=adverse events; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; GI=gastrointestinal; IV=intravenous; irAE=immune-related adverse events; T1DM= Type 1 diabetes mellitus.

Table 6 Dose Level Adjustments of INCB024360

Dose of INCB024360	Dose Level -1	Dose Level -2
	First Reduction of INCB024360	Second Reduction of INCB024360
25 mg BID	Discontinue treatment	—
100 mg BID	50 mg BID	25 mg BID

Chemotherapy

In Part B, Dose modification of cytotoxic chemotherapy will conform to the site's standards procedures. Dose modification of chemotherapy will not be permitted in DLT evaluation period.

Reduction of one chemotherapy agent and not the other agent is appropriate if, in the opinion of the Investigator, the toxicity is clearly related to one of the treatments. If, in the opinion of the Investigator, the toxicity is related to the combination of both chemotherapy agents, both drugs should be reduced according to recommended dose modifications. Subjects may have chemotherapy discontinued and continue on pembrolizumab. Similarly subjects may discontinue pembrolizumab and continue on chemotherapy if appropriate. Chemotherapy may be reduced, interrupted, or discontinued at the Investigator's discretion per the approved product labels and local regulations.

The Common Terminology Criteria for Adverse Events version 4.0 (CTCAE 4.0) must be used to grade the severity of adverse events. All dose modifications should be based on the AE requiring the greatest dose modification.

5.2.1.2.4 Infusion Reaction Dose Modifications

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. Dose modification and toxicity management guidelines on pembrolizumab-associated infusion reaction are provided in Table 7.

Table 7 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 (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**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 one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., 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 trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of MK-3475 with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory 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 trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.2.1.2.5 Procedures for Subjects Exhibiting Serotonin Syndrome (SS)

NOTE: As of Amendment 02, this section has been updated to reflect the removal of INCB024360 from Part B and updated information regarding the risks of SS with the use of INCB024360.

There is a rare chance that INCB024360 could cause an increase in serotonin levels in the brain that might trigger Serotonin Syndrome (SS) [49], (Section 12.5) when administered in combination with other serotonergic agents. Selective serotonin reuptake inhibitors (SSRIs) and selective serotonin/norepinephrine reuptake inhibitors (SNRIs), and MAOIs are permitted in the study. Due to the results of a preclinical study specifically evaluating the effect of epacadostat on the brain ECF concentrations of serotonin with linezolid, and the clinical experience with related medications (eg, SSRIs/SNRIs) that suggest that SS is low risk, the use of MAOIs is not prohibited in the current study.

The following procedures will be implemented if subjects exhibit the signs/symptoms of SS described in Table 8, including tremor; hyperreflexia; spontaneous, ocular, or inducible clonus; together with agitation, fever, diaphoresis, or muscle rigidity:

- Immediately interrupt INCB024360 administration. Administration of MK-3475 may continue.
- Immediately interrupt any SSRI, SNRI or MAOI administration.
- Provide appropriate medical management of the subject until all signs/symptoms are resolved (e.g., IV fluids and/or sympathomimetic amines for hypotension, benzodiazepines for agitation, administration of 5-hydroxytryptamine antagonists such as cyproheptadine).
- If subject chooses to withdraw from the study, or must restart treatment with SSRI, SNRI or MAOI, the subject should be scheduled for a follow-up visit. Treatment with SSRI, SNRI or MAOI may be initiated 2 weeks after resolution of signs and symptoms of SS.

Table 8 Sign and Symptoms of Serotonin Syndrome

Seriousness	Autonomic signs	Neurological signs	Mental status	Other
Mild	Afebrile or low-grade fever Tachycardia Mydriasis Diaphoresis or shivering	Intermittent tremor Akathisia Myoclonus Mild hyperreflexia	Restlessness Anxiety	
Moderate	Increased tachycardia Fever (up to 41°C) Diarrhea with hyperactive bowel sounds Diaphoresis with normal skin color	Hyperreflexia Inducible clonus Ocular clonus (slow continuous lateral eye movements) Myoclonus	Easily startled Increased confusion Agitation and hypervigilance	Rhabdomyolysis Metabolic acidosis Renal failure Disseminated intravascular coagulopathy (secondary to
Severe	Temperature often more than 41°C (Secondary to increased tone)	Increased muscle tone (lower limb > upper) Spontaneous clonus Substantial myoclonus or hyperreflexia	Delirium Coma	As above
Source: [Boyer EW, Shannon M. 2005]				

5.2.2 Timing of Dose Administration

NOTE: As of Amendment 02, INCB024360 is stopped from Part B. This section has been updated accordingly.

MK-3475

Trial treatment with MK-3475 in cohort 1 should be administered on Day 8 of Cycle 1 (in 4-week cycle) and on Day 1 of each subsequent cycle (in 3-week cycles) after all procedures/assessments have been completed as detailed in the Trial Flow Chart (Section 6.0). Trial treatment with MK-3475 in Part A cohort 2 and Part B should be administered on Day 1 of each cycle (in 3-week cycles). In subsequent cycles, all study treatments will be administered on an outpatient basis. Trial treatment of MK-3475 may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons except for Cycle 1 Day 8 of cohort 1.

MK-3475 will be administered as a dose of 200 mg using 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 (i.e., 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.

INCB024360 (Part A)

Subjects will take their dose of INCB024360 in the morning and evening, approximately 12 hours apart without regard to food. Subjects will self-administer INCB024360 except on C1D1, C1D5, C1D12 and C2D5 of cohort 1 and C1D1, C1D5, and C2D5 of Part A cohort 2 and Part B, when the morning dose will be given at the study site clinic for PK sampling. On days when INCB024360 is administered in the clinic, subjects will take INCB024360 and then begin infusion of MK-3475.

Chemotherapy (Part B)

Pre-medications will follow local institutional practice.

- Cisplatin

Cisplatin 75mg/m2 should be infused approximately 30 minutes after the pemetrexed infusion for the first 4 cycles and administered according to local practice and labels.

- Pemetrexed

Pemetrexed 500 mg/m2 will be administered as an IV infusion over 10 minutes Q3W until progression or unacceptable toxicity. All subjects should receive the appropriate supplementation of vitamin B12 and folic acid and corticosteroid prophylaxis as listed below (or as per local label):

- Folic Acid 350-1000 µg oral: at least 5 doses of folic acid must be taken during the 7 days preceding the first dose of pemetrexed, and folic acid dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed.
- Vitamin B12 1000 µg IM injection in the week preceding the first dose of pemetrexed and once every 3 cycles thereafter. Subsequent vitamin B12 injections may be given the same day as pemetrexed administration.
- Dexamethasone prophylaxis 4 mg, orally twice per day (or equivalent). Taken the day before, day of, and day after pemetrexed administration. Higher or additional doses are permitted for antiemetic prophylaxis during cycles 1-4 but not to exceed doses in MASCC guidelines.

- Carboplatin

Carboplatin AUC 5 or 6 will be administered as an IV infusion over 30-60 minutes on day 1 of every three week cycle following paclitaxel or pemetrexed infusions, for a maximum of 4 administrations.

The dose of carboplatin will be calculated using the Calvert Formula. Carboplatin AUC 5 and 6 do not to exceed 750mg and 900 mg.

Calvert Formula

Total Dose (mg) = (target AUC) x (CrCl + 25)

The estimated GFR used in the Calvert formula should not exceed 125 mL/min

Creatinine clearance should be calculated per institutional standard.

- Paclitaxel

Paclitaxel 200 mg/m2 will be administered as an IV infusion over 3 hours on day 1 of every three week cycle before carboplatin infusions, for a maximum of 4 administrations.

For additional details, refer to approved product labels for details regarding dose calculation, reconstitution, preparation of the infusion fluid, and administration for each of the standard of care chemotherapies.

5.2.3 Trial Blinding

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

5.3 Randomization or Treatment Allocation

Subjects participating in this trial will be allocated by non-random assignment.

5.4 Stratification

No stratification based on age, sex or other characteristics will be used in this trial.

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial 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 trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

5.5.1 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 (OTC), 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 (electronic Case Report Form). If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 4 weeks before the first dose of study treatment and 30 days after the last dose of study treatment should be recorded. Concomitant medications administered after 30 days after the last dose of study treatment should be recorded for AEs and SAEs as defined in Section 7.2.

5.5.2 Restricted Medications and Measures

NOTE: As of Amendment 02 and removal of INCB024360 from Part B, this section is no longer applicable in Part B.

Listed below are specific restrictions for concomitant therapy during the course of the trial:

- Use of 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 warfarin cannot be used, investigators should follow the guidelines in Table 9 and either closely monitor or closely monitor and reduce the subject's dose of warfarin upon initiating therapy with INCB024360.

Table 9 Warfarin Dose Adjustment Recommendation When Initiating Concurrent INCB024360 Treatment

	INCB024360 Dose	
Stable INR	**≤ 100 mg BID**	**200 mg BID**
INR ≤ 2.5	Close INR monitoring	Close INR monitoring
INR > 2.5	Close INR monitoring	Reduce warfarin by 20%-25% and close INR monitoring

5.5.3 Prohibited Medications and Measures

NOTE: As of Amendment 02, this section is updated to reflect the removal of INCB024360 from Part B and current safety information for INCB024360.

Subjects are prohibited from receiving the following therapies during the screening and treatment phase (including retreatment for post-complete response relapse) of this study unless otherwise noted below:

- Any investigational medication other than the trial treatment.
- Any anticancer medications, including systemic chemotherapy or biologic therapy other than the study medications.
- Any chronic immunological-suppressive treatment for any reason other than the management of adverse events, as described in Section 5.6.

  (NOTE: Inhaled or topical steroids are allowed, and systemic steroids at doses ≤ 10 mg/day prednisone or equivalents are allowed, as described in Section 5.6 and immune suppressants are allowed as prophylaxis for contrast allergy for imaging procedures.)

- 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 MK-3475 infusions are permitted during radiation therapy or procedure and INCB024360 should be stopped the day treatment begins. Trial treatment 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 a live attenuated vaccine within 4 weeks before the first dose of study treatment and while participating in the study. 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.
- Any melatonin supplements. (Part A)
- Melatonin receptor agonist (i.e. ramelteon) (Part A)
- Any UGT1A9 inhibitor, including, but not limited to acitretin, amitriptyline, androsterone, cyclosporine, dasatinib, diclofenac, diflunisal, efavirenz, erlotinib, flutamide, gefitinib, gemfibrozil, glycyrrhetinic acid, glycyrrhizin, imatinib, imipramine, ketoconazole (systemic), linoleic acid supplements, mefenamic acid, mycophenolic acid, niflumic acid, nilotinib, phenobarbital, phenylbutazone, phenytoin, probenecid, propofol, quinidine, ritonavir, sorafenib, sulfinpyrazone, valproic acid, and verapamil. (Part A)

  Note: Propofol, if administered for an on-study biopsy procedure, may be permitted. Administration of epacadostat on the morning of a procedure where propofol may be administered is permitted; however, the evening dose after the procedure should be held and participants may resume regular dosing the following day.

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 5.1.3) describe other medications that are prohibited during this study. There are no prohibited therapies during the post-treatment follow-up phase.

5.6 Rescue Medications & Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator, including, but not limited to, the items outlined below. Section 5.6.1 outlines supportive care guidelines for MK-3475 and INCB024360, respectively. Prophylactic medications are not allowed during Cycle 1. However, treatment should be instituted for patients who develop these symptoms and pre-medication for additional cycles will be allowed:

Systemic Corticosteroid Use

Systemic corticosteroids are permitted in the following situations:

- To mitigate potential immune-related AEs as guided in Table 5.
- As pre/post-medication to prevent AEs associated with chemotherapy or IV contrast.
- Brief, limited use of systemic corticosteroids (≤7 days) are permitted where such use is considered SOC (eg, for COPD exacerbation).
  - Replacement doses of steroids (for example, prednisone 5 to 7.5 mg daily) are permitted while on study, as is the use of local steroids.

Antiemetic Use

For participants receiving chemotherapy, antiemetic therapy should follow Multinational Association of Supportive Care in Cancer (MASCC) or appropriate local guidelines and should, for the first 4 cycles, include a 5-HT3 receptor antagonist, dexamethasone (or equivalent), and aprepitant (or equivalent NK-1 receptor antagonist) as per the guideline followed.

Colony-Stimulating Factors

For participants receiving chemotherapy, the American Society of Clinical Oncology (ASCO) guidelines for use of colony-stimulating factors (CSFs), or local equivalent, should be used for patient management [55]. In Part B, G-CSF can be used in cycle 1 as an appropriate supportive treatment for neutropenia.

5.7 Diet/Activity/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

MK-3475 or INCB024360 may have adverse effects on a fetus in utero. Furthermore, it is not known if MK-3475 or INCB024360 has transient adverse effects on the composition of sperm.

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if they are either:

1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

3) has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving trial treatment and for 120 days after the last dose of trial treatment by complying with use (or have their partner use) acceptable contraception during heterosexual activity

Acceptable methods of contraception are:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner

Combination method (requires use of two of the following):

- diaphragm with spermicide
- male condom
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill)

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.3 Pregnancy

If a subject inadvertently becomes pregnant while on treatment with MK-3475 and/or INCB024360, the subject will be immediately discontinued from treatment. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (e.g., 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 must be reported to the Sponsor and followed as described in Section 7.2.2.

5.7.4 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.

Subjects who stop breast-feeding prior to initiation of trial treatment and not expecting to resume of breast-feeding will not be excluded from the study.

Refer to Package inserts for chemotherapy.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial 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 trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures are provided in Section 7.1.4 – Other Procedures.

In this trial, a subject may discontinue from treatment but continue in the study in the follow-up, as long as the subject does not withdraw consent. Once a subject has discontinued treatment for CR or after receiving the maximum 35 infusions of MK-3475, he/she may be eligible for retreatment if deemed medically appropriate and the subject meets the criteria, as outlined in Section 7.1.5.5.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- The subject is lost to follow-up.

A subject must be discontinued from treatment (but will continue to be monitored in the trial) for any of the following reasons:

- Radiographic disease progression as assessed by the investigator per RECIST 1.1 (section 12.7. (exception if Sponsor approves treatment continuation).
- Unacceptable adverse experiences as described in Section 7.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Non-compliance with trial treatment or procedure requirements
- Administrative reasons
- Completed 35 treatments with MK-3475

  Note: 35 infusions (approximately. 2 years) of MK-3475 are calculated from the first infusion. Subjects who stop MK-3475 after receiving 35 treatments may be eligible for retreatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.5.5. For Part A, subjects who are already in second course as of Amendment 02 would be retreated in the Second Course Phase (Re-treatment) with up to 17 infusions (approximately 1 year) of MK-3475 additional trial treatments. New participants will not have re-treatment in Part A or Part B.

For Part A, epacadostat will be dosed BID every 12 hours (Q12H) during the treatment phase. Treatment may continue until the last day of the last cycle of pembrolizumab (eg, C35D21), unless a discontinuation criterion is met.

The End of Treatment and Follow-up visit procedures are listed in Sections 7.1.5.3 and 7.1.5.4.1 and the Trial Flow Chart - Section 6.0. After the end of treatment, each subject will be followed for a minimum of 90 days for adverse event monitoring. (Adverse events will be collected for up to 90 days after the end of treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy as described in Section 7.2).

5.8.1 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR and have been treated for at least 8 cycles (at least 24 weeks) and had 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. For Part A, subjects who are already in second course as of Amendment 02 would be eligible for up to 17 additional treatments (approximately 1 year) with MK-3475 and INCB 024360 (Second Course Phase: Re-treatment) at the discretion of the investigator. New participants will not have re-treatment in Part A or Part B. Additional details are provided in Section 7.1.5.5.

5.9 Subject Replacement Strategy

If a subject discontinues from the trial, a replacement subject may be enrolled if deemed appropriate by the investigator and Sponsor. The replacement subject will generally receive the same treatment or treatment sequence (as appropriate) as the subject being replaced. The replacement subject will be assigned a unique treatment/randomization number. The trial site should contact the Sponsor for the replacement subject's treatment/randomization number.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

5.11 Clinical Criteria for Early Trial Termination

The clinical trial may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the trial population as a whole is unacceptable. In addition, further recruitment in the trial or at (a) particular trial site(s) may be stopped due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

6.0 TRIAL FLOW CHART

6.1 Treatment Phase

6.1.1 Treatment Phase （Part A Cohort 1）

NOTE: As of Amendment 02, the final study visit will be the Safety Follow-up Visit and there will be no follow-up for survival status. For participants who were in Follow-up or Survival Follow-up, participation in the study is considered complete and no further visits are required. For those participants remaining in the study, procedures are simplified. The SoA has been amended and assessments no longer required have been deleted. Retreatment for new participants is no longer available.

Title Treatment:	Screening	Treatment Cycles [1]								End of Treatment	Post-Treatment	Notes
Cycle (Week)	(-4)	1 (0)					2 (4)		3 (7) and beyond	Discon	Safety Follow-up	Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.
Relative Day in Cycle (on Day)		1	5	8 [22]	12	28	1	2-21	1-21			
Scheduling Window (Days):	-28	-	-	-1	-	-	+3	-	±3	At time of Discon	30 (±7) days Post Discon	
Administrative Procedures												
Informed Consent [4]	X											
Inclusion/Exclusion Criteria	X											
Subject Identification Card	X											
Demographics and Medical History	X											
Prior/Concomitant Medication Review [5]	X	X ---------- X								X	X	
Trial Treatment Administration												
MK-3475 (Pembrolizumab) Administration Q3W		X		X			X		X			
INCB024360 (Epacadostat) Administration BID		X--------X		X----------X			X--------X		X			
Clinical Procedures/Assessments												
Review Adverse Events [6]	X---------- X											
Full Physical Examination [7]	X									X		
Directed Physical Examination [7]		X		X			X		X			
Vital Signs, Height and Weight [8]	X	X		X			X		X	X	X	

Title Treatment:	Screening	Treatment Cycles [1]								End of Treatment	Post-Treatment	Notes Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.
Cycle (Week)	(-4)	1 (0)					2 (4)		3 (7) and beyond	Discon	Safety Follow-up	
Relative Day in Cycle (on Day)		1	5	8 [22]	12	28	1	2-21	1-21			
Scheduling Window (Days):	-28	-	-	-1	-	-	+3	-	±3	At time of Discon	30 (±7) days Post Discon	
12-Lead ECG [9]	X	X					X				X	
ECOG Performance Status	X	X					X		X	X	X	
Arterial Blood Oxygen Saturation (SpO_2) Measurement [10]	X	X		X			X		X	X	X	
Laboratory Procedures/Assessments: analysis performed by local laboratory												
Pregnancy Test (Urine or Serum β-HCG) [11]	X											
Coagulation Parameters [12], [13], [14]	X											
Hematology and Chemistry [13], [14]	X			X			X		X	X	X	
Urinalysis [13], [14]	X								X	X	X	
FT3, FT4 and TSH [13], [14]	X								X	X	X	
KL-6, β-D glucan [14], [15]	X											
Laboratory Procedures/Assessments: analysis performed by central laboratory												
MK-3475 Pharmacokinetics [16]				X			X		X			
Anti-MK-3475 Antibodies [16]				X			X		X			
INCB024360 Pharmacokinetics [17]		X	X		X			X				
INCB024360 Pharmacodynamics [17]		X					X					
Blood for RNA Analyses [18]		X					X		X	X		
Blood for Plasma for Biomarker Analyses [18]		X					X			X		
Blood for Serum Biomarker Analyses [18]		X					X			X		
Blood for Genetic Analyses [19]		X										
Efficacy Measurements												
Tumor Imaging	X								X	X		The timing of imaging during the treatment phase is according to the site's SOC for tumor assessment until PD or initiation of a new anticancer regimen.
Tumor Tissue Collection [21]	X											

Title Treatment:	Screening	Treatment Cycles [1]								End of Treatment	Post-Treatment	Notes Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.
Cycle (Week)	(-4)	1 (0)					2 (4)		3 (7) and beyond	Discon	Safety Follow-up	
Relative Day in Cycle (on Day)		1	5	8 [22]	12	28	1	2-21	1-21			
Scheduling Window (Days):	-28	-	-	-1	-	-	+3	-	±3	At time of Discon	30 (±7) days Post Discon	

1) In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of MK-3475 for each cycle, and the window for each visit is ± 3 days unless otherwise specified. Treatment cycles are 4 weeks in Cycle 1 and 3 weeks (Q3W) in subsequent cycles.
2) Not applicable in Amendment 02.
3) Not applicable in Amendment 02.
4) Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g., within 4 weeks prior to the first dose of trial treatment). Screening number will be assigned when the study informed consent is signed.
5) Prior medications - Record all medications taken within 4 weeks of screening visit. Concomitant medications - Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for AEs as defined in Section 7.2.
6) Report all AEs occurring within 90 days after the last dose of trial treatment or 30 days of the end of treatment if the subject initiates new anticancer therapy, whichever is earlier. Afterwards, report only SAEs that are related to trial treatment. Adverse experiences and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness.
7) Perform physical examinations at predose on Day 1 of each cycle and Day 8 of Cycle 1. A full physical examination will be performed at screening and at the discontinuation.
8) Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.
9) ECG should be performed at predose and approximately 60 to 90 minutes after the first dose of INCB024360 for Day 1 of Cycles 1 and 2, and 30 day post-discontinuation.
10) Arterial blood oxygen saturation (SpO_2) should be measured at screening, Day 1 of each cycle, Day 8 of Cycle 1, at the discontinuation and at the safety follow-up (30 days post discon).
11) For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
12) Coagulation factors should be tested as part of the screening procedures for all subjects. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.
13) Laboratory tests for screening are to be performed locally within 10 days prior to the first dose of trial treatment. After Cycle 1, lab samples can be collected up to 72 hours prior to MK-3475. Urinalysis, FT3, FT4 and TSH should be performed every 2 cycles. See Section 7.1.3 for details regarding laboratory tests.
14) Unresolved abnormal labs that are drug related AEs should be followed until resolution. Labs do not need to be repeated after the end of treatment if labs are within normal range.
15) KL-6 and β–D glucan will be measured for pulmonary evaluation at screening (within 10 days prior to the first dose of study treatment) and thereafter if a subject develops suspected pneumonitis, an additional test may be performed at the descretion of the investigator.

Title Treatment:	Screening	Treatment Cycles [1)]								End of Treatment	Post-Treatment	Notes Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.
Cycle (Week)	(-4)	1 (0)					2 (4)		3 (7) and beyond	Discon	Safety Follow-up	
Relative Day in Cycle (on Day)		1	5	8 [22)]	12	28	1	2-21	1-21			
Scheduling Window (Days):	-28	-	-	-1	-	-	+3	-	±3	At time of Discon	30 (±7) days Post Discon	

16) Pre-dose trough PK samples for MK-3475 will be collected at Day 8 of Cycle 1, and Day 1 of Cycles 2, 4, 6 and 8 (following Cycle 8, every 4 cycles), until treatment discontinuation (or until the subject starts new anti-neoplastic therapy). All pre-dose PK samples for MK-3475 should be drawn within 24 hours before infusion of MK-3475. The peak (post-dose) samples will be collected at Day 8 of Cycle 1 and this sample should be drawn within 30 minutes after the end of infusion. Anti-MK-3475 antibodies should be drawn with all pre-dose trough PK samples. Procedures for sample collection are described in the Procedures Manual.

17) Trough (pre-dose) and post-dose PK samples for INCB024360 will be collected at Days 1, 5, and 12 of Cycle 1, and Day 5 of Cycle 2. All trough samples should be drawn before administration of INCB024360. . All post-dose samples should be drawn at 30 minutes, and 1, 2, 4, 6, 8 and 10 hours after the administration of INCB024360 at Days 1, 5 and 12 of Cycle 1. In addition, the post-dose sample should be drawn at 1 hours after the administration of INCB024360 at Day 5 of Cycle 2. Procedures for sample collection are described in the Procedures Manual. The investigator or qualified designee will remind the subject when they should not take their morning dose of INCB024360 on the day of full PK sampling.

18) Blood for RNA Analyses should be collected pre-dose on Day 1 of Cycle 1, 2, and 5, or at time of discontinuation. Blood for Plasma and Serum Biomarker Analyses should be collected pre-dose on Day 1 of Cycle 1 and Cycle 2, or at the time of discontinuation.

19) This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site.

20) Not applicable in Amendment 02.

21) Tumor tissue for biomarker analysis from an archival tissue sample or newly obtained biopsy (core or excisional: FNA/EBUS not adequate) of a tumor lesion not previously irradiated must be provided to the central vendor for characterization of PD-L1/IDO1 status. These samples are not required to be obtained within 4 weeks of enrollment. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual.

22) The scheduling window for Day 8 of Cycle 1 (-1 day) is applicable to Directed Physical Examination, Vital Signs and Weight, Arterial Blood Oxygen Saturation (SpO_2) Measurement and Hematology and Chemistry.

6.1.2 Treatment Phase （Part A Cohort 2）

NOTE: As of Amendment 02, the final study visit will be the Safety Follow-up Visit and there will be no follow-up for survival status. For participants who were in Follow-up or Survival Follow-up, participation in the study is considered complete and no further visits are required. For those participants remaining in the study, procedures are simplified. The SoA has been amended and assessments no longer required have been deleted. Retreatment for new participants is no longer available.

Title Treatment:	Screening	Treatment Cycles [1]						End of Treatment	Post-Treatment	Notes
Cycle (Week)	(-4)	1 (0)			2 (3)		3 (6) and beyond	Discon	Safety Follow-up	
Relative Day in Cycle (on Day)		1	5	21	1	2-21	1-21			
Scheduling Window (Days):	-28	-	-	-	+3	-	±3	At time of Discon	30 (±7) days Post Discon	
Administrative Procedures										
Informed Consent [4]	X									
Inclusion/Exclusion Criteria	X									
Subject Identification Card	X									
Demographics and Medical History	X									
Prior/Concomitant Medication Review [5]	X	X---------- X						X	X	
Trial Treatment Administration										
MK-3475 (Pembrolizumab) Administration Q3W		X			X		X			
INCB024360 (Epacadostat) Administration BID		X----------X			X----------X		X			
Clinical Procedures/Assessments										
Review Adverse Events [6]	X----------X									
Full Physical Examination [7]	X							X		
Directed Physical Examination [7]		X			X		X			
Vital Signs, Height and Weight [8]	X	X			X		X	X	X	
12-Lead ECG [9]	X	X			X				X	
ECOG Performance Status	X	X			X		X	X	X	
Arterial Blood Oxygen Saturation (SpO_2) Measurement [10]	X	X			X		X	X	X	

Title Treatment:	Screening	Treatment Cycles [1]						End of Treatment	Post-Treatment	Notes Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.
Cycle (Week)	(-4)	1 (0)			2 (3)		3 (6) and beyond	Discon	Safety Follow-up	
Relative Day in Cycle (on Day)		1	5	21	1	2-21	1-21			
Scheduling Window (Days):	-28	-	-	-	+3	-	±3	At time of Discon	30 (±7) days Post Discon	
Laboratory Procedures/Assessments: analysis performed by local laboratory										
Pregnancy Test (Urine or Serum β-HCG) [11]	X									
Coagulation Parameters [12], [13], [14]	X									
Hematology and Chemistry [13], [14]	X				X		X	X	X	
Urinalysis [13], [14]	X						X	X	X	
FT3, FT4 and TSH [13], [14]	X						X	X	X	
KL-6, β-D glucan [14], [15]	X									
Laboratory Procedures/Assessments: analysis performed by central laboratory										
MK-3475 Pharmacokinetics [16]		X			X		X			
Anti-MK-3475 Antibodies [16]		X			X		X			
INCB024360 Pharmacokinetics [17]		X	X			X				
INCB024360 Pharmacodynamics [17]		X			X					
Blood for RNA Analyses [18]		X			X		X	X		
Blood for Plasma for Biomarker Analyses [18]		X			X			X		
Blood for Serum Biomarker Analyses [18]		X			X			X		
Blood for Genetic Analyses [19]		X								
Efficacy Measurements										
Tumor Imaging	X						X	X		The timing of imaging during the treatment phase is according to the site's SOC for tumor assessment until PD or initiation of a new anticancer regimen.
Tumor Tissue Collection [21]	X									

1) In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of MK-3475 for each cycle, and the window for each visit is ± 3 days unless otherwise specified. Treatment cycles are 3 weeks (Q3W) in each cycle.
2) Not applicable in Amendment 02.
3) Not applicable in Amendment 02.
4) Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g., within 4 weeks prior to the first dose of trial treatment). Screening number will be assigned when the study informed consent is signed.

Title Treatment:	Screening	Treatment Cycles [1)]						End of Treatment	Post-Treatment	Notes Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.
Cycle (Week)	(-4)	1 (0)			2 (3)		3 (6) and beyond	Discon	Safety Follow-up	
Relative Day in Cycle (on Day)		1	5	21	1	2-21	1-21			
Scheduling Window (Days):	-28	-	-	-	+3	-	±3	At time of Discon	30 (±7) days Post Discon	

5) Prior medications - Record all medications taken within 4 weeks of screening visit. Concomitant medications - Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for AEs as defined in Section 7.2.
6) Report all AEs occurring within 90 days after the last dose of trial treatment or 30 days of the end of treatment if the subject initiates new anticancer therapy, whichever is earlier. Afterwards, report only SAEs that are related to trial treatment. Adverse experiences and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness.
7) Perform physical examinations at predose on Day 1. A full physical examination will be performed at screening and at the discontinuation.
8) Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.
9) ECG should be performed at predose and approximately 60 to 90 minutes after the first dose of INCB024360 for Day 1 of Cycles 1 and 2, and 30 day post-discontinuation.
10) Arterial blood oxygen saturation (SpO_2) should be measured at screening, Day 1 of each cycle, at the discontinuation and at the safety follow-up (30 days post discon).
11) For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
12) Coagulation factors should be tested as part of the screening procedures for all subjects. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.
13) Laboratory tests for screening are to be performed locally within 10 days prior to the first dose of trial treatment. After Cycle 1, lab samples can be collected up to 72 hours prior to MK-3475. Urinalysis, FT3, FT4 and TSH should be performed every 2 cycles. See Section 7.1.3 for details regarding laboratory tests.
14) Unresolved abnormal labs that are drug related AEs should be followed until resolution. Labs do not need to be repeated after the end of treatment if labs are within normal range.
15) KL-6 and β–D glucan will be measured for pulmonary evaluation at screening (within 10 days prior to the first dose of study treatment) and thereafter if a subject develops suspected pneumonitis, an additional test may be performed at the descretion of the investigator.
16) Pre-dose trough PK samples for MK-3475 will be collected at Day 1 of Cycles 1, 2, 4, 6 and 8 (following Cycle 8, every 4 cycles) until treatment discontinuation (or until the subject starts new anti-neoplastic therapy). All pre-dose PK samples for MK-3475 should be drawn within 24 hours before infusion of MK-3475. The peak (post-dose) samples will be collected at Day 1 of Cycle 1 and this sample should be drawn within 30 minutes after the end of infusion. Anti-MK-3475 antibodies should be drawn with all pre-dose trough PK samples. Procedures for sample collection are described in the Procedures Manual.
17) Trough (pre-dose) and post-dose PK samples for INCB024360 will be collected at Days 1 and 5 of Cycle 1, and Day 5 of Cycle 2. All trough samples should be drawn before administration of INCB024360. All post-dose samples should be drawn at 30 minutes, and 1, 2, 4, 6, 8 and 10 hours after the administration of INCB024360 at Day 5 of Cycle 1. In addition, the post-dose sample should be drawn at 1 hours after the administration of INCB024360 at Day 5 of Cycle 2. Procedures for sample collection are described in the Procedures Manual. The investigator or qualified designee will remind the subject when they should not take their morning dose of INCB024360 on the day of full PK sampling.
18) Blood for RNA Analyses should be collected pre-dose on Day 1 of Cycle 1, 2, and 5, or at time of discontinuation. Blood for Plasma and Serum Biomarker Analyses should be collected pre-dose on Day 1 of Cycle 1 and Cycle 2, or at the time of discontinuation.

Title Treatment:	Screening	Treatment Cycles [1)]						End of Treatment	Post-Treatment	Notes Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.
Cycle (Week)	(-4)	1 (0)			2 (3)		3 (6) and beyond	Discon	Safety Follow-up	
Relative Day in Cycle (on Day)		1	5	21	1	2-21	1-21			
Scheduling Window (Days):	-28	-	-	-	+3	-	±3	At time of Discon	30 (±7) days Post Discon	

19) This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site.
20) Not applicable in Amendment 02.
21) Tumor tissue for biomarker analysis from an archival tissue sample or newly obtained biopsy (core or excisional: FNA/EBUS not adequate) of a tumor lesion not previously irradiated must be provided to the central vendor for characterization of PD-L1/IDO1 status. These samples are not required to be obtained within 4 weeks of enrollment. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual.

6.1.3 Treatment Phase （Part B）

NOTE: As of Amendment 02, epacadostat administration is stopped and all participants remaining in the study will receive pembrolizumab and Chemotherapy. The final study visit will be the Safety Follow-up Visit and there will be no follow-up for survival status. For participants who were in Follow-up or Survival Follow-up, participation in the study is considered complete and no further visits are required. For those participants remaining in the study, procedures are simplified. The SoA has been amended and assessments no longer required have been deleted. Retreatment for participants is no longer available.

Title Treatment:	Screening	Treatment Cycles [1]								End of Treatment	Post-Treatment	Notes Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.
Cycle (Week)	(-4)	1 (0)					2 (3)		3 (6) and beyond	Discon	Safety Follow-up	
Relative Day in Cycle (on Day)		1	5	8	15	21	1	2-21	1-21			
Scheduling Window (Days):	-28	-	-	-	-	-	+3	-	±3	At time of Discon	30 (±7) days Post Discon	
Administrative Procedures												
Informed Consent [4]	X											
Inclusion/Exclusion Criteria	X											
Subject Identification Card	X											
Demographics and Medical History	X											
Prior/Concomitant Medication Review [5]	X	X----------X								X	X	
Trial Treatment Administration												
MK-3475 (Pembrolizumab) Administration Q3W		X					X		X			
Chemotherapy [6]		X					X		X			
Clinical Procedures/Assessments												
Review Adverse Events [7]	X----------X											
Full Physical Examination [8]	X									X		
Directed Physical Examination [8]		X		X	X		X		X			
Vital Signs, Height and Weight [9]	X	X		X	X		X		X	X	X	
12-Lead ECG [10]	X	X					X				X	

Title Treatment:	Screening	Treatment Cycles [1]								End of Treatment	Post-Treatment	Notes Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.
Cycle (Week)	(-4)	1 (0)					2 (3)		3 (6) and beyond	Discon	Safety Follow-up	
Relative Day in Cycle (on Day)		1	5	8	15	21	1	2-21	1-21			
Scheduling Window (Days):	-28	-	-	-	-	-	+3	-	±3	At time of Discon	30 (±7) days Post Discon	
ECOG Performance Status	X	X					X		X	X	X	
Arterial Blood Oxygen Saturation (SpO_2) Measurement [11]	X	X					X		X	X	X	
Laboratory Procedures/Assessments: analysis performed by local laboratory												
Pregnancy Test (Urine or Serum β-HCG) [12]	X											
Coagulation Parameters [13], [14], [15]	X											
Hematology and Chemistry [14], [15]	X			X	X		X		X	X	X	
Urinalysis [14], [15]	X								X	X	X	
FT3, FT4 and TSH [14], [15]	X								X	X	X	
KL-6, SP-D, β-D glucan [15], [16]	X			X	X		X		X	X	X	
Laboratory Procedures/Assessments: analysis performed by central laboratory												
MK-3475 Pharmacokinetics [17]		X					X		X			
Anti-MK-3475 Antibodies [17]		X					X		X			
INCB024360 Pharmacokinetics [18]		X	X					X				
INCB024360 Pharmacodynamics [18]		X					X					
Blood for RNA Analyses [19]		X					X		X			
Blood for Plasma for Biomarker Analyses [19]		X					X					
Blood for Serum Biomarker Analyses [19]		X					X					
Blood for Genetic Analyses [20]		X										

Title Treatment:	Screening	Treatment Cycles [1]								End of Treatment	Post-Treatment	Notes Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.
Cycle (Week)	(-4)	1 (0)					2 (3)		3 (6) and beyond	Discon	Safety Follow-up	
Relative Day in Cycle (on Day)		1	5	8	15	21	1	2-21	1-21			
Scheduling Window (Days):	-28	-	-	-	-	-	+3	-	±3	At time of Discon	30 (±7) days Post Discon	
Efficacy Measurements												
Tumor Imaging	X								X	X		The timing of imaging during the treatment phase is according to the site's SOC for tumor assessment until PD or initiation of a new anticancer regimen.
Tumor Tissue Collection (Optional) [22]	X											

1) In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of MK-3475 for each cycle, and the window for each visit is ± 3 days unless otherwise specified. Treatment cycles are 3 weeks (Q3W) in each cycle.
2) Not applicable in Amendment 02.
3) Not applicable in Amendment 02.
4) Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g., within 4 weeks prior to the first dose of trial treatment). Screening number will be assigned when the study informed consent is signed.
5) Prior medications - Record all medications taken within 4 weeks of screening visit. Concomitant medications - Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for AEs as defined in Section 7.2.
6) Chemotherapy will be administered for a maximum of 4 administrations. Pemetrexed maintenance therapy can be used after 4 administrations of chemotherapy.
7) Report all AEs occurring within 90 days after the last dose of trial treatment or 30 days of the end of treatment if the subject initiates new anticancer therapy, whichever is earlier. Afterwards, report only SAEs that are related to trial treatment. Adverse experiences and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness.
8) Perform physical examinations at predose on Day 1 and Day 8, 15 of cycle 1. A full physical examination will be performed at screening and at the discontinuation.

Title Treatment:	Screening	Treatment Cycles [1)]								End of Treatment	Post-Treatment	Notes Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.
Cycle (Week)	(-4)	1 (0)					2 (3)		3 (6) and beyond	Discon	Safety Follow-up	
Relative Day in Cycle (on Day)		1	5	8	15	21	1	2-21	1-21			
Scheduling Window (Days):	-28	-	-	-	-	-	+3	-	±3	At time of Discon	30 (±7) days Post Discon	

9) Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. However, temperature, pulse, respiratory rate and blood pressure will be performed on Day 8 and 15 of cycle 1. Height will be measured at screening only.
10) ECG should be performed at predose and approximately 60 to 90 minutes after the first dose of INCB024360 for Day 1 of Cycles 1 and 2, and 30 day post-discontinuation.
11) Arterial blood oxygen saturation (SpO_2) should be measured at screening, Day 1 of each cycle, at the discontinuation and at the safety follow-up (30 days post discon).
12) For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
13) Coagulation factors should be tested as part of the screening procedures for all subjects. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.
14) Laboratory tests for screening are to be performed locally within 10 days prior to the first dose of trial treatment. After Cycle 1, lab samples can be collected up to 72 hours prior to MK-3475. Urinalysis, FT3, FT4 and TSH should be performed every 2 cycles. See Section 7.1.3 for details regarding laboratory tests.
15) Unresolved abnormal labs that are drug related AEs should be followed until resolution. Labs do not need to be repeated after the end of treatment if labs are within normal range.
16) β–D glucan will be measured for pulmonary evaluation at screening (within 10 days prior to the first dose of study treatment) and thereafter if a subject develops suspected pneumonitis, an additional test may be performed at the descretion of the investigator.
17) Pre-dose trough PK samples for MK-3475 will be collected at Day 1 of Cycles 1, 2, 4, 6 and 8 (following Cycle 8, every 4 cycles) until treatment discontinuation (or until the subject starts new anti-neoplastic therapy). All pre-dose PK samples for MK-3475 should be drawn within 24 hours before infusion of MK-3475. The peak (post-dose) samples will be collected at Day 1 of Cycle 1 and this sample should be drawn within 30 minutes after the end of infusion. Anti-MK-3475 antibodies should be drawn with all pre-dose trough PK samples. Procedures for sample collection are described in the Procedures Manual.
As of amendment 2, the collection for PK and ADA samples should be stopped.
18) Trough (pre-dose) and post-dose PK samples for INCB024360 will be collected at Days 1 and 5 of Cycle 1, and Day 5 of Cycle 2. All trough samples should be drawn before administration of INCB024360. All post-dose samples should be drawn at 30 minutes, and 1, 2, 4, 6, 8 and 10 hours after the administration of INCB024360 at Day 5 of Cycle 1. In addition, the post-dose sample should be drawn at 1 hours after the administration of INCB024360 at Day 5 of Cycle 2. Procedures for sample collection are described in the Procedures Manual. The investigator or qualified designee will remind the subject when they should not take their morning dose of INCB024360 on the day of full PK sampling.

Title Treatment:	Screening	Treatment Cycles [1)]								End of Treatment	Post-Treatment	Notes Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.
Cycle (Week)	(-4)	1 (0)					2 (3)		3 (6) and beyond	Discon	Safety Follow-up	
Relative Day in Cycle (on Day)		1	5	8	15	21	1	2-21	1-21			
Scheduling Window (Days):	-28	-	-	-	-	-	+3	-	±3	At time of Discon	30 (±7) days Post Discon	

19) Blood for RNA Analyses should be collected pre-dose on Day 1 of Cycle 1, 2, and 5. Blood for Plasma and Serum Biomarker Analyses should be collected pre-dose on Day 1 of Cycle 1 and Cycle 2.
20) This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site.
21) Not applicable in Amendment 02.
22) Tumor tissue for biomarker analysis from an archival tissue sample or newly obtained biopsy (core or excisional: FNA/EBUS not adequate) of a tumor lesion not previously irradiated can be optionally provided to the central vendor for characterization of PD-L1/IDO1 status. These samples are not required to be obtained within 4 weeks of enrollment. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual.

6.2 Second Course Phase (Retreatment ONLY)

Note: For Part A, subjects who are already in second course as of Amendment 02 would be eligible to receive trial treatment for up to 17 additional administrations of INCB024360 + MK-3475 (approximately one year). Retreatment for new participants in Part A, or any participants in Part B will no longer be available.

Title Treatment:	Treatment Cycles [1]			End of Treatment	Post-Treatment	Notes Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.
Cycle (Week)	1 (0)	2 (3)	3 (6) and beyond	Discon	Safety Follow-up	
Relative Day in Cycle (on Day)	1-21	1-21	1-21			
Scheduling Window (Days):	-	±3	±3	At time of Discon	30 (±7) days Post Discon	
Administrative Procedures						
Eligibility Criteria	X					
Concomitant Medication Review [4]	X	X	X	X	X	
Trial Treatment Administration						
MK-3475 (Pembrolizumab) Administration Q3W	X	X	X			
INCB024360 (Epacadostat) Administration BID	X----------X	X----------X	X----------X			
Clinical Procedures/Assessments						
Review Adverse Events [5]	X----------X					
Full Physical Examination [6]	X			X		
Directed Physical Examination [6]		X	X			
Vital Signs and Weight [7]	X	X	X	X	X	
12-Lead ECG [8]	X	X		X	X	
ECOG Performance Status	X	X	X	X	X	
Arterial Blood Oxygen Saturation (SpO_2) Measurement [10]	X	X	X	X	X	
Laboratory Procedures/Assessments: analysis performed by local laboratory						
Pregnancy Test (Urine or Serum β-HCG) [10]	X					
Coagulation Parameters [11], [12], [13]	X					
Hematology and Chemistry [12] [13]	X	X	X	X	X	
Urinalysis [12] [13]	X		X	X	X	
FT3, FT4 and TSH [12] [13]	X		X	X	X	

Title Treatment:	Treatment Cycles [1]			End of Treatment	Post-Treatment	Notes Participants who discontinue study treatment for whatever reason will proceed directly to EOT and Safety Follow-up.
Cycle (Week)	1 (0)	2 (3)	3 (6) and beyond	Discon	Safety Follow-up	
Relative Day in Cycle (on Day)	1-21	1-21	1-21			
Scheduling Window (Days):	-	±3	±3	At time of Discon	30 (±7) days Post Discon	
KL-6, β-D glucan [13), 14)]	X					
Efficacy Measurements						
Tumor Imaging	X		X	X		The timing of imaging during the treatment phase is according to the site's SOC for tumor assessment until PD or initiation of a new anticancer regimen.

1) In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of MK-3475 for each cycle, and the window for each visit is ± 3 days unless otherwise specified. Treatment cycles are 3 weeks (Q3W).
2) Not applicable in Amendment 02.
3) Not applicable in Amendment 02.
4) Concomitant medications - Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for AEs as defined in Section 7.2.
5) Report all AEs occurring within 90 days after the last dose of trial treatment or 30 days of the end of treatment if the subject initiates new anticancer therapy, whichever is earlier. Afterwards, report only SAEs that are related to trial treatment. Adverse experiences and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness.
6) Perform physical examinations at predose on Day 1. A full physical examination will be performed at Cycle 1 and at the discontinuation.
7) Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure.
8) ECG should be performed at predose and approximately 60 to 90 minutes after the first dose of INCB024360 for Day 1 of Cycles 1 and 2, and 30 day post-discontinuation.
9) Arterial blood oxygen saturation (SpO_2) should be measured on Day 1 of each cycle, at the discontinuation and at the safety follow-up (30 days post discon).
10) For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of Second Course Phase. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
11) Coagulation factors should be monitored closely throughout the trial for any subject receiving anticoagulant therapy.
12) Laboratory tests for determining eligibility for Second Course Phase are to be performed locally within 10 days prior to the first dose of Second Course Phase. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. Urinalysis, FT3, FT4 and TSH should be performed every 2 cycles. See Section 7.1.3 for details regarding laboratory tests.
13) Unresolved abnormal labs that are drug related AEs should be followed until resolution. Labs do not need to be repeated after the end of treatment if labs are within normal range.
14) KL-6 and β–D glucan will be measured if a subject develops suspected pneumonitis; an additional test may be performed at the discretion of the investigator.
15) Not applicable in Amendment 02.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., 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.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Subject Identification Card.

Subjects will also be given a serotonin syndrome (SS) information sheet for signs and symptoms of SS prior to the first dose of INCB024360. This information sheet also instructs subjects to seek immediate medical care if any of these symptoms are observed.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the investigator.

Disease details regarding the subject's cancer other than the cancer under study will be recorded separately even if diagnosed greater than 10 years prior to the first dose of trial medication and not listed as medical history.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

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 4 weeks before the first dose of trial medication.

In addition, the investigator will review and record all prior cancer treatments including systemic treatments, radiation and surgeries even if taken greater than 4 weeks prior to starting the trial therapy. Prior treatments for the subject's cancer will be recorded separately and not listed as a prior medication.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial from start of study treatment through the 30-day safety follow-up visit. After the safety follow-up visit, record all medications related to reportable AEs as defined in Section 7.2.

In addition, the investigator will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. The new cancer therapies for the subject's cancer will be recorded separately and not listed as a concomitant medication.

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.5.1.

7.1.1.7 Assignment of Treatment/Randomization Number

All eligible subjects will be allocated, by non-random assignment, and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 treatment/randomization number.

No subject randomization will occur in this study. Eligible subjects will be assigned to each dose level. The investigator examines and confirms the eligibility of the subject, and then e-mail to the SPONSOR to register the subject including screening number, date of consent, allocation number/dose level or Cohort (if subject is enrolled), and date of the initial administration of study drug. In Part B, the investigators will inform the Sponsor of the chemotherapy (Cohort) that Investigators will select prior to treatment allocation. The SPONSOR confirms the registration of the subject.

Subjects who do not meet entry criteria will not be assigned an allocation number. Subjects enrolled in one dose level cannot be re-enrolled in another dose level. If a subject is not enrolled, the reason for exclusion from the study will be documented on this log (e-mail). The log should be kept by the investigator and the SPONSOR.

The SPONSOR will keep the investigator informed of the screening activities and enrollment in dose group availability.

Procedures for allocation number are described in the Procedures Manual.

7.1.1.8 Trial Compliance (Medication)

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

The preparation and administration of cisplatin, pemetrexed, carboplatin and paclitaxel will be performed according to local practice and labels.

MK-3475

Administration of MK-3475 will be witnessed by the investigator and/or trial staff. The total volume of MK-3475 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.

INCB024360

Subjects will take their dose of INCB024360 in the morning and evening, approximately 12 hours apart without regard to food. Subjects will self-administer INCB024360 except on C1D1, C1D5, C1D12 of Part A cohort 1, C1D1, C1D5 of Part A cohort 2 and Part B, and C2D5 of both Part A and Part B, when the morning dose will be given at the study site clinic for PK sampling. On days when INCB024360 is administered in the clinic, subjects will take INCB024360 and then begin infusion of MK-3475. The investigator or qualified designee will remind the subject when they should not take their morning dose of INCB024360.

INCB024360 compliance will be calculated by the Sponsor based on the drug accountability documented by the site staff and monitored by the Sponsor (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.

NOTE: As of Amendment 02, INCB024360 is stopped from Part B.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart (Section 6.0) and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Appendix 12.3). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs of unknown etiology associated with MK-3475 and INCB024360 exposure should be evaluated to determine if it is possibly an event of a potentially immunologic etiology; see Section 5.6.

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs. Subjects should be assessed for possible immune-related events prior to each visit. 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 immune-related AE, 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.

7.1.2.1.1 Distribution of Serotonin Syndrome (SS) Information Sheet

NOTE: As of Amendment 02, this section is updated to reflect the removal of epacadostat from the study and current safety information for epacadostat. SS information sheet will no longer provided.

7.1.2.2 Physical Exam

The investigator will perform a full physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed as specified in the Trial Flow Chart (Section 6.0). For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator will perform a directed physical exam as clinically indicated prior to Day 1 of each cycle and Day 8 of cycle 1 of trial treatment administration. In Part B, the investigator will perform directed physical exam on Day 1 of each cycle and Day 8 and 15 of cycle 1. After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs.

7.1.2.3 Vital Signs, Height and Weight

The investigator will take vital signs as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure.

Patients must be resting in a sitting position for approximately 10 minutes prior to obtaining vital signs. Height will be measured at screening only.

If blood pressure is >150/100 mmHg in a patient without a history of hypertension, or increased >20 mmHg (diastolic) from baseline measurement in a patient with a previous history of hypertension, the assessment should be repeated in 10 minutes for confirmation.

7.1.2.4 12-lead ECG

The investigator will perform a standard 12-lead ECG using local standard procedures as specified in the Trial Flow Chart (Section 6.0). Clinically significant abnormal findings at screening should be recorded as medical history. After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator will assess ECOG performance status (see Section 12.2) as specified in the Trial Flow Chart (Section 6.0).

7.1.2.6 Arterial Blood Oxygen Saturation (SpO_2) Measurement

The investigator will measure arterial blood oxygen saturation (SpO2) as specified in the Trial Flow Chart (Section 6.0).

7.1.2.7 Tumor Imaging and Assessment of Disease

The process for image collection can be found in the Procedures Manual. Tumor imaging should be acquired by computed tomography (CT, strongly preferred). Magnetic resonance imaging (MRI) should be used when CT is contraindicated or for imaging in the brain. The same imaging technique regarding modality and use of contrast should be used in a subject

throughout the tri al to optimize the visualization of existing and new tumor burden. CT or MRI scans should include the chest, abdomen, and pelvis. A chest CT performed for tumor imaging will be used for pulmonary radiographic evaluation (see Section 7.1.2.8).

Subject eligibility will be determined based on RECIST 1.1 (See Section 12.7).

7.1.2.7.1 Initial Tumor Imaging

The tumor imaging (CT or MRI) for screening should be performed within 4 weeks prior to the first dose of trial treatment. The site study team must review pre-trial images to confirm the subject has measurable disease per RECIST 1.1. 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 4 weeks prior to the first dose of trial treatment.

Subjects with previously treated brain metastases may participate provided they have stable brain metastases, i.e. without evidence of progression by imaging during screening (confirmed by MRI if MRI was used at prior imaging, or confirmed by CT imaging if CT used at prior imaging). Any neurologic symptoms must have returned to baseline and subjects must have no evidence of new or enlarging brain metastases, and have not used steroids for brain metastases for at least 14 days prior to trial initiation as per local site assessment. This exception does not include carcinomatous meningitis, as subjects with carcinomatous meningitis are excluded regardless of clinical stability.

7.1.2.7.2 Tumor Imaging During the Study

NOTE: As of Amendment 02, the use of irRECIST and iRECIST is discontinued. This section is no longer applicable. Participants with radiographic disease progression as determined by RECIST 1.1 by investigator assessment will discontinue from pembrolizumab monotherapy; no confirmatory scans are required. However, if the participant is achieving a clinically meaningful benefit, an exception to continue with pembrolizumab monotherapy may be considered following consultation with MSD.

7.1.2.7.3 End of Treatment and Follow-up Tumor Imaging

NOTE: As of Amendment 02, there is no protocol-specified imaging at end of treatment and no follow-up imaging is required. This section is no longer applicable and has been deleted.

7.1.2.7.4 Second Course (Retreatment) Tumor Imaging (Part A for ongoing participants only; not for new participants in Part A and all participants in Part B)

NOTE: As of Amendment 02, there is no protocol-specified imaging at second course of treatment is required. This section is no longer applicable and has been deleted.

7.1.2.8 Pulmonary Radiographic Evaluation for MK-3475-Induced Pneumonitis

Pulmonary radiographic imaging is used in a diagnosis of MK-3475-induced pneumonitis. A chest CT performed for tumor imaging may be used for pulmonary radiographic evaluation. For a subject with suspected pneumonitis based on respiratory symptoms, other clinical findings or laboratory findings, a chest CT should be performed immediately. If a finding on

pneumonitis is observed, the subject should be followed every month with chest imaging to monitor the pneumonitis.

Pulmonary radiographic evaluation will be performed according to the table in Section 6.0. The investigator will judge whether the variation after the trial treatment administration is an adverse experience or not and record it in the Case Report Form.

7.1.2.9 Tumor Tissue Collection

Participation in this trial will require submitting tumor sample for PD-L1 and IDO1 expression evaluation at central laboratories in Part A. These samples are not required to be obtained within 4 weeks of enrollment. Expression status of PD-L1 and IDO1 will not be reported until the end of the study. Subjects can be enrolled in this trial regardless of expression status of PD-1 and IDO1.

Note: Submission of formalin-fixed paraffin embedded tumor tissue sample blocks are preferred; if submitting unstained slides, the slides should be freshly cut and submitted to the testing laboratory per the specifications in the Procedures Manual.

Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial, including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the Procedure Manual.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 10.

Table 10 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin (β-hCG)
Hemoglobin	Alkaline phosphatase	Glucose	PT (INR)
Platelet count	Alanine aminotransferase (ALT)	Protein	aPTT
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Free triiodothyronine (FT3)
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam, if abnormal results are noted	Free thyroxine (FT4)
Absolute Neutrophil Count	Creatinine	Urine pregnancy test*	Thyroid stimulating hormone (TSH)
Absolute Lymphocyte Count	CRP		HIV antibody**
	Uric Acid		HBsAg**
	Calcium		HCV RNA**
	Chloride		KL-6
	Glucose		β-D glucan
	Phosphorus		Tumor Markers (as appropriate)
	Potassium		SP-D***
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood Urea Nitrogen		

* Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
** For screening visit only.
*** Part B only.

Laboratory tests (hematology, serum chemistry, urinalysis, coagulation parameters, thyroid function, KL-6, SP-D (Part B) and β-D glucan) for screening or entry into the Second Course Phase (Part A) should be performed locally within 10 days prior to the first dose of treatment. From Cycle 2, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator and found to be acceptable prior to Day 1 of each cycle.

PT/INR and aPTT will be collected as coagulation parameters.

TSH, FT3, and FT4 will be measured for thyroid function test.

Testing for HIV 1/2 antibodies, HBsAg, and HCV RNA will be performed at screening. If results of these tests obtained within 3 months before screening are available, they can be used even before consent is obtained.

For women of reproductive potential, a urine/serum pregnancy test will be performed within 72 hours of the first dose. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

KL-6 is a lung-specific marker for pneumonitis [56]. β-D glucan is a marker for fungus infectious disease [57], and is used for the differential diagnosis for pneumonitis. KL-6 and In Part A, KL-6 and β-D glucan will be measured before starting the treatment courses, and thereafter if a subject develops suspected pneumonitis, an additional test will be performed as needed by investigator's judgment. In Part B, β-D glucan will be measured before starting the tratment courses, and thereafter if a subject develops suspected pneumonitis, an additional test will be performed as needed by investigator's judgment.

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

To further evaluate MK-3475 immunogenicity and MK-3475 and INCB024360 exposure in this indication, sample collections for analysis of anti-drug antibodies (ADA) and PK are currently planned as shown in the Trial Flowchart (Section 6.0). If ongoing ADA and/or PK results continue to be consistent with existing ADA and/or PK data from other MK-3475 clinical trials, it may be decided to discontinue or reduce further sample collection in this study.

Pharmacokinetic data is planned to be analyzed by comparison to historical reference data in this patient population. Blood samples for PK and anti- pembrolizumab-antibodies collected may be stored only at this time. Further analysis may be performed if required. The results of these analyses, if performed, will be reported separately.

7.1.3.2.1 Blood Sample Collection for PK of MK-3475

Sample collection, storage and shipment instructions for samples will be provided in the Procedures Manual. Serum PK samples should be drawn according to the PK collection schedule for subjects who receive MK-3475.

Biomarker assessments may also be conducted at the discretion of the sponsor using excess PK samples.

7.1.3.2.2 Blood Sample Collection for Anti-MK-3475 Antibodies

Sample collection, storage and shipment instructions for samples will be provided in the Procedures Manual. Anti-MK-3475 antibody serum samples should be drawn according to the ADA collection schedule for subjects who receive MK-3475. Simultaneous PK sampling is required for interpretation of ADA analysis.

7.1.3.2.3 Blood Sample Collection for PK of INCB024360

Sample collection, storage and shipment instructions for samples will be provided in the Procedures Manual. Plasma samples will be obtained at the visits indicated in the Trial Flow Chart (Section 6.0.). Pharmacokinetics samples for INCB024360 will be required for all subjects enrolled in this study. Subjects will arrive at clinic having withheld their morning dose of INCB024360.

After the predose (predose is defined as within 24 hours before administration of MK-3475 and before administration of INCB024360) PK sample is drawn, subjects will take INCB024360 and then begin infusion of MK-3475. The exact date and time of the PK blood draws will be recorded along with the date and time of the last dose of trial treatment and last meal preceding the blood draw.

Biomarker assessments may also be conducted at the discretion of the sponsor using excess PK samples.

7.1.3.2.4 Blood Sample Collection for Pharmacodynamic Assessments of INCB024360

Sample collection, storage and shipment instructions for samples will be provided in the Procedures Manual. Plasma samples will be obtained for pharmacodynamic assessments at the visits designated in the Trial Flow Chart (Section 6.0).

Plasma PD samples will be analyzed for changes in the levels of tryptophan and kynurenine by liquid chromatography with tandem mass spectrometry to monitor systemic activity in modulating the IDO1 enzyme. Protein analytes such as relevant tumor markers and markers of immune function may be measured by enzyme-linked immunosorbent assay, or other relevant methods, using these samples.

Biomarker assessments may also be conducted at the discretion of the sponsor using excess PD samples.

7.1.3.2.5 Blood Collection for RNA Analyses, Biomarker Plasma Analyses, and Biomarker Serum Analyses

Sample Collection, storage and shipment instruction for RNA, plasma and serum samples will be provided in the Procedures Manual.

7.1.3.3 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the Procedures Manual.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

Subjects who discontinue/withdraw from treatment prior to completion of the treatment regimen should be encouraged to continue to be followed for all remaining study visits.

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the end of treatment should be performed at the time of discontinuation. Any

adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events and subjects who a) attain a CR or b) complete 35 administrations of MK-3475 (approximately 2 years) may discontinue treatment. After discontinuing treatment following assessment of CR or 35 administrations of MK-3475, these subjects should return to the site for a Safety Follow-up Visit and then proceed with assessments (see Section 7.1.5.4).

7.1.4.2 Blinding/Unblinding

This is an open label trial; there is no blinding for this trial.

7.1.4.3 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

Critical Equipment for this trial includes:

- Laboratory equipment – as required for inclusion labs and trial assessments
- Imaging equipment – as required for study objective
- Infusion equipment – as required to support administration of MK-3475

See protocol-specified guidance in the Administrative Binder and Procedures Manual.

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

Up to 4 weeks prior to enrollment, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1.

Written consent for the study must be obtained prior to performing any protocol specific procedure. After providing consent, subjects will be assigned a screening number. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 4 weeks prior to the first dose of trial treatment except for the following:

- Laboratory tests (hematology, serum chemistry, urinalysis, coagulation parameters, thyroid function test, KL-6, SP-D (Part B) and β-D glucan) are to be performed locally within 10 days prior to the first dose of trial treatment.
- For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. If urine pregnancy results cannot be

confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

- If results of HIV 1/2 antibodies, HBsAg, and HCV RNA test obtained within 3 months before screening are available, they can be used even before consent is obtained.
- Archival tumor biopsy for PD-L1/IDO1 characterization is not required to be obtained within 4 weeks prior to the first dose of trial treatment.

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met.

7.1.5.2 Treatment Period

The treatment period with the combination therapy will continue every 21 days for up to 35 infusions (approximately 2 years) as long as subjects are receiving benefit from treatment and have not had disease progression or met any criteria for study withdrawal.

7.1.5.3 End of Treatment

If a decision is made that the subject will permanently discontinue trial treatment, 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. The subject should be encouraged to return for the follow-up visit.

7.1.5.4 Post-Trial

7.1.5.4.1 Safety Follow-Up

NOTE: As of Amendment 02, the Safety Follow-up Visit will be the last visit in the study. This section has been amended accordingly.

The safety follow-up phase is the interval between the EOT visit and the scheduled safety follow-up visit, which should occur 30 days after the EOT visit or before the initiation of a new antineoplastic treatment, whichever comes first.

Subjects in Part A who are eligible for retreatment with the combination therapy (ie ongoing before the amendment 2 is approved) (as described in Section 7.1.5.5) may have up to 2 safety follow-up visits, 1 after the treatment period and 1 after the second course phase (re-treatment).

7.1.5.4.2 Follow-Up

NOTE: As of Amendment 02, the Follow-up Phase have been removed.

7.1.5.4.3 Survival Follow-Up

NOTE: As of Amendment 02, the Survival Follow-up Phase have been removed.

7.1.5.5 Second Course Phase (Retreatment Period): Part A only

Note: For Part A, subjects who are already in second course as of Amendment 02 would be eligible to receive trial treatment for up to 17 additional administrations of

INCB024360 + MK-3475 (approximately one year). No new participants in Part A or any participants in part B will have re-treatment (ie second course) available.

As of Amendment 01, all subjects who stop study treatment with SD or better may be eligible for up to one year (17 infusions) of additional MK-3475 and INCB024360 treatment if they progress after stopping study treatment from the initial treatment phase. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

- Either
    - Stopped initial treatment with study treatment after attaining an investigator-determined confirmed CR according to RECIST 1.1, and
        - Was treated for at least 8 administrations (at least 24 weeks) with study treatment before discontinuing treatment
        - Received at least two treatments with MK-3475 beyond the date when the initial CR was declared

    OR

    - Had SD, PR or CR and stopped study treatment after completion of 35 administrations (approximately 2 years) of MK-3475 for reasons other than disease progression or intolerability

    AND

- Experienced an investigator-determined radiographic disease progression after stopping their initial treatment
- Did not receive any anti-cancer treatment since the last dose of study treatment
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Section 5.1.2
- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female subject of childbearing potential* should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). *Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.
- Male subject should agree to use an adequate method of contraception starting with the first dose of study treatment through 120 days after the last dose of study treatment.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial 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 retreated at the same dose as when they last received INCB024360. Response or progression in this Second Course Phase (Re-treatment) will not count towards the ORR and PFS of the primary endpoint in this trial. Visit requirements are outlined in Section 6.0 – Trial Flow Chart.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the Electronic Data Capture (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

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

NOTE: As of Amendment 02, INCB024360 is stopped from Part B, and text relating to overdose of INCB024360 is no longer applicable for Part B.

In this trial, an overdose is any dose higher than ≥1000 mg (5 times the dose) of MK-3475 or ≥1000 mg BID of INCB024360 or ≥20% of prescribed dosage for chemotherapy. No specific information is available on the treatment of overdose of MK-3475 or INCB024360. 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 adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial.

Pregnancies and lactations of subjects and female partners of male subjects from the time the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations of subjects and female partners of male subjects that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;

- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

Refer to Table 11 f or additional details regarding each of the above criteria.

Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial,

or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 30 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - 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 lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon 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 trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each adverse event causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (i.e., to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the adverse experience to the single agent.

Table 11 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF REEXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Efficacy and Safety Evaluation Committee

The Efficacy and Safety Evaluation Committee (ESEC) will be established for the purpose of evaluating the safety information of this study from the specialist and objective viewpoints to ensure the safety of subjects. Efficacy will not be reviewed by the ESEC.

The details of the ESEC are prescribed by separate instructions.

7.3.2 Independent Pulmonary Radiographic Adviser

An independent pulmonary radiographic adviser will review pulmonary radiographic changes and its features using chest CT imaging if necessary.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any final database lock, changes made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with International Conference on Harmonisation (ICH) Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to final database lock, will be documented in a supplemental statistical analysis plan (SAP [sSAP]) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

The following analysis plan is applied to each Cohort in Part A (Cohorts 1 and 2) and Part B (Chemotherapy Cohorts 1, 2 and 3).

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized in below table. The comprehensive plan is provided in Sections 8.2 through 8.10.

Study Design Overview	A Phase I Study of INCB024360 alone and in combination with Pembrolizumab (MK-3475) and in combination with Pembrolizumab (MK-3475) and Chemotherapy in Patients with Advanced Solid Tumors (KEYNOTE-434)
Treatment Assignment	This is an open-label study.
Analysis Populations	All Subjects as Treated (ASaT)
Primary Endpoint(s)	Safety and tolerability of INCB024360 alone, INCB024360 in combination with MK-3475 and INCB024360 and Pembrolizumab in combination with Chemotherapy
Statistical Methods for Key Efficacy Analyses	The point estimate of ORR and 95% confidence interval will be provided using an exact binomial distribution.
Statistical Methods for Key Safety Analyses	Count and percentage of DLT in Cycle 1 and AE will be provided.
Interim Analyses	DLTs observed in Cycle 1 will be used to determine tolerability (see Section 5.2.1.2.1).
Multiplicity	No multiplicity adjustment is planned
Sample Size and Power	For DLT evaluation, on Part A, up to 9 patients for INCB024360 25 mg BID alone, 3 patients for INCB024360 100 mg alone, and 3 to 9 subjects for each INCB024360 dose combination with MK-3475 are estimated. On Part B, 6 subjects for each cohort are estimated. The total number of evaluable subjects is maximum of 60.

8.2 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the SPONSOR.

The Sponsor will generate the allocation schedule(s) for study treatment assignment for this protocol.

This trial is being conducted as an open-label trial (i.e. subjects, investigators, and SPONSOR personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned).

8.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.0 – Objectives & Hypotheses.

8.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below.

8.4.1 Safety Endpoints

Primary Endpoints

The primary endpoint in this study is the incidence of DLTs observed in the DLT evaluation period.

Other Major Variables

- Vital signs
- Physical examination
- ECOG performance status
- 12-lead ECG
- Pulmonary radiographic findings
- Adverse experiences
- Complete blood count
- Serum chemistry
- Urinalysis

All toxicities will be graded and recorded according to the CTCAE version 4.0. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes.

8.4.2 Pharmacokinetic Endpoints

Pharmacokinetics will be evaluated as a secondary objective for MK-3475 and INCB024360.

The serum concentrations of MK-3475 (C_{trough} and C_{max}) will be evaluated in combination of INCB024360 and in combination with INCB024360 and chemotherapy.

The pharmacokinetic profiles of INCB024360 will be assessed. Serial samples will be corrected alone and in combination with MK-3475 and MK-3475 in combination with chemotherapy. Pharmacokinetic parameters (C_{max}, T_{max}, C_{trough}, $t_{1/2}$, AUC_{0-t}) will be calculated from the plasma concentrations of INCB024360 for each treatment periods using a non-compartmental method with WinNONLIN.

8.4.3 ADA Endpoints

The presence of ADA will be evaluated when administered concomitantly.

8.4.4 Efficacy Endpoints

Efficacy will be evaluated as an exploratory objective for ORR, DOR, PFS, and OS per RECIST 1.1 by the local site.

Objective Response Rate (ORR) – based on RECIST 1.1 as assessed by the local site

Objective response rate is defined as the proportion of the subjects in the analysis population who have a complete response (CR) or partial response (PR). Responses are based on assessments by the local site per RECIST 1.1.

Duration of Overall Response (DOR) – based on RECIST 1.1 as assessed by the local site

For subjects who demonstrate CR or PR, duration of response is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause,

whichever occurs first. Response and progression are based on assessments by the local site per RECIST 1.1.

Progression-free survival (PFS) – based on RECIST 1.1 as assessed by the local site

Progression-free-survival (PFS) is defined as the time from first dose to the first documented disease progression per RECIST 1.1 based on assessments by the local site or death due to any cause, whichever occurs first.

Overall Survival (OS)

Overall survival (OS) is defined as the time from first dose to death due to any cause. Subjects without documented death at the time of the analysis will be censored at the date of the last follow-up.

8.4.5 Exploratory Biomarker Research

Tumor biopsy analyses to evaluate IDO1 expression (+/-), PD-L1 expression (positive versus negative/indeterminate) in tumor tissue and immune cell infiltrate at baseline and correlate expression with response, PFS and/or OS. The expression of exploratory histological biomarkers will also be assessed.

8.5 Analysis Populations

8.5.1 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this trial. The ASaT population consists of all allocated subjects who received at least one dose of trial treatment (INCB024360 administered alone or in combination with MK-3475 or MK-3475 in combination with chemotherapy). Subjects will be included in the dose level corresponding to the treatment dose they actually received for the analysis of safety data using the ASaT population.

At least one laboratory, 12-lead ECG or vital sign measurement obtained subsequent to at least one dose of treatment dose is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

8.5.2 PK/ADA Analysis Populations

The All Subjects who will be administered by INCB024360 alone and in combination with MK-3475 in advanced solid tumors (Part A) and in combination with MK-3475 and chemotherapy in advanced NSCLC (Part B), and will be drawn PK/ADA samples, will serve as the primary population for the analysis of PK/ADA data in this trial.

8.5.3 Efficacy Analysis Populations

The All Subjects as Treated (ASaT) population will serve as the primary population for the analysis of efficacy data in this trial excluding:

- Failure to receive at least one dose of trial treatment (INCB024360 alone or in combination with MK-3475 or in combination with MK-3475 and chemotherapy).

The exploratory Biomarker analyses will be based on subjects who have evaluable Biomarker measurements. No explicit imputation was made for missing data.

8.6 Statistical Methods

8.6.1 Statistical Methods for Safety Analyses

Frequencies of DLTs during the DLT evaluation period [the first 1 week (Part A: cohort 1) and 3 weeks (Part A: cohort 2 and Part B) after initiation of study treatment] will be summarized by tabulating by dose level. If data is available, tables of summary statistics (mean, standard deviation, median, and range) for time to onset and duration of the first grade DLT AEs will be provided. All adverse events occur during and after cycle 1 will also be summarized. Laboratory assessments will be summarized. Adverse events will be summarized by tabulating the number (%) of subjects experiencing at least one adverse event within each system organ class and within each preferred term. Complete blood count, chemistry panel, urinalysis, pulmonary radiographic change findings, adverse events, electrocardiogram, vital signs, physical examination and ECOG PS will be summarized.

8.6.2 Statistical Methods for Pharmacokinetic Analyses

Descriptive statistics of the pharmacokinetic parameters of MK-3475 and INCB024360 will be calculated. The pharmacokinetic parameters of INCB024360 will be compared INCB024360 mono-therapy versus INCB024360+MK-3475 combo-therapy and versus INCB024360+MK-3475 + chemotherapy combo-therapy.

8.6.3 Statistical Methods for Efficacy Analyses

The point estimate of ORR and 95% confidence interval (as determined by the upper and lower 97.5% one-sided confidence bounds) will be provided using an exact binomial distribution. Response categories for target and non-target lesions for subjects with advanced solid tumors (complete response, partial response, progressive disease, and stable disease), DOR, PFS and OS will be tabulated across the various doses levels and will be summarized descriptively using Kaplan-Meier method. The Kaplan-Meier graphs will also be provided.

An exploratory analysis of a potential correlation between IDO1 expression (+/-), PD-L1 expression levels and tumor response will be performed as appropriate.

8.7 Interim Analyses

No interim analysis is planned.

8.8 Multiplicity

Since the primary objective of this trial is to estimate safety and tolerability of INCB024360 alone and in combination with MK-3475 and MK-3475 in combination with chemotherapy, no statistical hypotheses are tested, so no multiplicity adjustments will be applied to any p-values generated or confidence intervals calculated. No adjustment for multiplicity is planned.

8.9 Sample Size and Power Calculations

The primary objective for the study is to evaluate the tolerability and safety profile of INCB024360 alone and in combination with MK-3475 in advanced solid tumors (Part A) and MK-3475 in combination with chemotherapy in advanced NSCLC (Part B). The primary endpoints for the study are DLT rate. A mTPI (modified toxicity probability interval) design suggested by Ji et al [1] targeting a 16.7% DLT rate for Part A and 30% for Part B will be employed in safety assessment. Dose escalation/tolerability evaluation rules were described in 5.2.1.2. For DLT evaluation, on Part A, up to 9 patients for INCB024360 25 mg BID alone, 3 patients for INCB024360 100 mg alone, and 3 to 9 subjects for each INCB024360 dose combination with MK-3475 are estimated. On Part B, 6 subjects for each cohort are estimated. The total number of evaluable subjects is maximum of 60.

8.10 Compliance (Medication Adherence)

Drug accountability data for study treatment will be collected during the study. Any deviation from protocol-directed administration will be reported.

MK-3475: Compliance with protocol-directed MK-3475 will be measured by subjects: (1) receiving unscheduled study agent infusions/injections, (2) missing an infusion/injection, (3) receiving incorrect study agent dose, and (4) receiving an infusion at rate greater than 10 mL/min. Numbers and percentages of subjects and infusion/injection visits with any deviation in these measures will be reported for the ASaT population.

INCB024360: In this study, as part of the routine recording of the amount of study treatment taken by each subject will be counted, reviewed, and recorded at regular intervals. These results will be used to calculate subject compliance.

Chemotherapy: In this study, as part of the routine recording of the amount of study treatment taken by each subject will be counted, reviewed, and recorded at regular intervals. These results will be used to calculate patient compliance.

For a subject who is followed for the entire study period, the "Number of INCB024360 Doses Should be on Therapy" is the total number of protocol specified doses from first treatment day to the last scheduled day for treatment administration for that subject. For a subject who discontinued from the study permanently, the "Number of INCB024360 Doses Should be on Therapy" is the total number of doses from first treatment day to the date the subject discontinued from the study.

For each subject, percent compliance will then be calculated using the following formula:

$$\text{Percent Compliance} = \frac{\text{Number of Doses on Therapy}}{\text{Number of Doses Should be on Therapy}} \times 100.$$

Summary statistics will be provided on percent compliance by treatment group for the ASaT population.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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 the Sponsor as summarized in Table 12.

Clinical supplies will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies.

Table 12 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
MK-3475 100 mg/ 4 mL (pembrolizumab)	Solution for Infusion	Provided centrally by the Sponsor
INCB024360 25 mg (epacadostat)	Tablet	Provided centrally by the Sponsor
INCB024360 100 mg (epacadostat)	Tablet	Provided centrally by the Sponsor

9.2 Packaging and Labeling Information

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

Subjects will receive bottles of INCB024360 to satisfy patient treatment for one cycle. No kitting is required for INCB024360. MK-3475 will be provided as a kitted supply (2 vials/kit).

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. Treatment (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

Section 5.8 outlines the criteria for allowing subjects who are discontinued from treatment to continue to be monitored in the trial.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;

2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and

all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAMA/FDAAA mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and

functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results,

due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

12.2 Eastern Cooperative oncology group (ECOG) Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

12.3 Common Terminology Criteria for Adverse Events (CTCAE) 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).

12.4 Prohibited Monoamine Oxidase Inhibitors and Drugs Associated with Significant Monoamine Oxidase Inhibitory Activity

NOTE: As of Amendment 02, this section is updated to reflect the removal of MAO inhibitors from prohibited medication list.

12.5 Publication on Serotonin Syndrome

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

CURRENT CONCEPTS

The Serotonin Syndrome

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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).[3,5] 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.[1-4,12,15-18] A single therapeutic dose of an SSRI has caused the serotonin syndrome.[19] Moreover, the addition of drugs that inhibit cytochrome isoforms CYP2D6 and CYP3A4 to therapeutic SSRI regimens has been associated with the condition.[16,20,21] 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.[16] 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").[4,8,15,16,22]

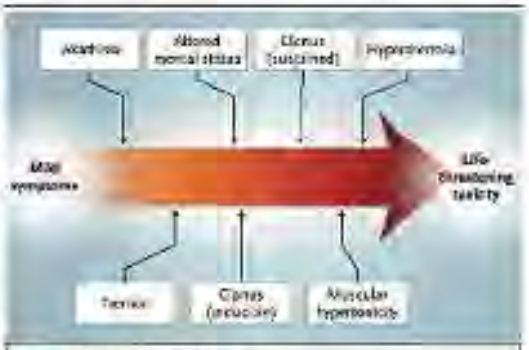

Figure 2. Spectrum of Clinical Findings.
Manifestations of the serotonin syndrome range from mild to life-threatening. The vertical arrows suggest the approximate point at which clinical findings initially appear in the spectrum of the disease, but all findings may not be consistently present in a single 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 hyperactivity. 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: nefazodone, amitriptyline, bupropion, 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: linezolid (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, Serafem, Luvox, Paxil, Celexa, Desyrel, Serzone, Buspar, Anafranil, Effexor, Nardil, Marplan, Depakote, Demerol, Duragesic, Sublimaze, Ultram, Talwin, Zofran, Kytril, Reglan, Imitrex, Mesulid, Redux, Pondimin, Zyvox, Norvir, Parnate, Tofranil, Remeron
Phenelzine and meperidine
Tranylcypromine and imipramine
Phenelzine and selective serotonin-reuptake inhibitors
Paroxetine and buspirone
Linezolid 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.[2,6] 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.[2,6] 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.[7,8]

Serotonergic neurons in the CNS are found primarily in the midline raphe nuclei, located in the brain stem from the midbrain to the medulla.[9] The rostral end of this system assists in the regulation of wakefulness, affective behavior, food intake, thermoregulation, migraine, emesis, and sexual behavior.[10] The neurons of the raphe in the lower pons and medulla participate in the regulation of nociception and motor tone.[10] In the periphery, the serotonin system assists in the regulation of vascular tone and gastrointestinal motility.[10]

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.[11-13] 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-

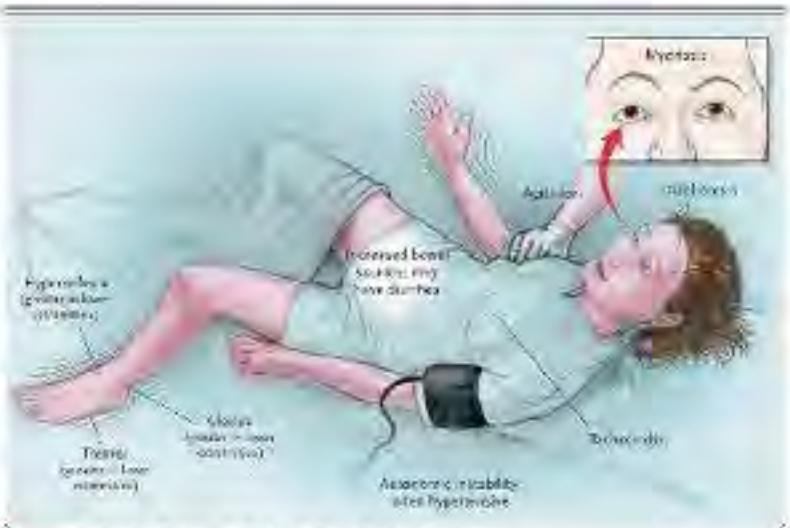

Figure 2. Findings in a Patient with Moderately Severe Serotonin Syndrome.
Hyperkinetic neuromuscular findings of tremor or clonus and hyperreflexia should lead the clinician to consider the diagnosis of the serotonin syndrome.

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.[36,37] 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.[3,11,34,40] 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.[3,5] 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

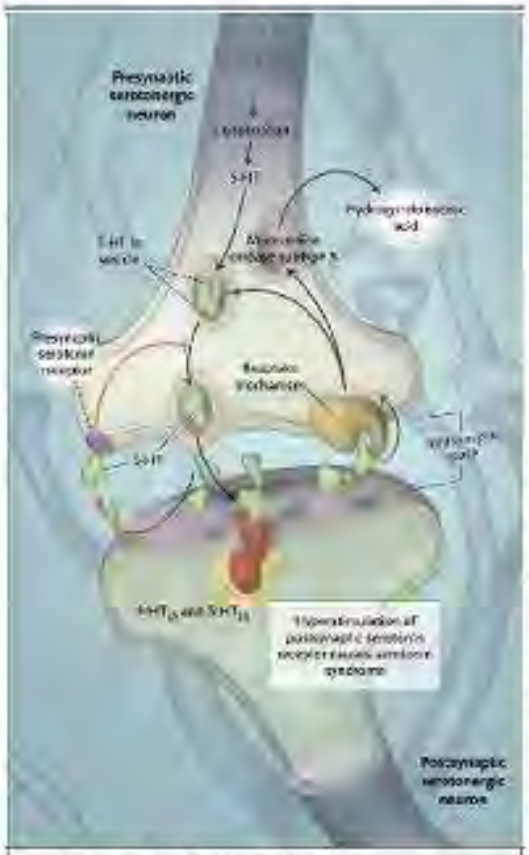

Figure 1. Serotonin Biosynthesis and Metabolism.

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 intersynaptic 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 hypothermia and hyperpyrexia occur in life-threatening cases, but muscle rigidity may mask the highly distinguishing findings of clonus and hyperreflexia and therefore cloud the diagnosis.[3,40]

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.[41] On physical examination, the skin is often mottled, with cyanotic areas contrasting with patches of bright red flushing.[42] 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.[46] 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-

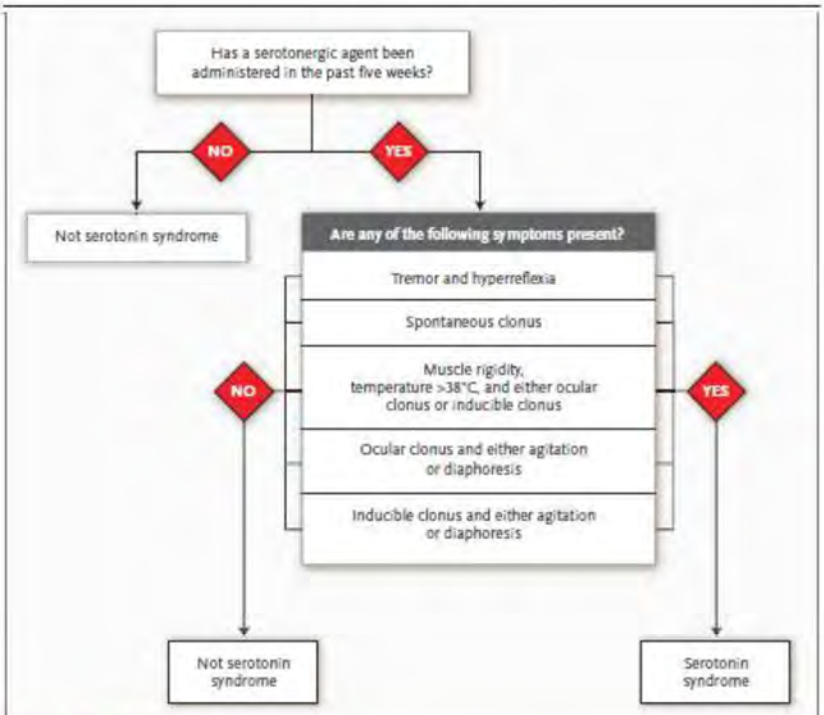

Figure 4. Algorithm for Diagnosis.
The neuromuscular features of clonus and hyperreflexia are highly diagnostic for the serotonin syndrome, and their occurrence in the setting of serotonergic drug use establishes the diagnosis. Clinicians should be aware that muscle rigidity can overwhelm other neuromuscular 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

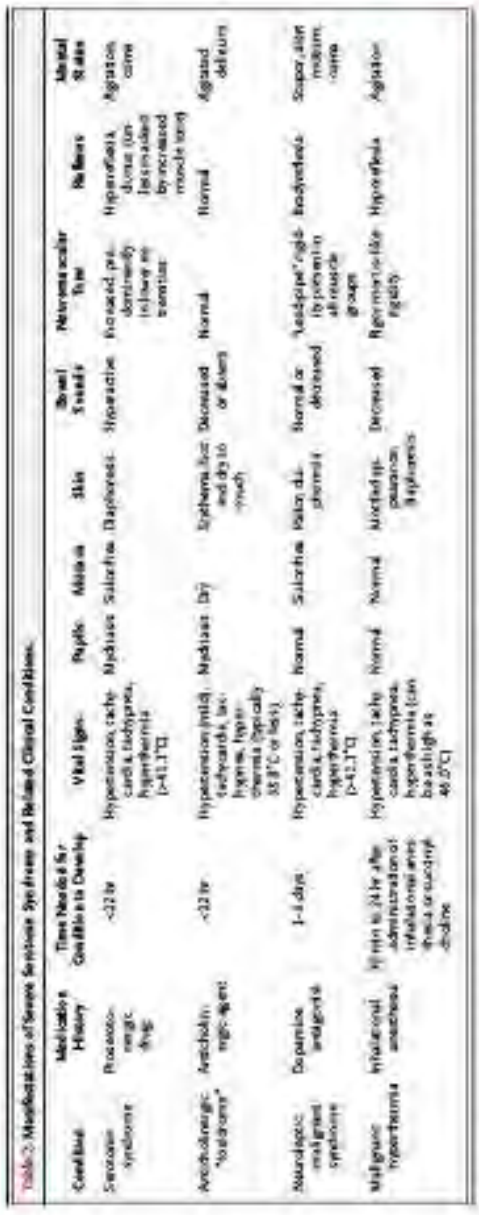

Table 2. Manifestations of Severe Serotonin Syndrome and Related Clinical Conditions.

Condition	Medication History	Time Needed for Condition to Develop	Vital Signs	Psyche	Mentation	Skin	Bowel Sounds	Neuromuscular Tone	Reflexes	Mental States
Serotonin syndrome	Presynaptic serotonergic drugs	<12 hr	Hypertension; tachycardia; tachypnea; hyperthermia (>41.1°C)	Hypervigilance	Confusion	Diaphoresis	Hyperactive	Increased, predominantly in lower extremities	Hyperreflexia, clonus (unbalanced by increased muscle tone)	Agitation, coma
Anticholinergic "toxidrome"	Anticholinergic agent	<12 hr	Hypertension (mild), tachycardia, tachypnea, hyperthermia (typically 38.8°C or less)	Mild psychosis	Dry	Erythema, hot and dry to touch	Decreased or absent	Normal	Normal	Agitated delirium
Neuroleptic malignant syndrome	Dopamine antagonists	1–4 days	Hypertension; tachycardia; tachypnea; hyperthermia (>41.1°C)	Normal	Subjective	Rales, diaphoresis	Normal or decreased	"Lead-pipe" rigidity (hypertonia in all muscle groups)	Bradyreflexia	Stupor, akinetic mutism, coma
Malignant hyperthermia	Inhalational anesthesia	Within 24 hr after administration of inhalational anesthetic or succinylcholine	Hypertension; tachycardia; tachypnea; hyperthermia (can be as high as 46.0°C)	Normal	Normal	Mottled, hypotension, 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.[45] 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 setpoint.

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.[7] 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.[7,25,45] 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.[35,39] 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.[39]

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12.6 Description of the iRECIST Process for Assessment of Disease Progression

NOTE: As of Amendment 02, iRECIST is no longer applicable and has been deleted from this section. All imaging will be performed as per local standard of care guidelines per RECIST 1.1. Participants with radiographic disease progression as determined by RECIST 1.1 by investigator assessment will discontinue from pembrolizumab monotherapy; no confirmatory scans are required. However, if the participant is achieving a clinically meaningful benefit, an exception to continue with pembrolizumab monotherapy may be considered following consultation with the MSD.

12.7 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria For Evaluating Response in Solid Tumors

RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

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12.8 List of Abbreviations

Abbreviation/Term	Definition
ADA	Anti-Drug Antibodies
AE	Adverse Event
ALP	alkaline phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
ASaT	All Subjects as Treated
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
BCG	Bacillus Calmette–Guérin vaccine
BID	twice daily
CFR	Code of Federal Regulations
CI	Confidence Interval
CNS	Central Nervous System
CR	Complete Response
CrCl	Calculated Creatinine Clearance
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte-Associated Antigen-4
DKA	diabetic ketoacidosis
DLT	dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of Response
ECG	Electrocardiogram
ECI	Events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOT	end of treatment
ERC	Ethics Review Committee
FFPE	Formalin-fixed, paraffin-embedded
GCP	Good Clinical Practice
G-CSF	Granulocyte-Colony Stimulating Factors
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus

Abbreviation/Term	Definition
IB	Investigator's Brochure
ICF	Informed Consent Form
iCPD	iRECIST confirmed progressive disease
iCR	iRECIST complete response
ICH	International Conference on Harmonization
IDO1	indoleamine 2,3 dioxygenase-1
IEC	independent ethics committee
Ig	immunoglobulin
IHC	Immunohistochemistry
iPR	iRECIST partial response
INR	International Normalized Ratio
IRB	Institutional Review Board
iRECIST	modified RECIST for immune-related RECISTbased therapeutics
irRECIST	Immune related RECIST (Modification of RECIST 1.1)
iSD	iRECIST stable disease
IUD	Intrauterine device
iUPD	iRECIST unconfirmed progressive disease
IV	Intravenous
LDH	Lactate Dehydrogenase
mAb	Monoclonal Antibody
MAOI	monoamine oxidase inhibitors
mcL	Microliters
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mg/kg	Milligram per Kilogram
mL	milliliter
MRI	Magnetic Resonance Imaging
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
MTD	maximum tolerated dose
NA or N/A	Not Applicable
NCI	National Cancer Institute
NSAID	Non-Steroidal Anti-inflammatory Drug
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall Response Rate
OS	Overall Survival
OTC	Over-the-counter
PD	pharmacodynamic or progressive disease
PD-1	Programmed Death-1
PD-L1	Programmed Death ligand-1
PET	positron emission tomography

Abbreviation/Term	Definition
PFS	Progression Free Survival
PI	principal investigator
PK	Pharmacokinetic
PO	Oral Administration
PR	Partial Response
PS	Performance Status
PT	Prothrombin Time
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SCCHN	squamous cell carcinoma of the head and neck
SD	Stable Disease
SNRI	serotonin/norepinephrine reuptake inhibitors
SOP	Standard Operating Procedures
SS	serotonin syndrome
sSAP	supplemental SAP
ß-HCG	Beta Human Chorionic Gonadotropin
SSRI	serotonin reuptake inhibitors
Treg	regulatory T cell
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal

12.9 Clinical Study Conduct System

Clinical study conduct system in Japan is provided in Attachment by Japanese language.

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – TRIAL PROCEDURES (Assessing and Recording Adverse Events). I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	